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Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review (Review)

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Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review (Review)

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[Intervention Review]

Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review

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ABSTRACT

Background

Convalescent plasma and hyperimmune immunoglobulin may reduce mortality in patients with viral respiratory diseases, and are currently being investigated in trials as potential therapy for coronavirus disease 2019 (COVID-19). A thorough understanding of the current body of evidence regarding the benefits and risks is required.

Objectives

To continually assess, as more evidence becomes available, whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in treatment of people with COVID-19.

Search methods

We searched the World Health Organization (WHO) COVID-19 Global Research Database, MEDLINE, Embase, Cochrane COVID-19 Study Register, Centers for Disease Control and Prevention COVID-19 Research Article Database and trial registries to identify completed and ongoing studies on 19 August 2020.

Selection criteria

We followed standard Cochrane methodology.

We included studies evaluating convalescent plasma or hyperimmune immunoglobulin for people with COVID-19, irrespective of study design, disease severity, age, gender or ethnicity.

We excluded studies including populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)) and studies evaluating standard immunoglobulin.

Data collection and analysis

We followed standard Cochrane methodology.

To assess bias in included studies, we used the Cochrane 'Risk of bias' 2.0 tool for randomised controlled trials (RCTs), the Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool for controlled non-randomised studies of interventions (NRSIs), and the assessment criteria for observational studies, provided by Cochrane Childhood Cancer for non-controlled NRSIs. We rated the certainty of evidence using the GRADE approach for the following outcomes: all-cause mortality at hospital discharge, mortality (time to event), improvement of clinical symptoms (7, 15, and 30 days after transfusion), grade 3 and 4 adverse events (AEs), and serious adverse events (SAEs).

Main results

This is the second living update of our review. We included 19 studies (2 RCTs, 8 controlled NRSIs, 9 non-controlled NRSIs) with 38,160 participants, of whom 36,081 received convalescent plasma. Two completed RCTs are awaiting assessment (published after 19 August 2020). We identified a further 138 ongoing studies evaluating convalescent plasma or hyperimmune immunoglobulin, of which 73 are randomised (3 reported in a study registry as already being completed, but without results). We did not identify any completed studies evaluating hyperimmune immunoglobulin.

We did not include data from controlled NRSIs in data synthesis because of critical risk of bias. The overall certainty of evidence was low to very low, due to study limitations and results including both potential benefits and harms.

Effectiveness of convalescent plasma for people with COVID-19

We included results from two RCTs (both stopped early) with 189 participants, of whom 95 received convalescent plasma. Control groups received standard care at time of treatment without convalescent plasma.

We are uncertain whether convalescent plasma decreases all-cause mortality at hospital discharge (risk ratio (RR) 0.55, 95% confidence interval (CI) 0.22 to 1.34; 1 RCT, 86 participants; low-certainty evidence).

We are uncertain whether convalescent plasma decreases mortality (time to event) (hazard ratio (HR) 0.64, 95% CI 0.33 to 1.25; 2 RCTs, 189 participants; low-certainty evidence).

Convalescent plasma may result in little to no difference in improvement of clinical symptoms (i.e. need for respiratory support) at seven days (RR 0.98, 95% CI 0.30 to 3.19; 1 RCT, 103 participants; low-certainty evidence). Convalescent plasma may increase improvement of clinical symptoms at up to 15 days (RR 1.34, 95% CI 0.85 to 2.11; 2 RCTs, 189 participants; low-certainty evidence), and at up to 30 days (RR 1.13, 95% CI 0.88 to 1.43; 2 studies, 188 participants; low-certainty evidence).

No studies reported on quality of life.

Safety of convalescent plasma for people with COVID-19

We included results from two RCTs, eight controlled NRSIs and nine non-controlled NRSIs assessing safety of convalescent plasma. Reporting of safety data and duration of follow-up was variable. The controlled studies reported on AEs and SAEs only in participants receiving convalescent plasma. Some, but not all, studies included death as a SAE.

The studies did not report the grade of AEs. Fourteen studies (566 participants) reported on AEs of possible grade 3 or 4 severity. The majority of these AEs were allergic or respiratory events. We are very uncertain whether convalescent plasma therapy affects the risk of moderate to severe AEs (very low-certainty evidence).

17 studies (35,944 participants) assessed SAEs for 20,622 of its participants. The majority of participants were from one non-controlled NRSI (20,000 participants), which reported on SAEs within the first four hours and within an additional seven days after transfusion. There were 63 deaths, 12 were possibly and one was probably related to transfusion. There were 146 SAEs within four hours and 1136 SAEs within seven days post-transfusion. These were predominantly allergic or respiratory, thrombotic or thromboembolic and cardiac events. We are uncertain whether convalescent plasma therapy results in a clinically relevant increased risk of SAEs (low-certainty evidence).

Authors' conclusions

We are uncertain whether convalescent plasma is beneficial for people admitted to hospital with COVID-19. There was limited information regarding grade 3 and 4 AEs to determine the effect of convalescent plasma therapy on clinically relevant SAEs. In the absence of a control group, we are unable to assess the relative safety of convalescent plasma therapy.

While major efforts to conduct research on COVID-19 are being made, recruiting the anticipated number of participants into these studies is problematic. The early termination of the first two RCTs investigating convalescent plasma, and the lack of data from 20 studies that

have completed or were due to complete at the time of this update illustrate these challenges. Well-designed studies should be prioritised. Moreover, studies should report outcomes in the same way, and should consider the importance of maintaining comparability in terms of co-interventions administered in all study arms.

There are 138 ongoing studies evaluating convalescent plasma and hyperimmune immunoglobulin, of which 73 are RCTs (three already completed). This is the second living update of the review, and we will continue to update this review periodically. Future updates may show different results to those reported here.

PLAIN LANGUAGE SUMMARY

Is plasma from people who have recovered from COVID-19 an effective treatment for people with COVID-19?

Coronavirus disease 2019 (COVID-19) is a highly infectious respiratory illness caused by a newly recognised type of coronavirus. Some people have severe infection, leading to hospitalisation, admission to intensive care or death. Currently, no vaccine or specific treatment is available.

People who have recovered from COVID-19 develop natural defences in their blood (antibodies). Antibodies are found in part of the blood called plasma. Plasma from blood donated from recovered patients, which contains COVID-19 antibodies, can be used to make two preparations. Firstly, convalescent plasma, which is plasma that contains these antibodies. Secondly, hyperimmune immunoglobulin, which is more concentrated, and therefore contains more antibodies.

Convalescent plasma and hyperimmune immunoglobulin have been used successfully to treat other respiratory viruses. These treatments (given by a drip or injection) are generally well-tolerated, but unwanted effects similar to those from standard plasma transfusion can occur.

What did we want to find?

We wanted to know whether plasma from people who have recovered from COVID-19 is an effective treatment for people with COVID-19, and whether this causes any unwanted effects.

Our methods

We searched major medical databases for clinical studies on treatment with convalescent plasma or hyperimmune immunoglobulin for people with COVID-19. Studies could be conducted anywhere in the world and include participants of any age, gender, ethnicity or disease severity.

The evidence is up to date to 19 August 2020.

Key results

We included 19 completed studies with 38,160 participants; 36,081 participants received convalescent plasma.

We found two randomised controlled trials (RCTs), with 189 participants; 95 participants received convalescent plasma. RCTs are clinical studies where people are randomly allocated to receive the treatment (intervention group) or to receive different or no treatment (control group). Methods used in RCTs are designed to produce the most reliable evidence.

We found eight studies that were not randomised but included a control group of participants who did not receive convalescent plasma (controlled NRSIs), with 2471 participants; 485 participants received convalescent plasma. Because of critical study limitations or missing data, we did not include these studies to evaluate the benefit of convalescent plasma.

The remaining nine studies were not randomised and did not include a control group (non-controlled NRSIs) but provided information about unwanted effects of convalescent plasma for 20,622 of the included participants.

To assess whether convalescent plasma is effective for COVID-19, we evaluated results from the RCTs. The control groups received standard care at the time of treatment without convalescent plasma. There was not enough evidence to determine whether convalescent plasma affected the risk of death at hospital discharge and our confidence in the evidence is low. Convalescent plasma may decrease the need for breathing support, but our confidence in the evidence is low.

To assess whether convalescent plasma causes unwanted effects, we also evaluated nine non-controlled NRSIs. We identified some serious unwanted effects, which could be related to convalescent plasma, including death, allergic reactions or respiratory complications. There was not enough evidence to determine whether convalescent plasma therapy causes serious unwanted events and our confidence in the evidence is low.

None of the included studies reported effects on quality of life.

Certainty of the evidence

Our certainty (confidence) in the evidence was low or very low because there were only two RCTs and most studies did not use reliable methods to measure their results. Furthermore, participants received various treatments alongside convalescent plasma, and some had underlying health problems.

Conclusion

We are uncertain whether plasma from people who have recovered from COVID-19 is an effective treatment for people hospitalised with COVID-19 and whether convalescent plasma affects the number of serious unwanted effects. These findings could be related to the natural progression of disease, other treatments or to convalescent plasma. Our searches found 138 ongoing studies, of which 73 are randomised. This is the second update of our review, and we will continue to update this review.

SUMMARY OF FINDINGS

Summary of findings 1. Convalescent plasma for people with COVID-19

Convalescent plasma for people with COVID-19

Patients or population: people with COVID-19

Settings: inpatient

Intervention: convalescent plasma transfusion

Comparison: no convalescent plasma transfusion

Outcomes and study design	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence	Comments
	Control group risk (without convalescent plasma) ^a	Risk with convalescent plasma				
All-cause mortality at hospital discharge						
Randomised controlled trials	256 per 1000	141 per 1000 (56 to 343)	RR 0.55 (95% CI 0.22 to 1.34)	86 (1 study)	⊕⊕⊕⊕ Low b,d	
Mortality (time to event)						
Randomised controlled trials (up to 30 days)	247 per 1000	158 per 1000 (82 to 309)	HR 0.64 (95% CI 0.33 to 1.25)	189 (2 studies)	⊕⊕⊕⊕ Low b,d	
Improvement of clinical symptoms, assessed by need for respiratory support						
Follow-up: 7 days						
Randomised controlled trials at day 7	98 per 1000	96 per 1000 (29 to 312)	RR 0.98 (95% CI 0.30 to 3.19)	103 (1 study)	⊕⊕⊕⊕ Low d	

Improvement of clinical symptoms, assessed by need for respiratory support

Follow-up: 15 days

Randomised controlled trials at day 14	319 per 1000	427 per 1000 (271 to 673)	RR 1.34 (95% CI 0.85 to 2.11)	189 (2 studies)	⊕⊕⊕⊕ Low b,d,e	
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Improvement of clinical symptoms, assessed by need for respiratory support

Follow-up: 30 days

Randomised controlled trials at day 28	527 per 1000	596 per 1000 (464 to 754)	RR 1.13 (95% CI 0.88 to 1.43)	188 (2 studies)	⊕⊕⊕⊕ Low b,d	
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Quality of Life

Randomised controlled trials	NA	NA	NA	0	NA	None of the identified studies reported this outcome.
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Grade 3 or 4 adverse events^f

Randomised controlled trials	NR	NR in a comparative design	NA	NA	NA	All included controlled trials reported safety data for the intervention group only, so we included the results here under non-controlled non-randomised studies of interventions.
Controlled non-randomised studies of interventions	NR	NR in a comparative design	NA	NA	NA	
Non-controlled non-randomised studies of interventions	Studies did not report the grade of adverse events. The majority of these adverse events were allergic or respiratory events. Two studies reported events that were probably of grade 3 or 4 (2 participants with 3 events in a study with 52 participants, and 4 participants with 5 events in a study with 46 participants)			566 (14 studies)	⊕⊕⊕⊕ Very low g,h	We were unable to summarise numerical data in any meaningful way. We have provided an overview of the reported adverse events for each study in Table 5 .

Serious adverse events

Randomised controlled trials	NR	NR in a comparative design	NA	NA	NA	All included controlled trials reported safety data for the intervention group only, so we included the results here under non-controlled non-randomised studies of interventions.
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Controlled non-randomised studies of interventions	NR	NR in a comparative design	NA	NA	NA
Non-controlled non-randomised studies of interventions	<p>The majority of participants were from one non-controlled non-randomised study of intervention (including 35,322 and reporting SAEs for 20,000 participants), which reported SAEs within four hours and seven days after convalescent plasma transfusion. Within four hours, 146 SAEs were reported, those were deaths, TACOs, TRALIs, and severe allergic reactions. Within seven days after transfusion, an additional 1136 SAEs were reported, those were thrombotic or thromboembolic complications, sustained hypotension, and cardiac events.</p> <p>Other SAEs reported in all studies (1 SAE in a study with 52 participants, and 3 SAEs in a study with 46 participants) were predominantly allergic or respiratory in nature, including: anaphylaxis and TRALIs.</p>			20,621 (17 studies)	<p>Low^h</p> <p>We were unable to summarise numerical data in any meaningful way. An overview of the reported SAEs is provided in Table 6 per study.</p>

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval; **HR:** hazard ratio; **NA:** not available; **NR:** not recorded; **RR:** risk ratio; **SAE:** serious adverse event; **TACO:** transfusion-associated circulatory overload; **TRALI:** transfusion-related acute lung injury

^aControl group risk extracted from included studies.

^bWe did not downgrade for risk of bias, even though one of the included studies has some concerns.

^cRisk of bias within this study is critical, so we downgraded three points for risk of bias.

^dWe downgraded two points for imprecision because of the small information size and results including both potential benefit and potential harm.

^eWe did not downgraded for inconsistency, even though studies used different scales and cut-offs to define clinical improvement, because one study sent us individual patient data for days 15 and 30 ([Gharbharan 2020](#)). We used the IPD data provided on the WHO COVID-19 disease severity score ([WHO 2020f](#)), and transferred the scale into the 6-point scale used by [Li 2020](#).

^fWe assume these adverse events are grade 3 to 4; not all of the studies reported grading of adverse events.

^gRisk of bias through confounding across studies is high for this outcome, so we downgraded one point for risk of bias.

^hWe included intervention arms of controlled studies and non-controlled studies only, so we started assessment from low-certainty evidence and did not summarise outcome data across studies.

BACKGROUND

Description of the condition

The clinical syndrome coronavirus disease 2019 (COVID-19) is a new, rapidly emerging zoonotic infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; WHO 2020a). On 11 March 2020, the World Health Organization (WHO) declared the current COVID-19 outbreak a pandemic, with the outbreak resulting in more than 21 million cases and over 760,000 deaths worldwide as of 16 August 2020 (WHO 2020b; WHO 2020c). Although there are similarities with historic coronavirus epidemics, with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) responsible for 813 and 858 deaths respectively, the scale and impact of the COVID-19 pandemic presents unprecedented challenges to health facilities and healthcare workers all over the world (WHO 2007; WHO 2019).

The hospitalisation rate for COVID-19 in the period 1 to 28 March 2020 was estimated to be 4.6 per 100,000 population in the USA (Garg 2020). Groups at particular high risk of hospitalisation were those aged 65 and above, and those with underlying medical conditions (Garg 2020). Early reports suggest that the case fatality rate ranges between 0.7% and 4%, with higher rates also reported (WHO 2020a; WHO 2020c). However, these numbers should be interpreted with great care due to the data pertaining to the early emergency response, which due to shortage of test kits has led to selective testing of people with severe disease, underreporting of cases and delays from confirmation of a case to time of death (Kim 2020). By studying the population that was quarantined on the Diamond Princess cruise ship in February 2020, researchers have been able to generate useful insights into the case fatality rate independent of the above mentioned factors. Here, the case fatality rate taking into account the delay from confirmation to death, was shown to be 2.6% (Russell 2020). A larger study, which also employed delay-adjusted methods, but performed a random-effects meta-analysis across 107 countries and the Diamond Princess cruise ship, found a case fatality rate of 2.8% (95% confidence interval (CI) 2.1 to 3.1; Canelo-Aybar 2020). However, the risk of dying from COVID-19 can vary considerably depending on age, ethnicity, access to health care, socioeconomic status and underlying health conditions (Williamson 2020).

The median incubation period of SARS-CoV-2 was reported to be five days, with 97.5% of cases developing symptoms within 11.5 days of infection (Lauer 2020). Common signs and symptoms can include fever, dry cough, fatigue and sputum production (WHO 2020a). Postviral olfactory dysfunction is reported in 5% to 85% of cases, with loss of both smell and taste reported (Izquierdo-Dominguez 2020). Other, less commonly reported signs and symptoms are shortness of breath, sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhoea, haemoptysis and conjunctival congestion (WHO 2020a). Of the reported cases, 80% are estimated to have a mild or asymptomatic course of infection, and an estimated 5% of cases are admitted to the ICU with acute respiratory distress syndrome (ARDS), septic shock or multiple organ failure, or both (Team 2020; WHO 2020a). A risk factor for developing infection and progressing to severe disease is old age, with people aged over 80 years at highest risk of mortality. Other risk factors are cardiovascular disease, obesity, hypertension, diabetes, chronic respiratory disease, cancer and compromised immune status (Chen 2020a; Huang 2020; Liang 2020; WHO 2020a; Wu 2020a). Recent

reports have suggested that people who are immune-compromised may not have an increased risk of being hospitalised with severe COVID-19 symptoms (D'Antiga 2020). However, evidence has been conflicting, with patients with malignancy and recipients of solid organ transplants reported potentially to have an increased risk of severe COVID-19 disease (Fung 2020).

SARS-CoV-2 is a positive-sense, single-stranded RNA (ribonucleic acid) virus with a large genome. Although not much is known about the specific mechanisms underlying severe disease in COVID-19, there are indications that the virus is capable of inducing an excessive immune reaction in the host, with highly activated but decreased numbers of CD4⁺ and CD8⁺ T cells detected in the peripheral blood of people with COVID-19 (Xu 2020a). Early reports also showed that people critically ill with COVID-19 frequently exhibit a hypercoagulable state and endothelial inflammation, which is hypothesised to lead to the high burden of thromboembolic events seen in this population (Driggin 2020). Preliminary reports into the pathophysiology of SARS-CoV-2 have further indicated that the observed decrease in human angiotensin-converting enzyme 2 (ACE2) activity may play a role in causing the rapid deterioration of patient lung function (Tolouian 2020; Van de Veerdonk 2020). ACE2 is a protein that functions as the receptor facilitating entry of SARS-CoV-2 into the host cell, and is most abundant on type II alveolar cells in the lungs.

Description of the intervention

Convalescent plasma, convalescent serum and hyperimmune immunoglobulin prepared from convalescent plasma, are interventions that have been used in the past to treat conditions when no vaccine or pharmacological interventions were available. Diphtheria, pneumococcal pneumonia, hepatitis A and B, mumps, polio, measles and rabies are conditions where convalescent plasma has been shown to be effective (Eibl 2008).

A systematic review has shown that convalescent plasma may have clinical benefit for people with influenza and SARS (Mair-Jenkins 2015). This systematic review included observational studies and randomised controlled trials (RCTs) investigating the use of convalescent plasma, serum or hyperimmune immunoglobulin for treating severe acute respiratory infections of laboratory-confirmed or suspected viral aetiology, and included investigations with patients of any age and sex. Control interventions consisted of sham, or placebo, therapy and no therapy. The authors concluded that, although the included studies were generally small and of low quality, with a moderate to high risk of bias, the use of convalescent plasma may reduce mortality and appears safe (Mair-Jenkins 2015). The authors also suggested that the effectiveness of convalescent plasma in reducing hospital length of stay is dependent on early administration of the therapy, and use as prophylaxis is more likely to be beneficial than treating severe disease. However, the optimal timing and dosage of convalescent plasma therapy is unknown.

There is conflicting evidence about the effect of convalescent plasma or hyperimmune immunoglobulin for treating severe acute respiratory infections. Studies investigating the effectiveness of hyperimmune immunoglobulin for influenza have been contradictory, with some RCTs showing effectiveness (Hung 2013), whereas others show no benefit (Beigel 2017; Beigel 2019; Davey 2019).

Although convalescent plasma is generally thought to be a safe and well-tolerated therapy, adverse events can occur. Limited information is available about specific adverse events related to convalescent plasma therapy, but symptoms that have been reported are similar to those for other types of plasma blood components, including fever or chills, allergic reactions, and transfusion-related acute lung injury (TRALI; [Beigel 2019](#); [Chun 2016](#); [Luke 2006](#)). Furthermore, the transfer of coagulation factors present in plasma products is potentially harmful for people with COVID-19, who are already at an increased risk of thromboembolic events ([Driggin 2020](#)). Plasma transfusions are also known to cause transfusion-associated circulatory overload (TACO). TACO and TRALI are especially important to consider, because COVID-19 patients with comorbidities, who might be eligible for experimental treatment with convalescent plasma therapy, are at an increased risk of these adverse events. There are risk-mitigation strategies that can be implemented to prevent TRALI. These include limiting donations from female donors, especially those with a history of pregnancy, and screening of donors for antibodies that are implicated in TRALI ([Otrock 2017](#)). In addition to the aforementioned adverse events, transfusion-transmitted infections, red blood cell alloimmunisation and haemolytic transfusion reactions have also been described following plasma transfusion, although they are less common ([Pandey 2012](#)). Pathogen inactivation can be implemented to decrease the risk of transmitting infections by transfusion ([Rock 2011](#)).

When compared to convalescent plasma, hyperimmune immunoglobulin has the advantage of preventing transfer of potentially harmful coagulation factors that are present in plasma products. The amount and antibody concentration can be more accurately dosed compared to convalescent plasma, and hyperimmune immunoglobulin can be prepared in a consistent manner ([Hung 2013](#)). Not many studies have reported on adverse events of hyperimmune immunoglobulin, but the safety profile of standard intravenous immunoglobulin is known and the adverse events reported here are also likely to occur in hyperimmune immunoglobulin therapy. Common adverse events of intravenous immunoglobulin that occur immediately after administration are: infusion site pain; swelling and erythema; and immediate systemic reactions, such as head and body aches, chills and fever ([Stiehm 2013](#)). Other, less common early adverse reactions to immunoglobulin therapy are pulmonary complications, such as pulmonary embolism, pulmonary oedema and pleural effusion, with TRALI also reported ([Baudel 2020](#); [Stiehm 2013](#)). Anaphylactic and anaphylactoid reactions to immunoglobulin therapy are rare ([Brennan 2003](#); [Stiehm 2013](#)). Delayed adverse events of immunoglobulin therapy, which occur within hours to days of initiation of immunoglobulin therapy, are persistent headaches (common), aseptic meningitis, renal failure, thromboembolic events, and haemolytic reactions ([Sekul 1994](#); [Stiehm 2013](#)). Transmission of infectious agents has been described after administration of intravenous immunoglobulin, but this risk is considered to be low ([Stiehm 2013](#)). Other, severe adverse events that occur late after administration are lung disease, enteritis and dermatological disorders ([Stiehm 2013](#)).

A theoretical risk related to virus-specific antibodies, which are transferred with convalescent plasma and hyperimmune immunoglobulin administration, is antibody-dependent enhancement of infection ([Morens 1994](#)). Here, virus-

binding antibodies facilitate the entry and replication of virus particles into monocytes, macrophages and granulocytic cells and thereby increase the risk of more severe disease in the infected host. Although antibody-dependent enhancement has not been demonstrated in COVID-19, it has been seen with previous coronavirus infections when the antibodies given targeted a different serotype of the virus ([Wan 2020](#); [Wang 2014](#)). A mechanism for antibody-dependent enhancement in COVID-19 has recently been proposed, with non-neutralising antibodies to variable S domains potentially enabling an alternative infection pathway via Fc receptor-mediated uptake ([Ricke 2020](#)). Antibody-dependent enhancement is therefore a potentially harmful consequence of convalescent plasma and hyperimmune immunoglobulin therapy for COVID-19. Safety of convalescent plasma for treatment of COVID-19 has recently been investigated in a large cohort from the US Food and Drug Administration (USFDA) Expanded Access Program ([Joyner 2020a](#)). Here, convalescent plasma did not clearly cause an excessive risk of adverse events within seven days of treatment, nor did it show an exceptionally high mortality rate at seven days (8.6%) ([Joyner 2020a](#)).

In summary, the benefits of the intervention, both for convalescent plasma or hyperimmune immunoglobulin, should be carefully considered in view of the risks of adverse events.

How the intervention might work

Convalescent plasma contains pathogen-specific neutralising antibodies, which can neutralise viral particles, and treatment with convalescent plasma or hyperimmune immunoglobulins confers passive immunity to recipients. The duration of conferred protection can differ depending on the timing of administration, ranging from weeks to months after treatment ([Casadevall 2020](#)).

By neutralising SARS-CoV-2 particles, early treatment with convalescent plasma is postulated to increase the patient's own capacity to clear the initial inoculum ([Casadevall 2020](#); [Robbins 1995](#)). This could lead to a reduction in mortality and fewer hospitalised patients progressing to the ICU. Furthermore, convalescent plasma may reduce the length of ICU stay in critically ill patients ([Mair-Jenkins 2015](#)), thus helping to lift pressure from global healthcare systems and increasing ICU capacity.

Preliminary evidence in humans and rhesus macaques has shown that reinfection with SARS-CoV-2 is not likely, with most (but not all) patients who recovered from COVID-19 producing sufficient amounts of neutralising antibodies to protect against reinfection ([Bao 2020a](#); [Wu 2020b](#)). This implies that convalescent plasma from people who have recovered from SARS-CoV-2 infection is capable of conferring passive immunity. A recently reported case series also indicated sufficient neutralising antibody titres in convalescent plasma to neutralise SARS-CoV-2 in five COVID-19 patients, who all recovered after treatment ([Shen 2020](#)). It is important to note, however, that research in other coronavirus species has shown that immunity may not be long-lasting, with two to three years of protection estimated from work with SARS and MERS ([Mo 2006](#); [Payne 2016](#)). Furthermore, there are indications that the severity of infection has an impact on antibody titres, with less severe disease leading to lower neutralising antibody response in people with SARS and COVID-19 ([Ho 2005](#); [Zhao 2020a](#)).

Why it is important to do this review

There is a clear, urgent need for more information to guide clinical decision-making for COVID-19 patients. Pharmacological treatment options are being investigated in many ongoing trials, with currently only treatment of dexamethasone proven to be effective in reducing mortality (Horby 2020), and remdesivir shown to reduce time to recovery (Beigel 2020). Current treatment further consists of supportive care with extracorporeal membrane oxygenation in severe cases and oxygen supply in mild cases (CDC 2020b; WHO 2020d). Despite these treatments, people hospitalised with COVID-19 are still at a high risk of mortality. A vaccine could aid in inducing immunity in the population and preventing transmission to those who are at risk for severe disease, but no vaccine is currently available, although multiple candidate vaccines are in development. Until these vaccines are available and distributed, convalescent plasma is a potential therapy for COVID-19 patients. Convalescent plasma, and hyperimmune immunoglobulin to a certain extent, can be prepared and made rapidly available by blood banks and hospitals when enough potential donors have recovered from the infection, using readily available materials and methods (Bloch 2020). However, its safety and efficacy are not well characterised, and there are costs associated with pursuing the use of convalescent plasma for treatment of COVID-19.

A multitude of clinical trials investigating the safety and effectiveness of convalescent plasma or hyperimmune immunoglobulins have been announced, and their results will need to be interpreted with care. Thus, there needs to be a thorough understanding of the current body of evidence regarding the use of convalescent plasma for people with COVID-19, and an extensive review of the available literature is required.

OBJECTIVES

To continually assess, as more evidence becomes available, whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in the treatment of people with COVID-19.

METHODS

Criteria for considering studies for this review

Types of studies

The protocol for this review was registered with the Center for Open Science on 17 April 2020 (Piechotta 2020a).

To assess the benefits and safety of convalescent plasma therapy for COVID-19 we included randomised controlled trials (RCTs), as such studies, if performed appropriately, give the best evidence for experimental therapies in highly controlled therapeutic settings. For RCT data, we used the methods recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a), as specified in the description of the methods. If we had identified non-standard RCT designs, such as cluster-randomised trials and cross-over trials, we had planned to include those and to apply the methods recommended in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b). We had planned to consider only the results from the first cycle of cross-over RCTs.

In case of insufficient evidence available from RCTs, we had planned to include prospective controlled non-randomised studies of interventions (NRSIs), including quasi-randomised controlled trials (e.g. assignment to treatment by alternation or by date of birth), controlled before-and-after (CBA) studies, and interrupted time series (ITS) studies. We had planned to use the methods proposed in the *Cochrane Handbook for Systematic Reviews of Interventions* for the inclusion of controlled NRSIs in systematic reviews (Reeves 2019).

As planned at the protocol stage, we further included retrospective controlled NRSIs, because of insufficient evidence (very low-certainty evidence or no evidence) available from RCTs and prospective controlled NRSIs and adapted the methods for the inclusion of controlled NRSIs in systematic reviews as specified by the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2019).

The evidence that we found from the RCTs was at high risk of bias and at critical risk of bias for the controlled NRSIs for safety outcomes, because none of the studies reported safety data for the control group. So we also included safety data from prospectively and retrospectively registered non-controlled NRSIs, for example, case series (please see [Differences between protocol and review](#)), and followed the methodology as specified in the protocol (Piechotta 2020a).

We followed the suggestions specified in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a), as far as possible, and applied the methodology outlined in the following sections. We considered studies including one or more participant(s) with coronavirus disease 2019 (COVID-19).

We included full-text publications, abstract publications, and results published in trials registries, if sufficient information was available on study design, characteristics of participants, interventions and outcomes. We did not apply any limitation with respect to the length of follow-up.

Types of participants

We included individuals with a confirmed diagnosis of COVID-19, with no age, gender or ethnicity restrictions.

We excluded studies including populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)). We also excluded studies including populations with mixed viral diseases (e.g. influenza), unless the trial authors provided subgroup data for people with COVID-19.

Types of interventions

We included the following interventions.

- Convalescent plasma from people who had recovered from SARS-CoV-2 infection
- Hyperimmune immunoglobulin therapy

We did not include studies on standard immunoglobulin.

We included the following comparisons for studies with a control arm.

- Convalescent plasma therapy versus control treatment, for example, drug treatments (including but not limited to

hydroxychloroquine, remdesivir), standard immunoglobulin. Co-interventions are allowed, but must be comparable between intervention groups.

We had planned to additionally include the following comparisons for studies with a control arm, but did not identify any studies.

- Convalescent plasma versus standard care or placebo
- Convalescent plasma therapy versus hyperimmune immunoglobulin
- Hyperimmune immunoglobulin versus standard care or placebo
- Hyperimmune immunoglobulin versus control treatment, for example, drug treatments (including but not limited to hydroxychloroquine, remdesivir). Co-interventions are allowed, but must be comparable between intervention groups.

Types of outcome measures

We evaluated core outcomes as predefined by the Core Outcome Measures in Effectiveness Trials Initiative for COVID-19 patients (COMET 2020).

Primary outcomes

Effectiveness of convalescent plasma for people with COVID-19

- All-cause mortality at hospital discharge
- Mortality (time to event)

Secondary outcomes

Effectiveness of convalescent plasma for people with COVID-19

- Improvement of clinical symptoms, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days
- 30-day and 90-day mortality
- Time to discharge from hospital
- Admission to the intensive care unit (ICU)
- Length of stay on the ICU
- Virological response, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days
- Quality of life, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available

Safety of convalescent plasma for people with COVID-19

- Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions)
- Number of participants with serious adverse events

Timing of outcome measurement

For time-to-event outcomes, such as mortality, discharge from hospital, and improvement of clinical symptoms, we included outcome measures representing the longest follow-up time available.

We included all other outcome categories for the observational periods that the study publications reported. We included those adverse events occurring during active treatment and had planned to include long-term adverse events as well. If sufficient data had been available, we planned to group the measurement time points of eligible outcomes, for example, adverse events and serious adverse events, into those measured directly after treatment (up to seven days after treatment), medium-term outcomes (15 days after treatment) and longer-term outcomes (over 30 days after treatment).

Search methods for identification of studies

We carry out weekly searches for completed and ongoing studies in all languages in order to limit language bias.

Electronic searches

We designed and tested search strategies for electronic databases according to methods suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2019), CD developed them and Cochrane Haematology's Information Specialist (IM) peer reviewed them. In this emerging field, we expected that at least the abstract would be in English. If studies were published in other languages than those our review team could accommodate (English, Dutch, German, French, Italian, Malay and Spanish), we involved [Cochrane TaskExchange](#) to identify people within Cochrane to translate these studies.

As publication bias might influence all subsequent analyses and conclusions, we searched all potential relevant trials registries in detail to detect ongoing as well as completed studies, but not yet published studies. Nowadays, it is mandatory to provide results at least in the trials registry. In case results were not published elsewhere, we had planned to extract and analyse these data. However, no outcome data have yet been added to the trials registries.

We searched the following databases and sources, from 1 January 2019 to 19 August 2020.

- Databases of medical literature
 - * MEDLINE (Ovid, 23 April to 19 August 2020), [Appendix 1](#)
 - * Embase (Ovid, 23 April to 19 August 2020), [Appendix 2](#)
 - * PubMed (for epublications ahead of print only; searched 19 August 2020), [Appendix 3](#)
 - * Center for Disease Control and Prevention COVID-19 Research Article Database (www.cdc.gov/library/researchguides/2019novelcoronavirus/databasesjournals.html; downloaded 19 August 2020), [Appendix 4](#)
 - * Cochrane COVID-19 Study Register (covid-19.cochrane.org; searched 19 August 2020), [Appendix 5](#)
- Trials registries and registry platforms to identify ongoing studies and results of completed studies
 - * ClinicalTrials.gov - COVID-19 subset (included in Cochrane COVID-19 Study Register)
 - * WHO International Clinical Trials Registry Platform (ICTRP) - COVID-19 subset (included in Cochrane COVID-19 Study Register)

Searching other resources

- We handsearched the reference lists of all identified studies, relevant review articles and current treatment guidelines for further literature; and
- contacted experts in the field, drug manufacturers and regulatory agencies in order to retrieve information on unpublished studies.

Data collection and analysis

Selection of studies

Two out of five review authors (SJV, KLC, VP, CK, NS) independently screened the results of the search strategies for eligibility for this review by reading the abstracts using [Covidence](#) software. We coded the abstracts as either 'retrieve' or 'do not retrieve'. In the case of disagreement or if it was unclear whether we should retrieve the abstract or not, we obtained the full-text publication for further discussion. Two review authors assessed the full-text articles of selected studies. If the two review authors were unable to reach a consensus, they consulted a third review author to reach a final decision.

We documented the study selection process in a flow chart, as recommended in the PRISMA statement ([Moher 2009](#)), and show the total numbers of retrieved references and the numbers of included and excluded studies. We list all articles that we excluded after full-text assessment and the reasons for their exclusion in the [Characteristics of excluded studies](#) table.

Data extraction and management

One review author (NS, SJV, KLC, CK or VP) performed all data extractions and assessments. Two other review authors (NS, SJV, KLC, CK or VP) verified the accuracy and (where applicable) the plausibility of extractions and assessment.

Two review authors (VP or NS) independently assessed eligible studies obtained in the process of study selection (as described above) for methodological quality and risk of bias. If the review authors were unable to reach a consensus, we consulted a third review author (SJV, KLC or CK).

One review author (NS, SJV, KLC, CK or VP) extracted data using a customised data extraction form developed in Microsoft Excel ([Microsoft Corporation 2018](#)); please see [Differences between protocol and review](#). Another review author (NS, SJV, KLC, CK or VP) verified the accuracy and (where applicable) the plausibility of extractions and assessment. We conducted data extraction according to the guidelines proposed by Cochrane ([Li 2019](#)). If the review authors were unable to reach a consensus, we consulted a third review author.

We collated multiple reports of one study so that the study, and not the report, is the unit of analysis.

We extracted the following information.

- General information: author, title, source, publication date, country, language, duplicate publications
- Quality assessment: study design, confounding, definition of risk estimates, selection bias, attrition bias, detection bias, reporting bias

- Study characteristics: trial design, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, treatment cross-overs, compliance with assigned treatment, length of follow-up
- Participant characteristics: age, gender, ethnicity, number of participants recruited/allocated/evaluated, disease, severity of disease, additional diagnoses, previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation), whether the donors were tested by nasal swabs or whether the plasma was tested
- Interventions: convalescent plasma therapy or hyperimmune immunoglobulin therapy, concomitant therapy, duration of follow-up, donors' disease severity, how donations were tested for neutralising antibody
 - * For studies including a control group: comparator (type)
- Outcomes
 - * Effectiveness of convalescent plasma for people with COVID-19:
 - all-cause mortality at hospital discharge
 - mortality (time to event)
 - improvement of clinical symptoms, assessed by need for respiratory support in accordance with the WHO Clinical Progression Scale ([WHO 2020e](#)) at up to 7 days, 8 to 15 days, 16 to 30 days
 - 30-day and 90-day mortality
 - time to discharge from hospital
 - admission to the ICU
 - length of stay on the ICU
 - virological response, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days
 - Quality of life, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available
 - * Safety of convalescent plasma for people with COVID-19:
 - number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. TRALI, TACO, TAD, acute transfusion reactions)
 - number of participants with serious adverse events

Assessment of risk of bias in included studies

Randomised controlled trials

We used the Risk of Bias 2.0 (RoB 2) tool to analyse the risk of bias in the underlying study results ([Sterne 2019](#)). Of interest for this review was the effect of the assignment to the intervention (the intention-to-treat (ITT) effect) and we performed all assessments with RoB 2 on this effect. The outcomes that we addressed are those specified for inclusion in [Summary of findings 1](#). Accordingly, the outcomes had been prioritised according to the Core Outcome Measures in Effectiveness Trials Initiative for Covid-19 patients ([COMET 2020](#)).

Two out of five review authors (SJV, KLC, VP, CK, NS) independently assessed the risk of bias for each study result. In case of discrepancies among their judgements or inability to reach consensus, we consulted a third review author to reach a final decision. We assessed the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2019c](#)).

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

For cluster-RCTs, we had planned to add an additional domain to assess bias arising from the timing of identification and recruitment of participants in relation to timing of randomisation, as recommended in the archived RoB 2 guidance for cluster-randomised trials (Eldridge 2016), and in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019b).

To address these types of bias we used the signalling questions recommended in RoB 2 and made a judgement using the following options:

- 'yes': if there is firm evidence that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question);
- 'probably yes': a judgement has been made that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question);
- 'no': if there is firm evidence that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias for the given the direction of the question);
- 'probably no': a judgement has been made that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question);
- 'no information': if the study report does not provide sufficient information to allow any judgement.

We used the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias:

- low risk of bias;
- some concerns;
- high risk of bias.

Subsequently we derived a 'Risk of bias' rating for each prespecified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judged the trial to be at low risk of bias for all domains for this result.
- 'Some concerns': we judged the trial to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.
- 'High risk of bias': we judge the trial to be at high risk of bias in at least one domain for the result or we judge the trial to have some concerns for multiple domains in a way that substantially lowers confidence in the results.

We used the RoB 2 Excel tool to implement RoB 2 (available on the riskofbiasinfo.org website) and stored and presented our detailed RoB 2 assessments as supplementary online material.

Controlled non-randomised studies of interventions

As reported above, we had planned to include controlled non-randomised studies of intervention (NRSI) trials if there was insufficient evidence from RCTs.

Two review authors (VP, NS) independently assessed eligible studies for methodological quality and risk of bias (using the Risk Of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool; Sterne 2016). The quality assessment strongly depends upon information on the design, conduct and analysis of the trial. The two review authors resolved any disagreements regarding quality assessments by discussion, and in case of discrepancies among their judgements, or inability to reach consensus, we had planned to consult a third review author until consensus could be reached. We asked the Cochrane Editorial and Methods Department (Theresa Moore) to review our judgements for reasonability. The categories for 'Risk of bias' judgements for controlled NRSIs using ROBINS-I are 'low risk', 'moderate risk', 'serious risk' and 'critical risk' of bias.

We assessed the following domains of bias.

- Bias due to confounding
- Bias in selection of participants into the study
- Bias in classification of interventions
- Bias due to deviations from intended interventions
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in selection of the reported result

For every criterion we made a judgement using one of five response options.

- Yes
- Probably yes
- Probably no
- No
- No information

Non-controlled non-randomised studies of interventions

As specified in the [Types of studies](#) section, the evidence that we found from the RCTs was at high risk of bias and the evidence from controlled NRSIs for safety outcomes was at critical risk of bias, because none of the studies reported safety data for the control group. So we also included safety data from prospective and retrospective non-controlled NRSIs.

Because we only included safety data from non-controlled NRSIs, we only assessed methodological quality and risk of bias for studies reporting any safety data.

Two review authors (VP, NS) assessed eligible studies for methodological quality and risk of bias (using the 'Risk of bias' assessment criteria for observational studies tool provided by Cochrane Childhood Cancer (see [Table 1](#); Mulder 2019). We performed and presented any 'Risk of bias' judgements per outcome per study.

The quality assessment strongly depends upon information on the design, conduct and analysis of the study. The two review authors (VP, NS) resolved any disagreements regarding the quality

assessments by discussion; in case of disagreement they would have consulted a third review author (SJV, KLC or CK).

We assessed the following domains of bias.

- Internal validity
 - * Unrepresentative study group (selection bias)
 - * Incomplete outcome assessment/follow-up (attrition bias)
 - * Outcome assessors unblinded to investigated determinant (detection bias)
 - * Important prognostic factors or follow-up not taken adequately into account (confounding)
- External validity
 - * Poorly defined study group (reporting bias)
 - * Poorly defined follow-up (reporting bias)
 - * Poorly defined outcome (reporting bias)
 - * Poorly defined risk estimates (analyses)

For every criterion, risk of bias judgements are 'high', 'unclear' or 'low'.

We used the Risk-of-bias VISualization tool (robvis) to generate risk of bias summary figures ([McGuinness 2020](#)).

Measures of treatment effect

Randomised controlled trials

For continuous outcomes, we had planned to record the mean, standard deviation and total number of participants in both the treatment and control groups. For dichotomous outcomes, we had planned to record the number of events and total number of participants in both the treatment and control groups.

For continuous outcomes using the same scale we had planned to perform analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales we had planned to perform analyses using the standardised mean difference (SMD). For interpreting SMDs, we had planned to re-express SMDs in the original units of a particular scale with the most clinical relevance and impact.

If available, we extracted and reported hazard ratios (HRs) for time-to-event outcomes (time to death). If HRs were not available, we made every effort to estimate the HR as accurately as possible using the available data and a purpose-built method based on the Parmar and Tierney approach ([Parmar 1998](#); [Tierney 2007](#)). If sufficient studies had provided HRs, we planned to use HRs rather than risk ratios (RRs) or MDs in a meta-analysis.

For dichotomous outcomes, we had planned to report the pooled RR with a 95% CI ([Deeks 2019](#)). If the number of observed events had been small (less than 5% of sample per group), and if studies had balanced treatment groups, we planned to report the Peto odds ratio (OR) with 95% CI ([Deeks 2019](#)).

Controlled non-randomised studies of interventions

For dichotomous outcomes, if available, we had planned to extract and report the RR with a 95% CI from statistical analyses adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of RRs (i.e. the RR post-intervention/RR pre-intervention).

For continuous variables, if available, we had planned to extract and report the absolute change from a statistical analysis adjusting for baseline differences (such as regression models, mixed models or hierarchical models), or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups/the post-intervention level in the control group; [EPOC 2017](#)).

Non-controlled non-randomised studies of interventions

For non-controlled NRSIs we did not carry out an analysis using quantitative data from indirect controls, as we are aware of the difficulties of indirect comparisons of participant groups with varying baseline characteristics, especially in the absence of individual patient data. Because authors of non-controlled NRSIs, often discuss their findings using information from other intervention and observational studies as implicit controls, we discussed our findings extensively in the context of what is known about the outcome of 'comparable' patients receiving other experimental treatments but not convalescent plasma therapy or hyperimmune immunoglobulin therapy. We did not meta-analyse the data but provided information from individual studies within tables.

Unit of analysis issues

We did not combine any data from different study designs. Meta-analysis was not appropriate for the identified controlled NRSIs because of critical risk of bias. Meta-analysis was also not appropriate for the non-controlled NRSIs as described above. We reported and presented results narratively, instead.

As recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2019d](#)), for studies with multiple treatment groups, we combined arms as long as they could be regarded as subtypes of the same intervention.

When arms could not be pooled this way, we had planned to compare each arm with the common comparator separately. For pair-wise meta-analysis, we had planned to split the 'shared' group into two or more groups with smaller sample size, and include two or more (reasonably independent) comparisons. For this purpose, for dichotomous outcomes, both the number of events and the total number of participants would be divided up, and for continuous outcomes, the total number of participants would be divided up with unchanged means and standard deviations (SDs).

Dealing with missing data

Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* suggests a number of potential sources for missing data, which we needed to take into account: at study level, at outcome level and at summary data level ([Higgins 2019d](#)). In the first instance, it is of the utmost importance to differentiate between data 'missing at random' and 'not missing at random'.

We requested missing data from the study authors. We contacted six principal investigators from included studies ([Duan 2020](#); [Gharbharan 2020](#); [Li 2020](#); [Liu 2020](#); [Rasheed 2020](#); [Zeng 2020](#)). We received three responses, one from [Gharbharan 2020](#) providing all requested information (see [Included studies](#)), one from [Liu 2020](#), stating that the authors were not able to provide additional

data for this version of the review, and one from [Rasheed 2020](#), stating that all or most requested information will be included in the journal publication. We contacted seven principal investigators from ongoing studies, which were planned to be completed ([ChiCTR2000030010](#); [ChiCTR2000030039](#); [ChiCTR2000030179](#); [ChiCTR2000030627](#); [NCT04264858](#); [NCT04345991](#); [NCT04376788](#)), but did not receive any responses. As we have not pooled any data at this point, we did not have to make any assumptions. If, for updates of this review, data are still missing, we will have to make explicit assumptions of any methods the included studies used. For example, we will assume that the data were missing at random or we will assume that missing values had a particular value, such as a poor outcome.

Assessment of heterogeneity

We did not combine any data from different study designs. Meta-analysis was not appropriate for the identified controlled NRSIs because of critical risk of bias. Meta-analysis was also not appropriate for the non-controlled NRSIs as described above. We reported and presented results narratively, instead.

We assessed heterogeneity of treatment effects between trials using a Chi² test with a significance level at $P < 0.1$. We used the I² statistic ([Higgins 2003](#)), to quantify possible heterogeneity (I² statistic $> 30\%$ to signify moderate heterogeneity, I² statistic $> 75\%$ to signify considerable heterogeneity; [Deeks 2019](#)). If heterogeneity had been above 80%, we would have explored potential causes through sensitivity and subgroup analyses. If we had not found a reason for heterogeneity, we would not have performed a meta-analysis, but would have only commented on results from all studies and presented these in tables.

Assessment of reporting biases

As mentioned above, we searched trials registries to identify completed studies that have not been published elsewhere, to minimise or determine publication bias. We included studies irrespective of their publication status as recommended in *Cochrane Handbook for Systematic Reviews of Interventions* ([McKenzie 2019](#)).

In an update of this review, we intend to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test ([Sterne 2019](#)), for meta-analyses involving at least 10 studies. We will consider $P < 0.1$ as significant for this test.

Data synthesis

If the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we pooled the data in meta-analysis. We performed analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Deeks 2019](#)). We did not conduct meta-analyses that involved both RCTs and controlled NRSIs. We conducted separate meta-analyses for each comparison.

We used the Review Manager Web software for analyses ([Review Manager Web](#)). One review author entered the data into the software, and a second review author checked the data for accuracy.

We used the random-effects model for all analyses as we anticipated that true effects would be related, but would not be the same for included studies. If we could not perform a meta-analysis, we commented on the results as a narrative with the results from all studies presented in tables.

For RCTs, when meta-analysis was feasible, we used the random-effects model for pooling the data. For binary outcomes, we based the estimation of the between-study variance using the Mantel-Haenszel method. We used the inverse variance method for continuous outcomes, outcomes that include data from cluster-RCTs, or outcomes where HRs are available. We planned to explore heterogeneity above 80% with subgroup analyses. If we could not find a cause for the heterogeneity then we had planned not to perform a meta-analysis, but comment on the results as a narrative with the results from all studies presented in tables.

We did not synthesise efficacy data from controlled NRSIs if they were at critical risk of bias. If a meta-analysis had been feasible for controlled NRSIs we had planned to analyse the different types of studies separately. We had planned to only analyse outcomes with adjusted effect estimates if these were adjusted for the same factors using the inverse-variance method as recommended in Chapter 24 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Reeves 2019](#)).

We did not meta-analyse data from non-controlled NRSIs, as there might be no additional benefit in meta-analysing data without a control group. We reported outcome data of each included trial within tables.

As most outcome data did not allow quantitative assessment, we presented results individually per study within tables.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses of the following characteristics.

- Severity of condition

We used the tests for interaction to test for differences between subgroup results.

We had further planned to perform additional subgroup analyses of the following characteristics.

- Age of participants (divided into applicable age groups, e.g. children; 18 to 65 years, 65 years and older)
- Pre-existing conditions (diabetes, respiratory disease, hypertension, immunosuppression)

We discussed adding additional subgroup analyses in the next update (please see characteristics and reasons in [Appendix 6](#)).

Sensitivity analysis

Considering the currently available evidence, any analyses were inappropriate for this version of the review. We will perform only one sensitivity analysis for the following in an update of this review.

- 'Risk of bias' assessment components (studies with a low risk of bias or some concerns versus studies with a high risk of bias)

To assess the influence of study quality on an outcome, we will perform sensitivity analyses per outcome, comparing studies with

at least one domain of high risk of bias to those without high risk of bias.

- Influence of completed, but not published studies
- Influence of premature termination of studies

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence for the following outcomes (please find the rationale for the amendment of graded outcomes in the [Differences between protocol and review](#)).

- All-cause mortality at hospital discharge
- Mortality (time to event)
- Improvement of clinical symptoms (assessed by need for respiratory support) at the following time points
 - * 7 days post-convalescent plasma transfusion
 - * 15 days post-convalescent plasma transfusion
 - * 30 days post-convalescent plasma transfusion
- Quality of life
- Grade 3 or 4 adverse events
- Serious adverse events

We followed the current GRADE guidance for these assessments in its entirety, as recommended in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020). We used GRADEpro GDT software to create a

'Summary of findings' table (Schünemann 2020). For RCTs, we used the overall 'risk of bias' judgement, derived from the RoB 2 Excel tool, to inform our decision on downgrading for risk of bias. We assessed the certainty of the evidence for non-controlled NRSIs as reported in the GRADE guidance 3, starting from low-certainty evidence (Balslem 2011). As we used the ROBINS-I tool to assess risk of bias for controlled NRSIs, we followed GRADE guidance 18, starting from high-certainty evidence with the opportunity to downgrade by three points for critical risk of bias (Schünemann 2019). For time-to-event outcomes we calculated absolute effects at specific time points, as recommended in the GRADE guidance 27 (Skoetz 2020). We phrased the findings and certainty of the evidence as suggested in the informative statement guidance (Santesso 2020).

RESULTS

Description of studies

Results of the search

For this update, we identified 4733 new records, in addition to the 3123 potentially relevant records from the first and second version (altogether 7856 references). After removing duplicates, we screened 3473 new records for this update (altogether 6190 records) based on their titles and abstracts, and we excluded 5949 records that did not meet the prespecified inclusion criteria. We evaluated the remaining 241 records and screened the full texts, or, if these were not available, abstract publications or trials registry entries. See [Figure 1](#) for the study flow diagram (Moher 2009).

Figure 1. Study flow diagram

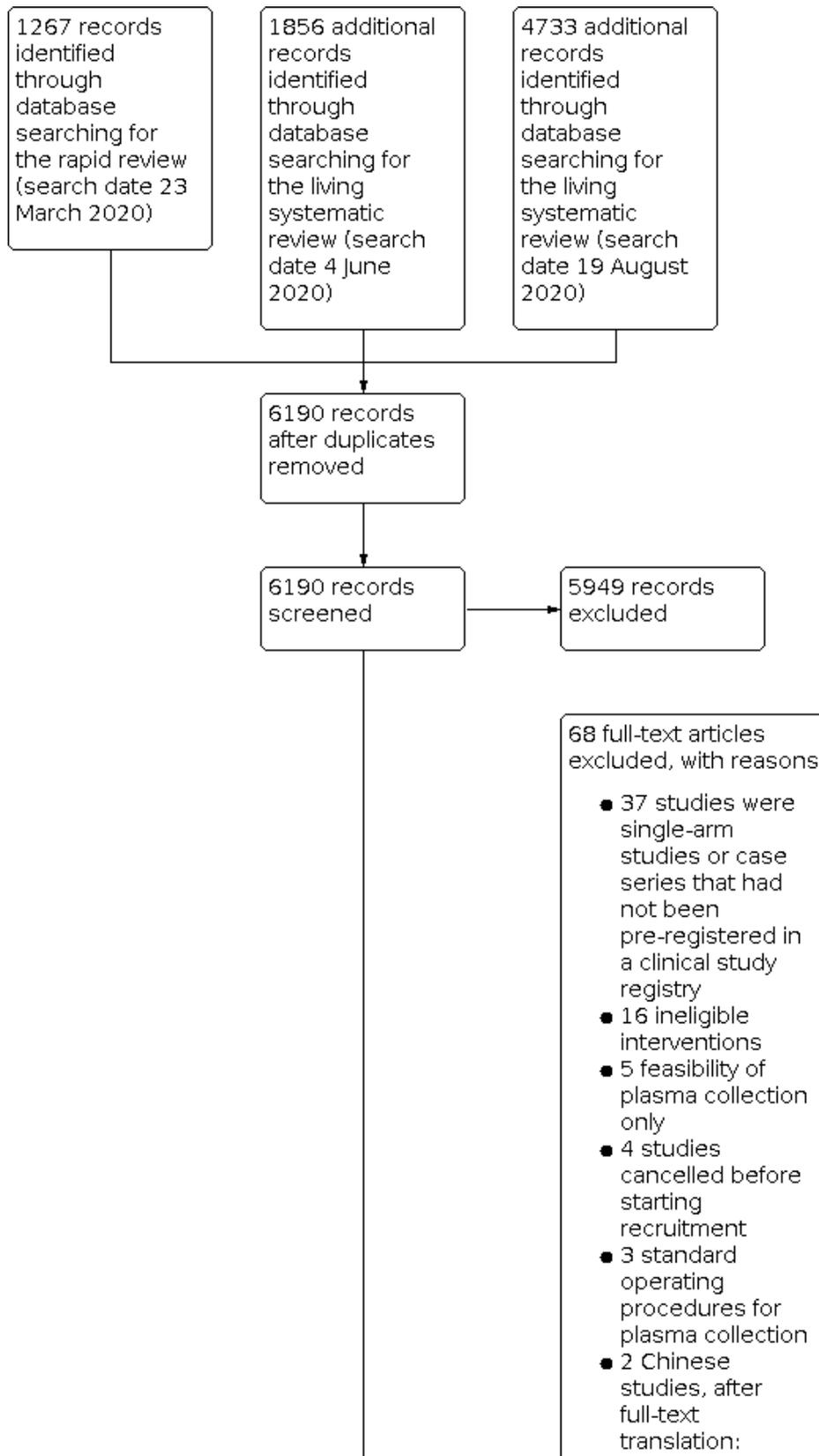


Figure 1. (Continued)

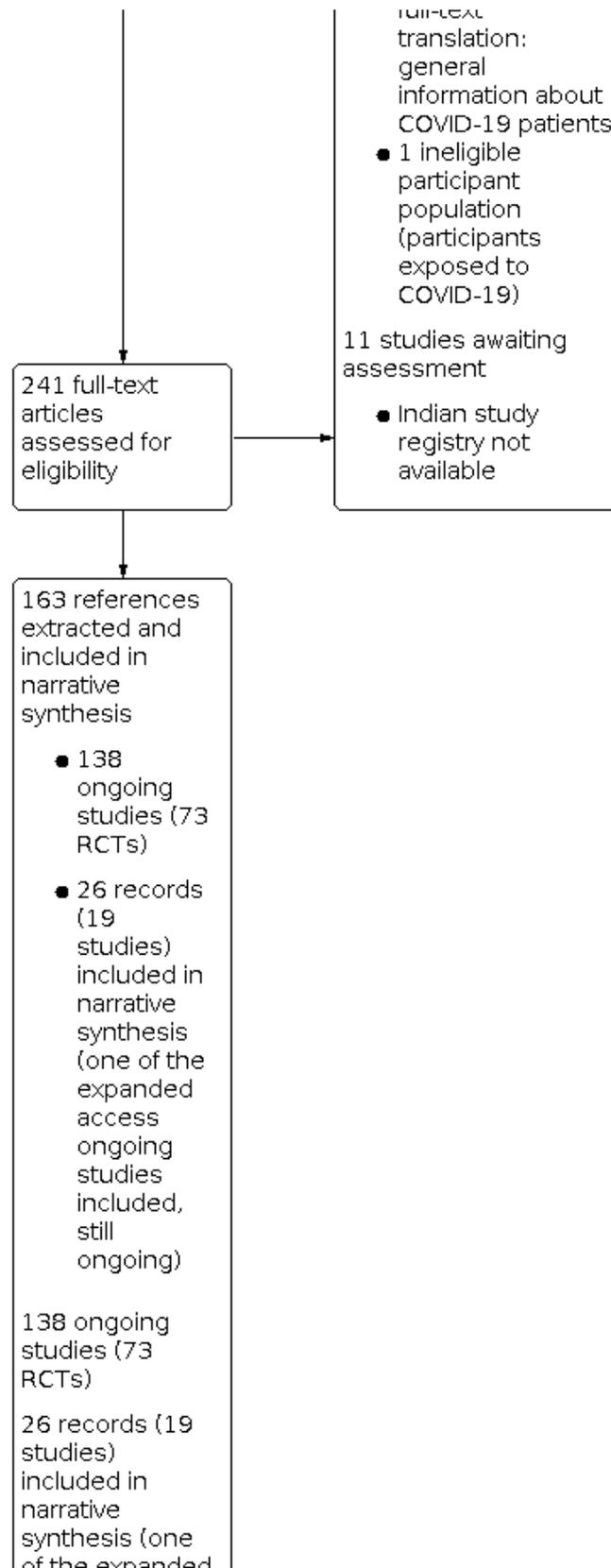


Figure 1. (Continued)



We identified 156 potentially eligible studies within 163 citations: 19 included studies (26 records) (Abdullah 2020; Abolghasemi 2020; Bradfute 2020; Donato 2020; Duan 2020; Dulipsingh 2020; Gharbharan 2020; Hegerova 2020; Jin 2020; Joyner 2020a; Li 2020; Liu 2020; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020; Rasheed 2020; Salazar 2020a; Xia 2020; Zeng 2020), and 138 ongoing studies (see 'Ongoing studies' below).

Included studies

We included 19 studies describing 38,160 participants in this review, of whom 36,081 received convalescent plasma (Abdullah 2020; Abolghasemi 2020; Bradfute 2020; Donato 2020; Duan 2020; Dulipsingh 2020; Gharbharan 2020; Hegerova 2020; Jin 2020; Joyner 2020a; Li 2020; Liu 2020; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020; Salazar 2020a; Rasheed 2020; Xia 2020; Zeng 2020).

Upon request, authors of one RCT provided us with additional outcome data (Gharbharan 2020). They provided us with the all-cause mortality rate at hospital discharge, Kaplan-Meier curves to estimate time to death, their definition of improvement of clinical symptoms, and individual participant-data for the outcome 'improvement of clinical symptoms at day 15 and day 30.'

Design and sample size

We included two RCTs (Gharbharan 2020; Li 2020); eight controlled NRSIs (Abolghasemi 2020; Duan 2020; Hegerova 2020; Liu 2020; Rasheed 2020; Salazar 2020a; Xia 2020; Zeng 2020); and nine non-controlled NRSIs (Abdullah 2020; Bradfute 2020; Donato 2020; Dulipsingh 2020; Jin 2020; Joyner 2020a; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020).

Efficacy outcomes

We evaluated efficacy and safety outcomes from two RCTs (Gharbharan 2020; Li 2020; 189 participants of whom 95 received convalescent plasma). Both RCTs were terminated early, Gharbharan 2020 because most of the participants were found to have SARS-CoV-2 antibodies present at baseline and Li 2020 because there were no more eligible participants due to containment of the epidemic in Wuhan, China. Neither of these studies cited safety concerns as the reasons for early termination.

We could not include outcome data from controlled NRSIs. One study (Rasheed 2020; 49 participants, of whom 21 received convalescent plasma), with a serious risk of bias, did not report any of our prioritised outcomes; and because of the critical risk of bias we could not include efficacy outcomes from four controlled registered NRSIs (Abolghasemi 2020; Duan 2020; Hegerova 2020; Salazar 2020a; 638 participants of whom 281 received convalescent plasma) and three controlled unregistered NRSIs (Liu 2020; Xia 2020; Zeng 2020; 1784 participants; 183 participants received convalescent plasma). See [Risk of bias in included studies](#).

Safety outcomes

For safety outcomes, we also evaluated non-controlled NRSIs, if they were pre-registered in a clinical study registry (Abdullah 2020; Bradfute 2020; Donato 2020; Dulipsingh 2020; Jin 2020; Joyner 2020a; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020).

Compared to the last version of this review, we changed our methods in this version and only included non-controlled NRSIs

if they were pre-registered in a clinical trials registry, to minimise selection bias (see [Types of studies](#) and [Differences between protocol and review](#)).

One of the included non-controlled NRSIs was pre-registered, but did not report whether adverse events occurred (Abdullah 2020). One controlled NRSI also did not report whether adverse events occurred (Salazar 2020a).

All the other included studies reported adverse events or serious adverse events, or both, for the participants receiving convalescent plasma only. We extracted safety data from 17 studies (35,943 participants) with safety data for 20,621 participants who received convalescent plasma (Abolghasemi 2020; Bradfute 2020; Donato 2020; Duan 2020; Dulipsingh 2020; Gharbharan 2020; Hegerova 2020; Jin 2020; Joyner 2020a; Li 2020; Liu 2020; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020; Rasheed 2020; Xia 2020; Zeng 2020). Of the nine non-controlled and pre-registered NRSIs, one is an ongoing, expanded access study (Joyner 2020a). The study authors have so far reported on the first 35,322 participants (with safety data for 20,000 participants) and meanwhile (as of 10 August 2020; [US Covid Plasma 2020](#)), enrolled 86,805 participants of whom 57,630 received convalescent plasma, so we decided to treat this record as an ongoing study (NCT04338360).

Setting

One RCT and three controlled NRSIs originated from China (Duan 2020; Li 2020; Xia 2020; Zeng 2020), the second RCT originated from the Netherlands (Gharbharan 2020), three controlled NRSIs originated from the USA (Liu 2020; Hegerova 2020; Salazar 2020a), one controlled NRSI originated from Iran (Abolghasemi 2020), and one controlled NRSI originated from Iraq (Rasheed 2020).

Of the nine additionally included non-controlled NRSIs that we analysed for safety outcomes, five originated from the USA (Bradfute 2020; Donato 2020; Dulipsingh 2020; Joyner 2020a; Madariaga 2020), one originated from China (Jin 2020), one originated from Iraq (Abdullah 2020), one originated from Italy (Perotti 2020), and one originated from Mexico (Olivares-Gazca 2020).

Participants

The RCT by Li 2020 and the controlled NRSIs by Hegerova 2020, Liu 2020, Rasheed 2020, Salazar 2020a and Xia 2020 included participants with clinical symptoms meeting the definitions of severe or life-threatening disease. The second RCT, by Gharbharan 2020, and controlled NRSI by Abolghasemi 2020, included moderate to severely ill participants. Duan 2020 transfused convalescent plasma in severely ill individuals. The controlled NRSI by Zeng 2020 evaluated critically ill individuals, admitted to ICU.

The majority of the additional studies evaluated for safety outcomes transfused convalescent plasma in individuals with severe or life-threatening disease (Abdullah 2020; Bradfute 2020; Dulipsingh 2020; Jin 2020; Joyner 2020; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020). One of these studies included at least one or more participant(s) with moderate disease severity (Jin 2020), and one study included participants with moderate to severe disease severity (Donato 2020).

Interventions

All included completed studies evaluated convalescent plasma. We did not identify any completed studies evaluating hyperimmune immunoglobulin (IgG).

All of the controlled studies that we evaluated for efficacy and safety outcomes transfused different doses and volumes of convalescent plasma.

Randomised controlled trials

[Gharbharan 2020](#) randomised participants into two groups. The convalescent plasma group received one or two doses of 300 mL volume of plasma alongside standard therapy (which also included European Medicines Agency (EMA)-approved drugs such as chloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, anakinra) and the control group received standard therapy without convalescent plasma. Serum samples of donors were analysed for the presence of neutralising antibodies by performing a plaque reduction neutralisation test (PRNT) with a target PRNT50 titre greater than 1:80.

[Li 2020](#) randomised participants into two groups. The convalescent plasma group received one or more doses of 4 mL/kg to 13 mL/kg per recipient body weight with a median volume of 200 mL (interquartile range (IQR) 200 mL to 300 mL) transfused alongside standard therapy (which included antivirals, antibiotics, standard immunoglobulin, Chinese herbal medications, steroids, interferon) and the control group received standard therapy without convalescent plasma. Only convalescent plasma units with an receptor-binding domain (RBD) of S protein (S-RBD)-specific IgG titre of at least 1:640, correlating to serum antibody neutralisation titre of 1:80, were used for the study.

Controlled non-randomised studies of interventions

[Abolghasemi 2020](#) transfused one or two doses of 500 mL volume of convalescent plasma alongside conventional treatment (which included routine antiviral therapy including lopinavir/ritonavir, hydroxychloroquine and an anti-inflammatory agent). These participants were compared to patients receiving conventional therapy (matched for age, gender and presence of hypertension and diabetes mellitus). Donated plasma was tested by the semi-quantitative enzyme-linked immunosorbent assay (ELISA) and rapid strip test antibody identification test for COVID-19, and contained antibody titre cut-off index greater than 1.1.

[Duan 2020](#) transfused one dose of 200 mL of convalescent plasma alongside standard therapy (which included antivirals, antibiotics, antifungals, steroids) and compared to historic controls matched for age, gender and disease severity who received standard therapy. They evaluated neutralising activity against SARS-CoV-2 in these plasma units by classical plaque reduction test using a recently isolated viral strain with an antibody cut-off titre of over 1:160.

[Hegerova 2020](#) was a matched cohort study that retrospectively compared 20 participants, who were transfused one unit of convalescent plasma under an expanded access protocol alongside standard therapy (which included azithromycin, hydroxychloroquine and remdesivir) to 20 matched controls (matched for age, comorbidities, WHO score, Sequential Organ Failure Assessment (SOFA) score and severity of illness). Antibody titres were not reported.

[Liu 2020](#) was a matched cohort study that retrospectively compared 39 participants, who were transfused two doses of 250 mL of convalescent plasma alongside standard therapy (which included antivirals, antibiotics, steroids, stem cells, hydroxychloroquine and immunomodulatory agents) to matched controls using a propensity score. They performed calendar period matching on the following variables: administration of hydroxychloroquine and azithromycin; intubation status and duration; length of hospital stay; and oxygen requirement on the day of transfusion. They matched control patients to plasma recipients by length of stay prior to transfusion and measured antibody titre using a two-step spike protein-directed ELISA with a target anti-spike titre of at least 1:320 dilution.

[Rasheed 2020](#) transfused one dose of 400 mL convalescent plasma alongside standard therapy (which included hydroxychloroquine and azithromycin). A rapid immunochromatographic COVID-19 IgG/IgM test was used to screen the donors and the recipients for the presence of SARS-CoV-2 antibodies. Donors with SARS-CoV-2 IgG index greater than 1, and donors with IgG index equal to or more than 1.25 were selected. Patients who received convalescent plasma were compared to an age and sex-matched control group.

[Salazar 2020a](#) conducted a prospective, propensity score-matched study that compared 136 participants, who were transfused 1 to 2 units of convalescent plasma alongside standard therapy (which included steroids, tocilizumab, antiviral therapy and azithromycin) to 251 non-transfused matched controls using a propensity score (matching criteria included age, sex, body mass index (BMI), comorbidities, and baseline ventilation requirement 48 hours from admission, and in a second matching analysis, ventilation status at day zero). Subgroup analysis was also performed on participants transfused within or after 72 hours of admission and patients transfused within 72 hours of admission with an anti-RBD IgG titre greater than 1:1350 (via ELISA).

[Xia 2020](#) was a matched cohort study that retrospectively compared 138 participants, who were transfused 200 to 1200 mL of convalescent plasma alongside standard therapy (which included oxygen therapy, ventilation and extracorporeal membrane oxygenation (ECMO)) to 1430 matched controls. Antibody titres were not reported.

[Zeng 2020](#) was a matched cohort study that transfused six participants one to two doses of convalescent plasma (median 300 mL each dose, range 200 mL to 600 mL) alongside standard therapy (which included antivirals, antibiotics, steroids, hydroxychloroquine) and compared this group retrospectively to matched controls. Gold immunochromatography for SARS-CoV-2 IgM and IgG tests were performed using blood samples, however they did not report any antibody titres.

Non-controlled, non-randomised studies of interventions

In the nine additional non-controlled NRSIs that we evaluated for safety outcomes, dose and volume of plasma also varied greatly. The total volume of convalescent plasma transfused varied between 200 mL and 2400 mL, with participants receiving between one to eight doses of plasma. Six studies reported antibody titres ([Bradfute 2020](#); [Donato 2020](#); [Dulipsingh 2020](#); [Jin 2020](#); [Madariaga 2020](#); [Perotti 2020](#)), and one study reported presence of antibodies by lateral flow immunoassay ([Olivares-](#)

Gazca 2020). Four studies reported neutralising antibody titres (Bradfute 2020; Donato 2020; Jin 2020; Perotti 2020).

Plasma donors

Of the included studies, 12 reported some information on plasma donors (Abolghasemi 2020; Bradfute 2020; Donato 2020; Dulipsingh 2020; Hegerova 2020; Jin 2020; Li 2020; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020; Rasheed 2020; Salazar 2020a). Ten studies reported the gender of donors and included both male and female donors (Abolghasemi 2020; Donato 2020; Dulipsingh 2020; Gharbharan 2020; Li 2020; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020; Rasheed 2020; Salazar 2020a), but most of these studies excluded prior pregnancy or tested for HLA and/or HNA antibodies. The majority of donors in Gharbharan 2020 were male (91%).

Four studies provided information on previously reported symptoms and disease severity of convalescent plasma donors (Duan 2020; Hegerova 2020; Madariaga 2020; Rasheed 2020). Duan 2020 reported that donors had been admitted to hospital, but no other information on severity of illness was available. Hegerova 2020 included donors who were all symptomatic but none required hospitalisation, Madariaga 2020 included donors with severe or life-threatening disease, and Rasheed 2020 included donors with moderate disease.

In the nine studies that reported assessment of donor recovery, all donors were symptom-free and completely recovered from disease prior to donating plasma (Abolghasemi 2020; Bradfute 2020; Duan 2020; Dulipsingh 2020; Hegerova 2020; Li 2020; Madariaga 2020; Olivares-Gazca 2020; Salazar 2020a). Six studies specified that donors had a negative SARS-CoV-2 RT-PCR test prior or at time of convalescent plasma donation (Duan 2020; Jin 2020; Li 2020; Olivares-Gazca 2020; Perotti 2020; Salazar 2020a). It was not always clear on what kind of specimen the RT-PCR test had been performed; three studies reported that the tests were performed on upper respiratory tract swabs (Li 2020; Olivares-Gazca 2020; Perotti 2020), one study reported that the test was performed on sputum (Duan 2020), whereas two did not report information on the origin of the donor sample (Jin 2020; Salazar 2020a).

Outcomes

We evaluated efficacy and safety outcomes in the two RCTs and eight controlled NRSIs. In Gharbharan 2020, the primary outcome was all-cause mortality. Secondary outcomes were improvement of clinical symptoms assessed by the ordinal 8-point WHO disease severity scale at day 15, hospital length of stay and safety.

In Li 2020, the primary outcome was time to clinical improvement within 28 days, defined as patient discharged alive or reduction of 2 points on a 6-point disease severity scale ranging from 1 (discharge) to 6 (death). Secondary outcomes were 28-day mortality, time to hospital discharge and clearance of viral PCR results within 72 hours.

In Abolghasemi 2020, primary outcomes were mortality and length of hospital stay (unclear duration of follow-up). In Duan 2020, primary outcome was safety. Secondary outcomes included improvement of clinical symptoms, radiological and laboratory parameters within three days of transfusion. In Liu 2020, primary outcomes reported were supplemental oxygen requirements and survival at days 1, 7, 14 post-transfusion. In Rasheed 2020, primary

outcomes were safety, duration of viral shedding and mortality. In Salazar 2020a, primary outcome was 28-day mortality. In Zeng 2020, the primary outcome was survival and secondary outcomes were clearance of viral PCR and radiological improvement.

Hegerova 2020 and Xia 2020 did not report primary outcomes. Outcomes reported in Hegerova 2020 included safety, time to clinical improvement and hospital length of stay. Outcomes reported in Xia 2020 included safety, viral clearance, and time to clinical improvement.

We evaluated safety outcomes in all studies that reported these outcomes. Fourteen studies (566 participants) reported assessment of adverse events of possibly grade 3 or grade 4 severity (Abolghasemi 2020; Donato 2020; Duan 2020; Dulipsingh 2020; Hegerova 2020; Jin 2020; Li 2020; Liu 2020; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020; Rasheed 2020; Xia 2020; Zeng 2020).

Seventeen studies (35,944 participants) assessed serious adverse events for 20,622 of the included participants (Abolghasemi 2020; Bradfute 2020; Donato 2020; Duan 2020; Dulipsingh 2020; Gharbharan 2020; Hegerova 2020; Jin 2020; Joyner 2020a; Li 2020; Liu 2020; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020; Rasheed 2020; Xia 2020; Zeng 2020).

Please refer to the [Characteristics of included studies](#) for more detailed information.

Ongoing studies

Of the 138 ongoing studies, nine are expanded access studies from the USA (NCT04338360; NCT04358211; NCT04360486; NCT04363034; NCT04372368; NCT04374370; NCT04420988; NCT04445207; NCT04472572). As the NCT04338360 study has reported on the first 35,322 participants (with safety data for 20,000 participants; Joyner 2020a), and has enrolled a further 86,805 participants (of whom 57,630 received convalescent plasma) into the study as of 7 August 2020 (US Covid Plasma 2020), we decided to treat this record as an ongoing study.

Seventy-three are RCTs (ChiCTR2000030010; ChiCTR2000030179; ChiCTR2000030627; ChiCTR2000030702; ChiCTR2000030929; EUCTR2020-001310-38; IRCT20200310046736N1; IRCT20200404046948N1; IRCT20200409047007N1; IRCT20200413047056N1; ISRCTN85216856; NCT02735707; NCT04332835; NCT04333251; NCT04344535; NCT04345289; NCT04345523; NCT04345991; NCT04346446; NCT04348656; NCT04355767; NCT04356534; NCT04358783; NCT04359810; NCT04361253; NCT04362176; NCT04364737; NCT04366245; NCT04372979; NCT04373460; NCT04374487; NCT04374526; NCT04375098; NCT04376788; NCT04377568; NCT04380935; NCT04381858; NCT04381936; NCT04383535; NCT04385043; NCT04385186; NCT04385199; NCT04388410; NCT04390503; NCT04391101; NCT04392414; NCT04393727; NCT04395170; NCT04397757; NCT04403477; NCT04405310; NCT04415086; NCT04418518; NCT04421404; NCT04425837; NCT04425915; NCT04428021; NCT04429854; NCT04433910; NCT04438057; NCT04438694; NCT04442191; NCT04442958; NCT04452812; NCT04456413; NCT04467151; NCT04468009; NCT04479163; NCT04483960; NCT04497324; NCT04516811; NL8633; RBR-7jqpnw).

Of these, 31 are expected to be completed in 2020, and plan to evaluate between 15 and 1200 participants (ChiCTR2000030010; ChiCTR2000030179; ChiCTR2000030627; ChiCTR2000030702; ChiCTR2000030929; IRCT20200310046736N1; IRCT20200404046948N1; IRCT20200409047007N1; IRCT20200413047056N1; RCTN85216856; CT04332835; CT04345523; NCT04345991; NCT04346446; NCT04348656; NCT04356534; NCT04376788; NCT04380935; NCT04381858; NCT04383535; NCT04385186; NCT04385199; NCT04388410; NCT04392414; NCT04393727; NCT04397757; NCT04403477; NCT04405310; NCT04442958; NCT04479163; NCT04497324). Of these studies, 14 RCTs were scheduled to be completed by the time of writing (ChiCTR2000030010; ChiCTR2000030179; ChiCTR2000030627; ChiCTR2000030702; ChiCTR2000030929; IRCT20200310046736N1; NCT04345523; NCT04345991; NCT04376788; NCT04380935; NCT04383535; NCT04385199; NCT04405310; NCT04479163). Another six RCTs are reported as being completed in the study registries, but results are not published yet and study investigators did not reply to our requests or no contact details of the principal investigator are given to request data (IRCT20200404046948N1; IRCT20200409047007N1; IRCT20200413047056N1; NCT04346446; NCT04356534; NCT04442958).

Four further, large RCTs are planned to be completed in 2021: NCT04418518, randomising 1200 participants; NCT04345289, evaluating 1500 participants; NCT02735707, evaluating 7100 participants; and NCT04381936 randomising 12,000 participants to six different treatment options (lopinavir-ritonavir, corticosteroid, hydroxychloroquine, azithromycin, tocilizumab and convalescent plasma).

Please refer to [Characteristics of ongoing studies](#) and to [Table 2](#) for more detailed information.

Studies awaiting assessment

During the editorial process, we identified two new preprint publications of ongoing studies (Agarwal 2020; Avendano-Sola 2020). Both studies were published after our last systematic search. We briefly assessed both studies, and recognise that their inclusion would not have had an impact on our conclusions. We therefore decided together with Cochrane's Methods Support Unit to keep them under 'awaiting classification' and include both in the next update of this review.

We further identified nine study entries in a trial registry from India that might fit our inclusion criteria, but the registry was not available (24 August to 1 September 2020) to clarify details of the studies (CTRI/2020/04/024706; CTRI/2020/04/024804; CTRI/2020/04/024915; CTRI/2020/05/025209; CTRI/2020/05/025299; CTRI/2020/05/025328; CTRI/2020/05/025346; CTRI/2020/06/025803; CTRI/2020/06/026123).

Excluded studies

We excluded 68 references that did not match our inclusion criteria.

- Thirty-seven studies were single-arm studies or case series that had not been pre-registered in a clinical study registry (Ahn 2020; Anderson 2020; Bao 2020b; Bobek 2020; Cantore 2020; Clark 2020; Enzmann 2020; Erkurt 2020; Fan 2020; Figlerowicz 2020; Grisolia 2020; Im 2020; Jamous 2020; Jiang 2020a; Karatas 2020; Kong 2020; Liu 2020a; Martinez-Resendez 2020; McCuddy 2020; Mira 2020; Niu 2020; Pei 2020; Peng 2020; Salazar 2020b; Shen 2020; Soleimani 2020; Taher 2020; Tan 2020; Wang 2020; Wright 2020; Xu 2020b; Yang 2020; Ye 2020; Zhang 2020a; Zhang 2020b; Zhang 2020c; Çınar 2020).
- Sixteen studies were performed with an intervention other than convalescent plasma or hyperimmune immunoglobulin (Cao 2020a; Chen 2020b; Chen 2020c; Díez 2020; Hu 2020; ISRCTN86534580; Jiang 2020b; Lin 2020; NCT04261426; NCT04344379; NCT04350580; NCT04368013; Robbiani 2020; Shi 2020; Xie 2020; de Assis 2020).
- Five studies pertained to feasibility of collection of convalescent plasma only (Budhai 2020; Hashim 2020; NCT04344015; NCT04344977; NCT04360278).
- Four studies were cancelled by the investigator before recruiting participants into the study (ChiCTR2000030312; ChiCTR2000030381; ChiCTR2000030442; NCT04325672).
- Three studies reported standard operating procedure related to plasma donation (Brasil Ministerio 2020; Franchini 2020; Ministerio de Salud 2020).
- Two references were in Chinese (Qiu 2020; Tu 2020). Both were translated and assessed by Rujan Shrestha and Ya-Ying Wang via Cochrane TaskExchange. The papers reported on a generalised collection of information about the COVID-19 infection of two participants relating to aetiology, pathology, symptoms, clinical presentation and some generalised pharmacological treatment methods.
- One study included an irrelevant participant population (participants exposed to COVID-19; NCT04323800).

Risk of bias in included studies

Risk of bias in randomised controlled trials

We assessed methodological quality and risk of bias for two RCTs (Gharbharan 2020; Li 2020), using the 'Risk of bias' tool recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019c).

Overall judgement

Overall, we rated the risk of bias for mortality outcomes and outcomes assessing improvement of clinical symptoms to be of some concern for Gharbharan 2020, and to be low for Li 2020 (see [Figure 2](#) and [Figure 3](#)). For safety outcomes, we rated risk of bias to be high in both studies (see [Figure 4](#)). The support for judgement for both studies per outcome category and bias domain is available online at DOI: 10.5281/zenodo.3994365 (Piechotta 2020b).

Figure 2. Risk of bias 2.0 assessment for: treatment with convalescent plasma compared to treatment without convalescent plasma for people with COVID-19 (mortality)

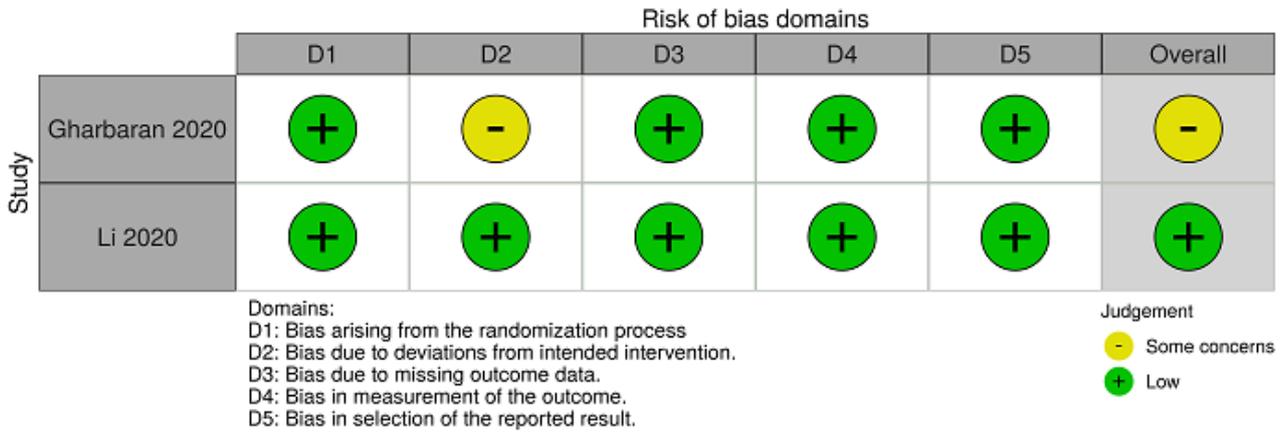


Figure 3. Risk of bias 2.0 assessment for: treatment with convalescent plasma compared to treatment without convalescent plasma for people with COVID-19 (clinical improvement)

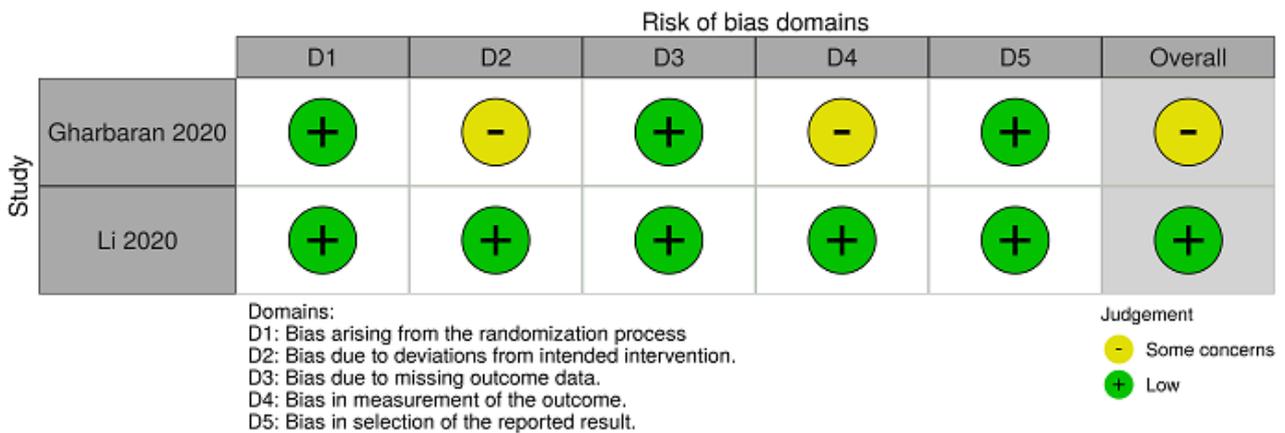
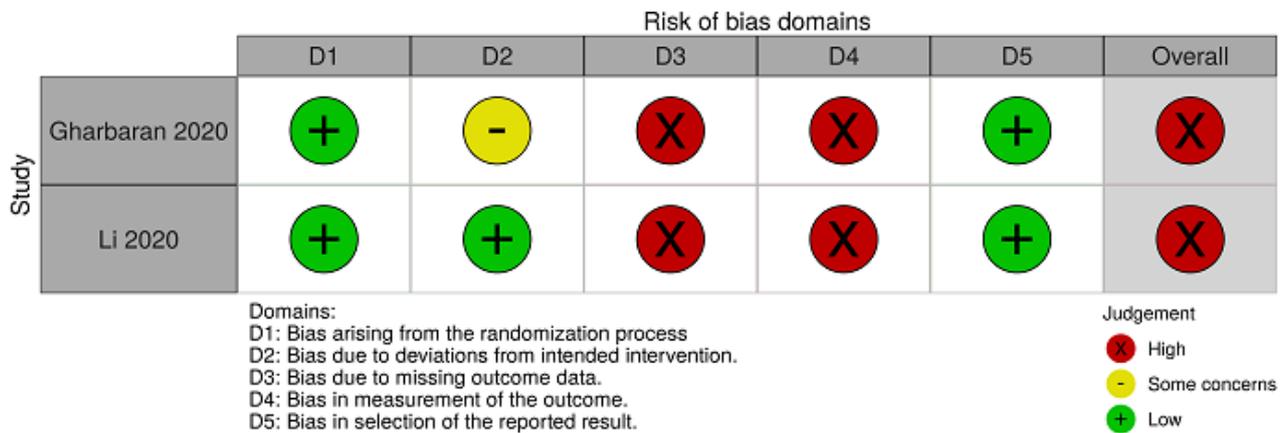


Figure 4. Risk of bias 2.0 assessment for: treatment with convalescent plasma compared to treatment without convalescent plasma for people with COVID-19 (safety)



Randomisation process

We assessed this domain on a study level. We judged the risk of bias coming from the randomisation process to be low for both studies, because the allocation was random and concealed until participants were enrolled and assigned to interventions.

Deviations from intended intervention

We assessed this domain on a study level. Participants were aware of the assigned intervention in both studies. However, [Gharbbaran 2020](#) provided no information on whether co-interventions were balanced across arms. We therefore judged risk of bias for this domain and study to be of some concern. Co-interventions were not fully balanced across arms in the other study ([Li 2020](#)), but we did not identify any evidence of a protocol deviation. We therefore judged risk of bias for this domain and study to be low.

Missing outcome data

We assessed this domain on an outcome level.

We judged risk of bias for missing outcome data to be low for mortality outcomes in both studies, because outcome data were available for all participants.

We judged risk of bias for missing outcome data for outcomes addressing improvement of clinical symptoms to be low for both studies. [Gharbbaran 2020](#) did not report one of the prespecified time points in their preprint article, but provided these data upon request; [Li 2020](#) provided all outcome data for all participants.

We judged risk of bias for missing outcome data for safety outcomes to be high in both studies, because outcome data were only available for the intervention group.

Measurement of the outcome

We judged risk of bias for measurement of the outcome to be low for mortality outcomes in both studies, because the method of measuring was appropriate and measurement or ascertainment of the outcome could not have differed between groups.

We judged risk of bias for measurement of the outcome for outcomes addressing improvement of clinical symptoms to be of some concerns for [Gharbbaran 2020](#), because outcome assessors were aware of the intervention, but it was unlikely that assessment of the outcome was influenced by the awareness of intervention received; and to be low for [Li 2020](#), because outcome assessment was performed by an investigator who was blinded to the study group allocation.

We judged risk of bias for measurement of safety outcomes to be high in both studies, because only transfusion-related adverse events were measured in the intervention group.

Selection of the reported results

We judged the risk of reporting bias to be low for mortality outcomes because both studies reported results in accordance with the statistical analysis plan.

We judged the risk of reporting bias for outcomes addressing improvement of clinical symptoms also to be low for both studies. [Gharbbaran 2020](#) because it reported results in accordance with the statistical analysis plan. [Li 2020](#) added post-hoc analyses and compared rates of improvement at days 7, 14, and 28. This was probably done after unblinded outcome data were available for analysis. However, time points were prioritised by WHO and COMET-initiative after the study was set up ([COMET 2020](#)). We suppose that conducting the post-hoc analyses was not done by choosing particular results to present a specific view of the data, but to address WHO/COMET recommendations. Our assessor's judgement therefore deviates from the algorithm result.

We judged the risk of bias of reporting bias for safety outcomes to be high for both studies because only transfusion-related adverse events were reported.

Risk of bias in controlled non-randomised studies of interventions

We assessed methodological quality and risk of bias for these studies ([Abolghasemi 2020](#); [Duan 2020](#); [Hegerova 2020](#); [Liu 2020](#); [Rasheed 2020](#); [Salazar 2020a](#); [Xia 2020](#); [Zeng 2020](#)), using the

Risk Of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool (Sterne 2016).

Overall bias

Overall, we rated the risk of bias for mortality outcomes and outcomes addressing improvement of clinical symptoms to be serious in one study (Rasheed 2020). For all other assessed outcomes, we rated the risk of bias within and across studies to be

critical. Studies are too problematic to provide any useful evidence, however better evidence is not yet available. Salazar 2020a did not report adverse event outcomes; bias assessment was therefore not applicable. We present the full judgement per study and category, including the support for judgement in Appendix 7 and Appendix 8; and the 'Risk of bias' summaries per outcome in Figure 5, Figure 6, and Figure 7.

Figure 5. ROBINS-I assessment for: treatment with convalescent plasma compared to treatment without convalescent plasma for people with COVID-19 (mortality)

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Abolghasemi 2020	-	!	!	+	!	!	!	!
Duan 2020	X	!	!	+	X	!	!	!
Hegerova 2020	-	!	!	+	+	-	!	!
Liu 2020	X	-	!	+	+	-	!	!
Rasheed 2020	X	X	+	+	+	X	X	X
Salazar 2020a	-	-	!	+	+	!	!	!
Xia 2020	X	!	-	+	+	!	!	!
Zeng 2020	X	-	!	+	+	+	!	!

Domains:	Judgement
D1: Bias due to confounding.	! Critical
D2: Bias due to selection of participants.	X Serious
D3: Bias in classification of interventions.	- Moderate
D4: Bias due to deviations from intended interventions.	+ Low
D5: Bias due to missing data.	
D6: Bias in measurement of outcomes.	
D7: Bias in selection of the reported result.	

Figure 6. ROBINS-I assessment for: treatment with convalescent plasma compared to treatment without convalescent plasma for people with COVID-19 (clinical improvement)

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Abolghasemi 2020	-	!	!	+	!	-	!	!
Duan 2020	X	!	!	+	!	!	!	!
Hegerova 2020	-	!	!	+	+	-	!	!
Liu 2020	X	-	!	+	+	-	!	!
Rasheed 2020	X	X	+	+	+	X	X	X
Salazar 2020a	-	-	!	+	+	!	!	!
Xia 2020	X	!	-	+	+	!	!	!
Zeng 2020	X	-	!	+	+	+	!	!

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
! Critical
X Serious
- Moderate
+ Low

Figure 7. ROBINS-I assessment for: treatment with convalescent plasma compared to treatment without convalescent plasma for people with COVID-19 (safety) Note: one of the controlled NRSIs did not report the outcome and is therefore not included in the figure (Salazar 2020a).

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Abolghasemi 2020								
Duan 2020								
Hegerova 2020								
Liu 2020								
Rasheed 2020								
Xia 2020								
Zeng 2020								

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
 Critical
 Serious
 Moderate
 Low

Bias due to confounding

We judged the risk of bias due to confounding to be moderate for three studies for mortality outcomes and outcomes addressing improvement of clinical symptoms, because they adjusted for most important confounding factors. [Abolghasemi 2020](#) matched their groups based on gender, age, comorbidities, and chest CT scan. [Hegerova 2020](#) adjusted for age, comorbidities, clinical symptoms, organ failure, and severity of illness. [Salazar 2020a](#) adjusted for age, comorbidities, and ventilation requirements.

We judged the risk of bias due to confounding to be serious for five studies for mortality outcomes and outcomes addressing improvement of clinical symptoms. [Duan 2020](#) adjusted for age, gender, and disease severity, but did not adjust for important confounding factors, including comorbidities, previous treatments and time of disease onset. [Liu 2020](#) adjusted for antiviral treatments, intubation status and duration, length of hospital

stay, and oxygen requirement on the day of transfusion, but did not adjust for important confounding factors including age and gender. [Rasheed 2020](#) only adjusted for age and gender, but did not adjust for any other important confounding factors. Two studies did not adjust for any confounding factors ([Xia 2020](#); [Zeng 2020](#)).

Assessment of risk of bias due to confounding was not applicable for all studies for safety outcomes, because they reported adverse events for the intervention group only; either after plasma transfusion or transfusion-related events only, and one study did not report any adverse events ([Salazar 2020a](#)).

Bias in selection of participants into the study

We judged the risk of bias in selection of participants into the study to be moderate for [Liu 2020](#), [Salazar 2020a](#) and [Zeng 2020](#) for mortality outcomes and outcomes addressing improvement of clinical symptoms. In [Liu 2020](#) and [Salazar 2020a](#), selection into

the study may have been related to intervention and outcome, but the study authors used appropriate methods to adjust for the selection bias. [Zeng 2020](#) performed allocation to intervention and control group based on donor availability.

We judged the risk of bias in selection of participants into the study to be serious for [Rasheed 2020](#) for mortality outcomes and outcomes addressing improvement of clinical symptoms. [Rasheed 2020](#) was registered after completion of recruitment. It is unclear whether the inclusion criteria were defined based on available participants or whether inclusion criteria had been defined before recruitment.

We judged the risk of bias in selection of participants into the study to be critical for four studies for mortality outcomes and outcomes addressing improvement of clinical symptoms. [Abolghasemi 2020](#) only allocated people with milder clinical symptoms that did not have a plasma match at the day of admission or within the next three days into the control group because of ethical considerations. [Duan 2020](#) included a small sample size and it was unclear how they selected participants into the intervention group, and for how long they followed up participants of the historical control group. [Hegerova 2020](#) reported on 20 participants that are part of the USA Expanded Access Programme ([Joyner 2020a](#)), into which more than 86,000 participants have been enrolled. [Hegerova 2020](#) did not provide any details about how they selected the 20 participants they reported on and from which pool of patients they chose their control group. [Xia 2020](#) did not report how participants were allocated to receive convalescent plasma or not.

Assessment of risk of bias in selection of participants into the study was not applicable for all studies for safety outcomes, because they reported adverse events for the intervention group only; either after plasma transfusion or transfusion-related events only, and [Salazar 2020a](#) did not report any adverse events.

Bias in classification of interventions

We judged the risk of bias in classification of interventions to be low for [Rasheed 2020](#) for mortality outcomes and outcomes addressing improvement of clinical symptoms, because intervention and control group were well-defined and allocation was done prospectively.

We judged the risk of bias in classification of interventions to be moderate for [Xia 2020](#) for mortality outcomes and outcomes addressing improvement of clinical symptoms, despite retrospective group assignment, because the study cohort includes all patients that have been admitted to the study centre and the intervention and control group were well-defined.

We judged the risk of bias in classification of interventions to be critical for six studies for mortality outcomes and outcomes addressing improvement of clinical symptoms ([Abolghasemi 2020](#); [Duan 2020](#); [Hegerova 2020](#); [Liu 2020](#); [Salazar 2020a](#); [Zeng 2020](#)), because they either assigned participants to the control group retrospectively or did not report when group assessment was done. Knowledge of patient outcomes at the time of assignment to the control group could have had a major impact on the selection and classification of interventions.

Assessment of risk of bias in classification of interventions was not applicable for all studies for safety outcomes, because they reported adverse events for the intervention group only; either

after plasma transfusion or transfusion-related events only, and one study did not report any adverse events ([Salazar 2020a](#)).

Bias due to deviations from intended interventions

Bias due to deviations from intended intervention was not applicable for adverse event outcomes for [Salazar 2020a](#), because they did not report the outcome.

For all other studies and outcomes, we judged the risk of bias due to deviations from intended intervention to be low, because all assessed participants received the intended interventions.

Bias due to missing data

We judged the risk of bias due to missing data to be low for six studies for mortality outcomes, because results were reasonably complete ([Hegerova 2020](#); [Liu 2020](#); [Rasheed 2020](#); [Salazar 2020a](#); [Xia 2020](#); [Zeng 2020](#)). We judged the risk of bias due to missing data to be serious for [Duan 2020](#) for mortality outcomes, because they reported mortality for participants in the intervention group until day three of follow-up, and it was unclear how long they followed the control group. We judged the risk of bias due to missing data to be critical for [Abolghasemi 2020](#) for mortality outcomes, because they did not describe the observation period.

We judged the risk of bias due to missing data to be low for six studies for outcomes addressing improvement of clinical symptoms ([Hegerova 2020](#); [Liu 2020](#); [Rasheed 2020](#); [Salazar 2020a](#); [Xia 2020](#); [Zeng 2020](#)), because results were reasonably complete. We judged the risk of bias due to missing data to be serious for one study ([Duan 2020](#)) for outcomes addressing improvement of clinical symptoms, as [Duan 2020](#) did not report how long they followed the control group and they did not assess clinical status in terms of respiratory support. Risk of bias due to missing data was critical for [Abolghasemi 2020](#), as the authors did not describe the observation period.

Bias due to missing data was not applicable for adverse event outcomes for [Salazar 2020a](#), because they did not report the outcome. For all other studies, we judged the risk of bias due to missing data to be critical for all studies for safety outcomes, because studies did not report safety data for the control group.

Bias in measurement of outcomes

We judged the risk of bias in measurement of outcomes to be low for [Zeng 2020](#) for mortality outcomes, and outcomes addressing improvement of clinical symptoms, because they calculated illness from the onset of disease for both groups and followed all participants until death or discharge.

We judged the risk of bias in measurement of outcomes to be moderate for three studies for mortality outcomes and outcomes addressing improvement of clinical symptoms ([Abolghasemi 2020](#); [Hegerova 2020](#); [Liu 2020](#)), because start of observation and median follow-ups were comparable between groups. However, outcome assessors were not blinded to the intervention and one study was performed retrospectively ([Hegerova 2020](#)).

We judged the risk of bias in measurement of outcomes to be serious for [Rasheed 2020](#) for mortality outcomes and outcomes addressing improvement of clinical symptoms, because outcome assessors were aware of the received intervention, and it was not reported whether the observation started at the same time for both

groups. However, observation probably started after enrolment into the study.

We judged the risk of bias in measurement of outcomes to be critical for three studies (Duan 2020; Salazar 2020a; Xia 2020) for mortality outcomes and outcomes addressing improvement of clinical symptoms, because it was unclear whether the follow-up was comparable between groups, and assessors were aware of the intervention received.

Bias in measurement of outcomes was not applicable for adverse event outcomes for Salazar 2020a, because they did not report the outcome. For all other studies, we judged the risk of bias in measurement of outcomes to be critical for safety outcomes, because none of the studies reported safety data for the control group.

Bias in selection of the reported results

We judged the risk of bias in selection of the reported results to be serious for Rasheed 2020 for mortality outcomes and outcomes addressing improvement of clinical symptoms, because follow-up was defined as up to eight weeks in the trials registry, but actual follow-up was not mentioned in the preprint article.

We judged the risk of bias in selection of the reported results to be critical for Rasheed 2020 for safety outcomes, because they reported adverse events for the intervention group only.

We judged the risk of bias in selection of the reported results to be critical for seven studies (Abolghasemi 2020; Duan 2020; Hegerova 2020; Liu 2020; Salazar 2020a; Xia 2020; Zeng 2020), and all outcomes; with the exception of adverse event outcomes for Salazar 2020a, because they did not report the outcome. Abolghasemi 2020 only defined the primary study outcome in the trials registry and reported different outcomes in the journal publication, which were poorly defined. The other six studies (Duan 2020; Hegerova 2020; Liu 2020; Salazar 2020a; Xia 2020; Zeng 2020), were performed retrospectively, and the selection of all reported results are likely biased.

Risk of bias in non-controlled, non-randomised studies of interventions (for safety assessment)

We assessed methodological quality and risk of bias for eight non-controlled NRSIs (Bradfute 2020; Donato 2020; Dulipsingh 2020; Jin 2020; Joyner 2020a; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020), using the 'Risk of bias' assessment criteria tool for observational studies provided by Cochrane Childhood Cancer (see Table 1; Mulder 2019; Figure 8). We only assessed risk of bias for safety outcomes. We therefore only assessed risk of bias for those non-controlled NRSIs that reported safety data. Abdullah 2020 did not report whether adverse events occurred so we did not assess risk of bias for this study.

Figure 8. Cochrane Childhood Cancer assessment tool for observational studies 'Risk of bias' assessment for: convalescent plasma for people with COVID-19 (safety)

Study	Risk of bias							Overall
	D1	D2	D3	D4	D5	D6	D7	
Bradfute 2020	⊗	⊕	⊕	⊕	⊖		⊗	⊗
Donato 2020	⊖	⊕	⊕	⊕	⊖		⊗	⊗
Dulipsingh 2020	⊖	⊕	⊖	⊕	⊖		⊗	⊗
Jin 2020	⊗	⊕	⊖	⊖	⊖		⊗	⊗
Joyner 2020	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Madariaga 2020	⊖	⊕	⊕	⊕	⊖		⊗	⊗
Olivares-Gazca 2020	⊖	⊕	⊕	⊕	⊖		⊗	⊗
Perotti 2020	⊖	⊕	⊕	⊕	⊕		⊗	⊗

D1: Representative study group (selection bias)
D2: Outcome detectors blinded to intervention (detection bias)
D3: Complete outcome assessment/follow-up (attrition bias)
D4: Well-defined study group (reporting bias)
D5: Well-defined outcome (reporting bias)
D6: Well-defined risk estimates (analyses)
D7: Important prognostic factors or follow-up taken adequately into account (confounding)

Judgement
⊗ High
⊖ Unclear
⊕ Low

Overall judgement

In addition to the high risk of bias due to the non-randomised and non-controlled study design, we rated the overall risk of bias within and across studies to be high. We present the full judgement per trial and category in Figure 8 and the support for judgement in Appendix 9.

Representative study group (selection bias)

We judged risk of selection bias to be low for Joyner 2020a because of the prospective study design, the large population size, and the fact that 20,000 consecutively enrolled participants were considered in this analysis for safety data.

We judged selection bias to be unclear for five studies because all were prospectively registered (Donato 2020; Dulipsingh 2020; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020), but had low numbers of participants (10 to 47 participants) with no control groups included.

We judged risk of selection bias to be high for two studies (Bradfute 2020; Jin 2020). Jin 2020 was a retrospectively registered study, and only included six participants. Bradfute 2020 had planned to enrol 30 participants but enrolled 13 (included 12) participants.

Outcome detectors blinded to intervention (detection bias)

All studies were unblinded, however assessment of outcome was probably not biased through the awareness of the intervention. Therefore, we judged the risk of detection bias as low for all studies.

Complete outcome assessment/follow-up (attrition bias)

We assessed attrition bias in terms of whether studies (equally) assessed outcomes for all participants.

We judged the risk of attrition bias to be low for six studies (Bradfute 2020; Donato 2020; Joyner 2020a; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020), because they assessed and reported adverse events and symptoms for all participants.

We judged the risk of attrition bias to be unclear for the two studies (Dulipsingh 2020; Jin 2020). Dulipsingh 2020 reported one event for one participant, but it was unclear whether all participants were assessed or similarly assessed. Jin 2020 assessed the outcome for all participants, however the observation period was unclear.

Well-defined study group and outcome (reporting bias)

We assessed reporting bias in terms of whether the study group and intervention were well-defined and whether the outcomes were

equally reported for all participants and the length of follow-up was mentioned.

Well-defined study group and intervention

We judged the risk of reporting bias to be low for six studies (Bradfute 2020; Donato 2020; Dulipsingh 2020; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020), because both the study population and intervention were well described.

Jin 2020 and Joyner 2020a described the study population, but reported only limited information on the intervention. We therefore judged the risk of reporting bias to be unclear for these two studies.

Well-defined outcomes

We judged the risk of reporting bias to be low for Perotti 2020 because the observation period and results were reported for all participants.

We judged the risk of reporting bias to be unclear for seven studies that reported the outcome for all participants but the observation period was unclear (Bradfute 2020; Donato 2020; Dulipsingh 2020; Jin 2020; Madariaga 2020; Olivares-Gazca 2020). Joyner 2020a reported serious adverse events only.

Other potential sources of bias

We further considered confounding and poorly-defined risk estimates as potential sources of bias.

Important prognostic factors or follow-up taken adequately into account (confounding)

All studies were at high risk of confounding because none of the studies adjusted for confounding factors, including concomitant treatments.

Well-defined risk estimates (analyses)

We judged the risk of bias in risk estimates to be low for Joyner 2020a because they expressed cumulative incidences as point estimates with 95% credible intervals. None of the other studies performed any analyses.

Effects of interventions

See: [Summary of findings 1](#) Convalescent plasma for people with COVID-19

In [Summary of findings 1](#), we present certainty of the evidence for our prioritised outcomes (please see 'Summary of findings and assessment of the certainty of the evidence' in [Data synthesis](#)).

Effectiveness of convalescent plasma for people with COVID-19

In [Table 3](#) and [Table 4](#) we provide an overview of effectiveness outcomes that had been reported in the primary studies. Most of the included studies did not provide data on the effectiveness of the intervention in accordance with our prespecified outcomes, but used different definitions to assess mortality, clinical improvement, or virological response.

We could not include outcome data from the controlled NRSIs. One study did not report any of our outcomes of interest (Rasheed 2020), and we did not evaluate efficacy data from seven controlled NRSIs because of the critical risk of bias (Abolghasemi 2020; Duan 2020;

Hegerova 2020; Liu 2020; Salazar 2020a; Xia 2020; Zeng 2020), as described in [Data synthesis](#).

A ratio (HR or RR) greater than 1 favours convalescent plasma for desirable outcomes; those are: improvement of clinical symptoms, time to discharge from hospital, length of stay on the ICU, and virological response.

A ratio (HR or RR) less than 1 favours convalescent plasma for undesirable outcomes; those are: all-cause mortality at hospital discharge, time to death, 30-day and 90-day mortality, admission to the ICU, grade 3 and 4 adverse events, and serious adverse events.

All-cause mortality at hospital discharge

Randomised controlled trials

One RCT provided outcome data for all-cause mortality at hospital discharge upon request (Gharbharan 2020). Of 43 participants in the convalescent plasma group, six had died and 37 had been discharged. In comparison, 11 of 43 participants in the control group had died, and 32 had been discharged (RR 0.55, 95% CI 0.22 to 1.34; low-certainty evidence; see [Analysis 1.1](#)). The evidence is uncertain whether there is a difference between patients receiving convalescent plasma or not.

Controlled non-randomised studies of interventions

Two controlled NRSIs reported all-cause mortality at hospital discharge (Abolghasemi 2020; Zeng 2020). We did not include results from those studies in data synthesis, because of the critical risk of bias.

Mortality (time to event)

Randomised controlled trials

Two RCTs, which included 189 participants, reported mortality (time to event) (Gharbharan 2020*; Li 2020). Evidence suggests that compared to the control group, convalescent plasma may decrease the risk of death but the evidence is uncertain (HR 0.64, 95% CI 0.33 to 1.25; low-certainty evidence; [Analysis 1.2](#)).

*We used a digitising software (GetData Graph Digitizer), to estimate the HR from the mortality curve provided by Gharbharan 2020.

Subgroup analysis: severity of disease

One RCT reported subgroup analyses for participants with severe disease and participants with life-threatening disease (Li 2020). No participant with severe disease died in the convalescent plasma arm, therefore the study authors could not calculate a HR. For participants with life-threatening disease, the evidence is uncertain whether convalescent plasma therapy decreases the risk of death (HR 0.86, 95% CI 0.34 to 2.41; [Analysis 1.3](#)).

Controlled non-randomised studies of interventions

Two controlled NRSIs reported mortality (time to event) (Liu 2020; Salazar 2020a). We did not include results from those studies in data synthesis, because of the critical risk of bias.

Improvement of clinical symptoms (assessed by need for respiratory support)

Randomised controlled trials

Both RCTs assessed improvement of clinical symptoms on an ordinal scale (189 participants). [Gharbharan 2020](#) used the 8-point WHO COVID19 disease severity scale ([WHO 2020f](#)) and defined improvement as a 1-point reduction. The outcome was reported in the preprint article for day 15, and individual patient data (IPD) was provided upon request for days 15 and 30 (see [Table 5](#)).

[Li 2020](#) defined clinical improvement as discharged or a reduction of 2 points on a 6-point disease severity scale:

- 6 points death
- 5 points hospitalisation plus ECMO or invasive mechanical ventilation
- 4 points hospitalisation plus noninvasive ventilation or high-flow supplemental oxygen
- 3 points hospitalisation plus supplemental oxygen (not high-flow or noninvasive ventilation)
- 2 points hospitalisation with no supplemental oxygen
- 1 point hospital discharge

Improvement of clinical symptoms was reported at days 7, 14, and 28 (see [Table 5](#)). The study authors added a post hoc analysis to compare the rates of improvement at these days.

To increase the comparability of results, we used the IPD data that were available for days 15 and 30 for [Gharbharan 2020](#), and transferred the scale into the 6-point scale used by [Li 2020](#), and considered a 2-point reduction as a clinical improvement.

The evidence is uncertain for the effect of convalescent plasma on clinical symptoms, assessed by need for respiratory support at day 7 (RR 0.98, 95% CI 0.30 to 3.19; 1 RCT, low-certainty evidence; see [Analysis 1.4](#)). Convalescent plasma transfusion may increase improvement of clinical symptoms, as assessed by need for respiratory support at up to 15 days (RR 1.34, 95% CI 0.85 to 2.11; 2 RCTs, 189 participants; low-certainty evidence; see [Analysis 1.5](#)), and up to 30 days (RR 1.13, 95% CI 0.88 to 1.43; 2 RCTs; low-certainty evidence; [Analysis 1.6](#)), but the evidence is uncertain.

Subgroup analysis: severity of disease

One RCT reported the subgroup data for the severity of disease ([Li 2020](#)). We did not find any evidence for subgroup differences amongst participants with severe or life-threatening disease for the three reported time points (at 7, 14 and 28 days, see [Analysis 1.7](#); [Analysis 1.8](#); [Analysis 1.9](#), respectively).

Controlled non-randomised studies of interventions

None of the controlled NRSIs reported improvement of clinical symptoms, assessed by need for respiratory support with standardised scales.

30-day and 90-day mortality

Randomised controlled trials

The outcome was reported in one RCT ([Li 2020](#)), with 103 participants. [Li 2020](#) reported no significant difference in 28-day mortality between both groups (RR 0.65, 95% CI 0.29 to 1.46; [Analysis 1.10](#)). The study authors did not evaluate 90-day mortality.

Controlled non-randomised studies of interventions

None of the controlled NRSIs reported 30-day or 90-day mortality.

Time to discharge from hospital

Randomised controlled trials

Both RCTs (189 participants) reported time to discharge from hospital. Evidence suggests no difference between both groups (HR 1.44, 95% CI 0.98 to 2.11; [Analysis 1.11](#)). [Li 2020](#) further reported the median time from randomisation to discharge. The median time from randomisation to discharge in the convalescent plasma group was 28 days (IQR 13 to indeterminate) and was not determinable (IQR 19 to indeterminate) in the control group.

Controlled non-randomised studies of interventions

None of the controlled NRSIs reported time to discharge from hospital.

Admission to the ICU

None of the controlled studies reported this outcome.

Length of stay on the ICU

None of the controlled studies reported this outcome.

Virological response

Randomised controlled trials

One RCT ([Li 2020](#)), including 87 participants reported virological response, expressed as rates of negative SARS-CoV-2 viral PCR test, at 24 hours, 48 hours and 72 hours of observation. Evidence suggests that people treated with convalescent plasma had a higher virological response compared to people in the control group at 24 hours (RR 2.98, 95% CI 1.33 to 6.65; [Analysis 1.12](#)), 48 hours (RR 2.09, 95% CI 1.29 to 3.41; [Analysis 1.13](#)), and 72 hours (RR 2.33, 95% CI 1.54 to 3.52; [Analysis 1.14](#)).

Controlled non-randomised studies of interventions

Two controlled NRSIs reported virological response ([Xia 2020](#); [Zeng 2020](#)). We did not include results from these studies in data synthesis, because of the critical risk of bias.

Quality of life

None of the controlled studies reported this outcome.

Safety of convalescent plasma for people with COVID-19

For safety outcomes we included data from RCTs, controlled NRSIs, and non-controlled NRSIs. As the controlled studies reported adverse events or serious adverse events only for participants who received convalescent plasma, we have listed all studies together.

Number of participants with grade 3 and grade 4 adverse events

Fourteen studies (566 participants) reported assessment of adverse events ([Abolghasemi 2020](#); [Donato 2020](#); [Duan 2020](#); [Dulipsingh 2020](#); [Hegerova 2020](#); [Jin 2020](#); [Li 2020](#); [Liu 2020](#); [Madariaga 2020](#); [Olivares-Gazca 2020](#); [Perotti 2020](#); [Rasheed 2020](#); [Xia 2020](#); [Zeng 2020](#)).

Two studies reported the occurrence of adverse events that were possibly grade 3 or 4 severity ([Li 2020](#); [Perotti 2020](#)), but they did not report the degree of severity (see [Table 6](#)).

Li 2020 (52 participants, intervention arm of the RCT only) mentioned that one participant experienced chills and rashes within two hours of convalescent plasma transfusion, which they classified as non-severe allergic transfusion reaction and also a probable non-severe febrile non-haemolytic transfusion reaction. The participant recovered fully after treatment with dexamethasone and promethazine. In addition, there was one non-severe allergic transfusion reaction classified as a serious adverse event (further described below).

One non-controlled NRSI (Perotti 2020; 46 participants), reported five events in four participants, including chills and fever, urticaria, one anaphylaxis, one possible transfusion-related acute lung injury (TRALI) and one subsegmental pulmonary embolus (but relation unlikely/excluded).

Another non-controlled NRSI (Dulipsingh 2020; 46 participants), reported that one participant developed a transfusion reaction after receiving the first unit of convalescent plasma, but did not provide any more details regarding the event or the grade of severity.

Eleven studies (reporting on 422 participants) reported no adverse events that were possibly of grade 3 or grade 4 severity.

Reporting of adverse events was variable across these studies. In the controlled studies, there was reporting on adverse events only in participants who received convalescent plasma, with no reporting in the control group. The duration of follow-up for observation of adverse events varied across all studies. In addition, it was difficult to ascertain whether some of the adverse events were related to convalescent plasma transfusion, or due to underlying disease or other treatments, or both.

The evidence is of very low certainty and none of the studies reported this outcome for any control group or adjusted for confounding. Because of missing control groups, we are also not able to assess the relative risk of grade 3 and 4 adverse events for convalescent plasma therapy.

Number of participants with serious adverse events

Seventeen studies (35,943 participants) assessed serious adverse events for 20,622 of the included participants (Abolghasemi 2020; Bradfute 2020; Donato 2020; Duan 2020; Dulipsingh 2020; Gharbharan 2020; Hegerova 2020; Jin 2020; Joyner 2020a; Li 2020; Liu 2020; Madariaga 2020; Olivares-Gazca 2020; Perotti 2020; Rasheed 2020; Xia 2020; Zeng 2020).

Three studies reported on the occurrence of serious adverse events (Joyner 2020a; Li 2020; Perotti 2020), see Table 7.

Joyner 2020a reported safety data for 20,000 of 35,322 transfused participants from an ongoing USFDA (Food and Drug Administration) Expanded Access Program. The study authors evaluated the incidence of serious adverse events in the first four hours after convalescent plasma transfusion, and additionally, within seven days after transfusion. Overall, 1282 events were reported, 146 of which occurred during the first four hours of observation, and 1136 additional events occurred within seven days after transfusion of convalescent plasma. A detailed report of the observed events is provided in Table 7.

Li 2020 (52 participants, intervention arm from the included RCT) mentioned that one participant suffered from shortness of breath, cyanosis, and severe dyspnoea within six hours of convalescent plasma transfusion, which they classified as possible severe transfusion-associated dyspnoea (TAD). After medical treatment the symptoms gradually improved over two hours.

Three serious events occurred in the single-arm study by Perotti 2020 (46 participants): anaphylaxis/hypersensitivity, TRALI (relation possible) and subsegmental pulmonary embolism (but relation is considered to be unlikely/excluded).

No serious adverse events occurred in 14 studies (524 participants).

Reporting of serious adverse events was variable across the included studies. The controlled studies reported on serious adverse events in participants receiving convalescent plasma only with no reporting in the control group. Consequently, we were not able to assess the relative risk of serious adverse events for convalescent plasma therapy. The duration of follow-up for observation of serious adverse events varied across all studies. Some, but not all, studies included death as a serious adverse event. In addition, it was difficult to ascertain whether some of the adverse events were related to convalescent plasma transfusion, or due to underlying disease or other treatments, or both. There was insufficient evidence to determine whether convalescent plasma therapy results in a clinically relevant increased risk of serious adverse events and our certainty in the evidence is low.

DISCUSSION

Summary of main results

The aim of this review was to assess the effectiveness and safety of convalescent plasma and hyperimmune immunoglobulin in the treatment of coronavirus disease 2019 (COVID-19). This is the second update of our living systematic review.

We identified two RCTs, both of which were stopped early; one because of the containment of the epidemic at the study location (Li 2020), and one because most of the participants were found to have SARS-CoV-2 antibodies present at baseline (Gharbharan 2020). We also identified five controlled, registered, NRSIs, three controlled, unregistered NRSIs, and nine non-controlled NRSIs (for safety outcomes only). The studies evaluated 38,160 participants, of whom 36,081 received convalescent plasma. We did not identify any completed studies that evaluated hyperimmune immunoglobulin. We identified a further 138 ongoing studies evaluating convalescent plasma or hyperimmune immunoglobulin, of which 73 are randomised and of which six are already completed, but without published results so far.

Risk of bias

We judged the risk of bias of the included RCTs to be at some concerns for one RCT (Gharbharan 2020), and low for the second RCT (Li 2020), for mortality outcomes and outcomes assessing improvement of clinical symptoms; and high for both RCTs for safety outcomes. The risk of bias for mortality outcomes and outcomes assessing improvement of clinical symptoms was serious in one controlled NRSI (Rasheed 2020), and all other outcomes for controlled NRSIs were at an overall critical risk of bias.

For safety outcomes, we also included and assessed non-controlled NRSIs in addition to the controlled studies. One non-controlled NRSI did not report safety data, and we included eight non-controlled NRSIs for safety outcomes. The overall risk of bias of the assessed non-controlled NRSIs was low for one study, and high for the remaining studies.

Effectiveness of convalescent plasma for people with COVID-19

We do not know whether the following results are related to the underlying natural history of the disease, other concomitant treatment, or convalescent plasma. We only used results from controlled studies to assess effectiveness of convalescent plasma. We did not include data of controlled NRSIs in data synthesis because of critical risk of bias. Overall certainty of evidence was low to very low, due to study limitations, small information size, and results including both potential benefits and harms.

All-cause mortality at hospital discharge

We included one RCT (reporting on 86 participants) to assess this outcome. From this study, we are very uncertain whether convalescent plasma has any effect on all-cause mortality at hospital discharge.

Mortality (time to event)

We included two RCTs (189 participants) to assess this outcome. Treatment with convalescent plasma may decrease the risk of death, but the evidence is uncertain (low-certainty evidence).

Improvement of clinical symptoms (as assessed by need for respiratory support)

We included two RCTs (reporting on 189 participants) to assess this outcome. Convalescent plasma may result in little to no difference of improvement of clinical symptoms at seven days (low-certainty evidence). The evidence suggests that convalescent plasma may increase improvement of clinical symptoms at up to 15 days and up to 30 days.

The higher uncertainty in the evidence at day 15 compared to day 30 originates from the fact that the included studies used different scales and cut-offs to assess clinical improvement. The principal investigators of one RCT ([Gharbharan 2020](#)), provided us with the individual participant data for day 30, which allowed us to transfer the results to the scale and cut-off used by [Li 2020](#). However, for day 15 we had to meta-analyse the data reported in the primary studies, and thus downgraded one point for inconsistency.

Quality of life

None of the included studies reported this outcome, which may not be surprising given the severity and acuity of this disease.

Safety of convalescent plasma for people with COVID-19

We included results from RCTs, controlled NRSIs, and non-controlled NRSIs if they were pre-registered in a clinical study registry to assess the safety of convalescent plasma. Of the 19 studies, 17 reported safety outcomes; one controlled NRSI and one non-controlled NRSI did not report any safety outcomes. Reporting of adverse events and serious adverse events was variable across these studies. In most of the RCTs and controlled NRSIs, there was reporting on adverse events and serious adverse events only in participants who received convalescent plasma, with no

reporting of these outcomes in the control group. The duration of follow-up for observation of adverse events and serious adverse events varied across all studies. Some, but not all, studies included death as a serious adverse event. In addition, it was difficult to ascertain whether some of these events were related to convalescent plasma transfusion or due to underlying disease and/or other treatments.

Adverse events

None of the studies reported the grade of adverse events after convalescent plasma transfusion. Fourteen studies (566 participants) reported on adverse events (of possible grade 3 or 4 severity). The majority of these adverse events were from two studies and comprised of allergic or respiratory events. We are very uncertain whether or not convalescent plasma therapy affects the risk of moderate to severe adverse events (very low-certainty evidence).

Serious adverse events

Seventeen studies (35,944 participants) assessed serious adverse events for 20,622 of the included participants. The majority of participants were from one non-controlled NRSI (20,000 participants), which reported on serious adverse events within the first four hours and additionally, within the first seven days after convalescent plasma transfusion. This study included death as a serious adverse event. There were 63 deaths but of these, 12 were possibly and one was probably related to transfusion. Overall, 1282 events were reported, 146 of those occurred within the first four hours of observation, and 1136 additional events occurred within seven days after transfusion of convalescent plasma. These events comprised allergic or respiratory adverse events, which include anaphylaxis, transfusion-associated dyspnoea (TAD) and transfusion-related acute lung injury (TRALI), thrombotic or thromboembolic events and cardiac events. There was insufficient evidence to determine whether convalescent plasma therapy results in a clinically relevant increased risk of serious adverse events and our certainty in the evidence is low.

Overall completeness and applicability of evidence

We identified two RCTs (both were stopped early), five controlled registered NRSIs, three controlled unregistered NRSIs, and nine non-controlled NRSIs (for safety outcomes only), evaluating convalescent plasma in adults, most with severe COVID-19. These studies included 38,160 participants; 36,081 participants received convalescent plasma. Most of these participants had also received different treatment options, either solely or in combination. These included antivirals, antifungals or antibiotics, corticosteroids, hydroxychloroquine and respiratory support (ECMO, mechanical ventilation or oxygen). For effectiveness of convalescent plasma therapy, we included two RCTs (189 participants) and one controlled NRSI only (49 participants). We did not include the other seven controlled NRSIs (2422 participants) to assess effectiveness of convalescent plasma because of the critical risk of bias within studies, mainly originating from brief descriptions of the selection of the control groups, different observation periods of intervention and control groups, and relevant confounding factors were not considered in the analyses (e.g. age, gender, severity of disease, comorbidities).

During the editorial process, we identified two new preprint publications of ongoing RCTs. Both were published after our

last systematic search. We briefly assessed both RCTs, and recognised that the inclusion would not have an impact on our conclusions. We therefore classified them under awaiting assessment and will include both in the next update of this review.

The controlled studies did not report adverse events for the control arm. One large, non-controlled NRSI provided serious adverse events data (reported data for 20,000 of 35,322 transfused participants) within seven days after convalescent plasma transfusion. Convalescent plasma therapy may not result in a clinically relevant increased risk of serious adverse events (low-certainty evidence). The evidence for grade 3 and 4 adverse events is very uncertain, as adverse events were inconsistently reported across study designs.

We identified 10 ongoing studies in an Indian study registry. As the study registry was unavailable for more than one week (24 August to 1 September 2020) we could not assess in detail whether they fit the inclusion criteria of this review. The registry entries await our classification once the study registry is available again.

We identified 138 ongoing studies, nine are expanded access studies from the USA, and 73 are RCTs. Of these studies, six RCTs are indicated in the study registry to be completed already ([IRCT20200404046948N1](#); [IRCT20200409047007N1](#); [IRCT20200413047056N1](#); [NCT04346446](#); [NCT04356534](#); [NCT04442958](#)), but results are not published yet and study investigators did not reply to our requests or no contact details of the principal investigator are given to request data. An additional 31 RCTs are planned to be completed in 2020. The publication of the results of these studies will necessitate a further update of this review. The conclusions of subsequent updated reviews may differ from those of the present review, and may allow for a better judgement regarding the effectiveness and safety of convalescent plasma therapy.

Certainty of the evidence

It is important to note that the outcome measures are heterogeneous with wide variation in reporting across the included studies.

We identified two unblinded RCTs, both of which were stopped early; one because there were no more eligible participants due to containment of the epidemic in Wuhan, China ([Li 2020](#)), and one because most of the participants were found to have SARS-CoV-2 antibodies present at baseline ([Gharbharan 2020](#)). It is unclear to what extent these early terminations may bias the results of the studies. The certainty of the evidence in the reported outcomes was further reduced because of the small information size and results including both potential benefit and potential harm for convalescent plasma therapy.

We identified eight controlled NRSIs ([Abolghasemi 2020](#); [Duan 2020](#); [Hegerova 2020](#); [Liu 2020](#); [Rasheed 2020](#); [Salazar 2020a](#); [Xia 2020](#); [Zeng 2020](#)). For one study, we rated the risk of bias for mortality and outcomes assessing improvement of clinical symptoms to be serious ([Rasheed 2020](#)). For all other assessed outcomes, we rated the risk of bias within and across studies to be critical. We did not include outcome data at critical risk of bias in data synthesis. The certainty of the evidence in the reported outcomes was further reduced because of the small

information size and results mostly including both potential benefit and potential harm for convalescent plasma therapy.

Because all of the included controlled studies report safety data only for the intervention group, we considered the results in a similar way to the non-controlled NRSIs. We were unable to pool numerical data in any meaningful way and therefore reported results separately per study. The evidence for grade 3 and 4 adverse events is of very low certainty, but convalescent plasma therapy may not result in a clinically relevant increased risk of serious adverse events (low-certainty evidence). However, without a control group, the outcomes cannot be considered in context, and we are unable to assess the relative safety for convalescent plasma therapy.

Potential biases in the review process

To avoid potential bias in the review, we had planned to include the best available evidence. However, as COVID-19 is a novel disease, results from large RCTs are not yet available. In fact, we could only identify two RCTs, eight controlled NRSIs, and nine non-controlled NRSIs. Of note here is that one study ([Rasheed 2020](#)), was referred to as an RCT, but because the randomisation process was not described and the study authors did not provide us with more details, we decided to include this study as controlled NRSI. To increase the informative value of our review, we are tracking all registered trials and will continually update this review as more evidence becomes available. As explained above, both RCTs were stopped early, leading to the enrolment of fewer participants than planned and consequently a lower power to detect an effect. One of the studies ([Li 2020](#)), was stopped because of the containment of the disease at the study location. We anticipate that the lower numbers of people hospitalised with COVID-19 and eligible for inclusion will also be a concern for other, ongoing studies that are not international. There are currently still many new trials being registered in trials registries, as can be seen from the additional 32 RCTs added to the list of ongoing studies in this update of the review.

Two experienced Information Specialists developed a sensitive search strategy, to identify all ongoing and completed studies. We searched all relevant databases and trials registries, and two review authors conducted all review steps independently and in duplicate. We are confident that we identified all relevant published and ongoing studies and will monitor them closely in the future. However, it is unclear whether ongoing studies will be completed before the global containment of the pandemic.

Another consideration for this rapidly evolving field is the availability of preprint articles that have not yet undergone peer review. In this review, we also included such preprints. However, we are aware of the potentially lower quality of these publications, and that results could change once the peer-reviewed journal publications are available.

Our review author team is adapting review methods and tools to the development of research output. In the last version of this review ([Piechotta 2020c](#)) we used the former 'Risk of bias' tool to assess risk of bias for RCTs ([Higgins 2011](#)). In this updated version, we assessed both RCTs ([Gharbharan 2020](#); [Li 2020](#)), using Risk of Bias 2 ([Sterne 2019](#)). Through the assessment with updated criteria, our overall 'Risk of bias' judgement for the first included RCT ([Li 2020](#)), changed. Using the former 'Risk of bias' tool, we rated the

risk of bias to be unclear for mortality outcomes, and outcomes assessing improvement of clinical symptoms, and to be high for safety outcomes. Using the updated tool, we rated the risk of bias in [Li 2020](#) to be low for mortality outcomes and outcomes assessing improvement of clinical symptoms, and to be high for safety outcomes. The change of 'Risk of bias' judgement also changed our GRADE assessment of the outcome improvement of clinical symptoms up to day 7 (from very low to low).

We think that the former 'Risk of bias' tool was more sensitive to subjective interpretations, which may have led to an overly strict judgement. We think that the reassessment, using the revised criteria, corrected our judgement from potential personal biases.

Although we have limited to very limited confidence in the available evidence, we are not aware of any further deficiencies in our review process. However, we are certain that the results are likely to be substantially different and conclusions may change as soon as peer-reviewed, high-certainty evidence becomes available.

Agreements and disagreements with other studies or reviews

This systematic review identified very low-certainty evidence on the effectiveness and very low- to low-certainty evidence on the safety of convalescent plasma for people with COVID-19.

There have been three recent meta-analyses evaluating the effectiveness and safety of convalescent plasma in the treatment of COVID-19. [Joyner 2020b](#) aggregated patient outcome data and used the longest reported follow-up for each study and compared between case and control cohorts using fixed-effect meta-analyses models. The authors included three RCTs, five controlled NRSIs and four case series containing 804 participants, and found a 57% reduction in mortality rate (13%) in the controlled studies compared to non-transfused matched patients receiving standard therapy (26%; odds ratio (OR) 0.43; $P < 0.001$). In [Sarkar 2020](#), the authors screened four databases and identified two RCTs and five cohort studies including 5444 participants. They concluded that there is very low- to low-quality evidence that convalescent plasma transfusion reduces mortality (OR 0.44, 95% CI 0.25 to 0.77) from seven studies (5444 participants) and increases clinical improvement (OR 2.06, 95% CI 0.8 to 4.9) from five studies (259 participants). It is unclear which mortality time points they used for analysis and how they defined clinical improvement.

In our analysis, our primary outcome of all-cause mortality at hospital discharge was reported from one RCT and could not be ascertained for the second RCT as not all participants were discharged. We did not pool point estimates for mortality because of differing reporting of mortality time points in the included studies. This may result in substantial implications on the potential pooling of effect estimates. Furthermore, there was variable follow-up duration in one study (15 to 60 days). Therefore, we felt that the pooling of effect estimates from these RCTs with variable mortality time points may result in significant bias.

In addition, [Joyner 2020b](#) classified [Rasheed 2020](#) as a RCT in their review. However, [Rasheed 2020](#) reported that controls were matched to participants according to the disease stage, age, and sex and assigned patients to convalescent plasma based on ABO compatibility and limited availability of plasma. In our opinion, this

does not fit the criteria for a randomised allocation method and we classified it as a controlled NRSI. We also wrote to the authors of [Rasheed 2020](#) to clarify their methods of randomisation and plan to include that information in the next update of our review, once available.

The large-scale clinical administration of convalescent plasma in the USA was regulated under [Expanded Access Program \(EAP\)](#) by the FDA with individual patient authorisation and collection of data. Over five months the programme served 2700 hospitals and reported 71,000 units of convalescent plasma infused. The initial purpose of the analysis was to provide data to establish the safety of administration of convalescent plasma ([Joyner 2020a](#)). However, the data were thought to contain signals of efficacy and reanalysed, and although the data set does not include any data from control patients, it was felt by the FDA and US administration that there was sufficient evidence of efficacy to widen access to convalescent plasma under the Emergency Use Authorisation (EUA) issued on 23 August 2020 ([FDA 2020](#)). Their unadjusted analysis also showed treatment given early after diagnosis (within 3 days) is associated with lower 7-day and 30-day mortality, and transfusion of convalescent plasma with high SARS-CoV-2 IgG antibody levels (> 18.45 signal-to-cut-off ratio (S/Co)) compared to medium (4.62 to 18.45 S/Co) or low (< 4.62 S/Co) IgG levels was furthermore associated with lower mortality ([Joyner 2020b](#); [Joyner 2020c](#)). This could be an explanation as to why other studies investigating convalescent plasma may not be able to detect a clinically relevant difference, although these findings are preliminary and should be confirmed in clinical trials. Access has now been provided for use of COVID-19 convalescent plasma for patients with serious or immediately life-threatening COVID-19 disease who are not eligible or who are unable to participate in randomised clinical trials. There is however, no obligation for doctors or hospitals to provide data and it is widely thought that the EUA will not make it easier to increase recruitment to clinical trials.

[Cochrane NMA 2020](#) also regularly evaluates outcomes of people with COVID-19 receiving convalescent plasma against standard care. Their last update was from 17 July 2020, reporting on all-cause mortality from two included RCTs (RR 0.60, 95% CI 0.33 to 1.10; 189 participants; very-low certainty evidence). They also assessed adverse events and serious adverse events and provided relative risk estimates, but we felt that this was not assessable due to missing reporting of adverse events from participants in control groups. Our assessments were similar for clinical improvement at days 7 and 14, and they did not report past day 28. They also did not include [Rasheed 2020](#) as a RCT.

From previous infectious outbreaks, a systematic review and meta-analysis found low-certainty evidence for the use of convalescent plasma for treating people with infections with different aetiologies ([Mair-Jenkins 2015](#)). The authors reported a systematic review and meta-analysis of the literature on the use of convalescent plasma and hyperimmune immunoglobulin in treating severe acute respiratory infections of viral aetiology, and found that this treatment is likely to be both safe and effective in preventing mortality. The study identified a 75% reduction in the odds of mortality in their exploratory post hoc meta-analysis across all viral aetiologies. The studies included in this review were performed with people treated with convalescent plasma for SARS and influenza. The limited number of identified studies and the low quality of included, mainly non-controlled NRSIs

restricted the authors' ability to analyse extensively the risks and benefits of convalescent plasma therapy. Recommendations from the authors were to investigate the use of convalescent plasma and hyperimmune immunoglobulin in large, well-designed clinical trials or other formal evaluations to obtain better-certainty evidence, and to evaluate the optimal treatment regimen.

Results from several large RCTs on the use of convalescent plasma and hyperimmune immunoglobulin in treating severe influenza have recently been made public (Beigel 2017; Beigel 2019; Davey 2019; Hung 2013). However, the results from these studies are inconsistent, with some studies showing a beneficial effect of convalescent plasma for treating people with severe influenza, whereas other studies show no benefit. The studies were well designed and reported in detail the timing of the intervention and relevant outcomes. One study reported effectiveness of hyperimmune immunoglobulin, but only in a post hoc analysis of a subgroup of participants treated within five days of symptom onset (Hung 2013). In a different study, for the subgroup analysis of people with influenza B, the effect of hyperimmune immunoglobulin also resulted in a demonstrable clinical and virological benefit (Davey 2019). Different mechanisms in the human immune system and their role in responding to different circulating influenza strains might further explain why the results of clinical trials of convalescent plasma and hyperimmune immunoglobulin for influenza varied (Davey 2019). Influenza A immunity is reported to carry over to the next years, known as heterosubtypic immunity (Kreijtz 2011), and the current outbreak of COVID-19 cannot, in that sense, be compared with seasonal influenza. Notwithstanding these differences, which might explain why the aforementioned influenza studies were not successful in clearly demonstrating benefit, the possibility of a null effect of convalescent plasma over a suitable comparator cannot be ruled out with the currently available evidence on COVID-19.

The adverse events associated with plasma transfusions are well characterised. Critically ill patients receiving plasma transfusions have an especially high risk of transfusion-associated circulatory overload (TACO), which is the leading cause of transfusion-related mortality (Pandey 2012). Many countries have now introduced risk mitigation strategies to decrease the risk of TRALI. In the UK in 2018, there was only one confirmed case of TRALI.

In this systematic review of the literature, which mainly identified studies that included people with COVID-19 with severe or critical illness, we identified a small proportion of participants experiencing any grade 3 or 4 adverse events, or serious adverse events. With the information available at this moment from published trials registry entries, it is apparent that the majority of clinical trials are enrolling people with COVID-19 who have progressed to moderate or severe disease. Despite there being some evidence from other infectious diseases that early therapy might be more effective (Mair-Jenkins 2015), targeting this population is justifiable given the evident lack of effective interventions for COVID-19. The population that is eligible for treatment in these trials with convalescent plasma is potentially at high risk of transfusion reactions, and when treating critically ill people with COVID-19, their status should be carefully monitored.

AUTHORS' CONCLUSIONS

Implications for practice

The currently available evidence on the effectiveness and safety of convalescent plasma and hyperimmune immunoglobulin for treatment of people hospitalised with COVID-19 is of low to very low certainty. Thus, any conclusions that are drawn based on these data are of limited value and these conclusions are subject to change as more reliable results become available. For the primary outcomes, there was not enough evidence to determine the effect of convalescent plasma on all-cause mortality at hospital discharge, time to death, or improvement of clinical symptoms, assessed by the need for respiratory support. Other outcomes that were reported in a subset of the included studies were length of stay on the intensive care unit (ICU) and time to discharge from hospital, but reporting of these outcomes was not complete. None of the studies assessed quality of life. Most studies assessed the risks of the intervention, but reporting was heterogeneous. Due to limited information regarding grade 3 and 4 adverse events to determine the effect of convalescent plasma therapy on clinically relevant serious adverse events, and the absence of a control group, the outcomes cannot be considered in context, and we are unable to assess the relative safety for convalescent plasma therapy. More thorough investigations, preferably well-designed clinical trials, are needed in order to assess the benefits and risks of convalescent plasma therapy for people with COVID-19.

Implications for research

For the second version of this living systematic review investigating the use of convalescent plasma or hyperimmune immunoglobulin for people with COVID-19, we included data from two small randomised controlled trials (RCTs). The recruitment rate of one RCT was lower than expected, leading to the enrolment of far fewer participants than planned, and the second RCT was terminated early due to the presence of SARS-CoV-2 antibodies in most of the participants at baseline. This led to consequently lower power to detect an effect in both studies. We anticipate the lower rates of COVID-19 hospital admissions relative to the earlier phase of the pandemic in some countries, and head-to-head studies evaluating other potential beneficial drugs to treat COVID-19 will also be a concern for other, ongoing studies. There are currently still many new studies being registered in trials registries, as can be identified from the list of ongoing studies in this review.

In addition to the low numbers of eligible participants for all these studies, the importance of good study design should be stressed. We identified many ongoing, single-arm intervention studies and expanded access registrations, whereas there urgently needs to be good-quality evidence on the use of convalescent plasma for COVID-19. This evidence should ideally be from RCTs with an appropriate control arm and preferably with a blinded design. The importance of reporting outcomes consistently for all study arms, and ensuring comparability of study arms in terms of co-interventions, cannot be overstated. Although the numbers of infected individuals are declining, many countries are experiencing second waves, and therefore careful consideration of study design is warranted.

Another consideration for research in this rapidly evolving field is the availability of preprint articles that have not yet undergone peer review. In this review, the status of publications has been

included in the [Characteristics of included studies](#) table. However, it is important to continue to be aware of the uncertainty over the reliability of these publications.

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Wu 2020b

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Abdullah 2020
Study characteristics

Methods	<ul style="list-style-type: none"> • Trial design: prospective case-series • Type of publication: journal publication • Setting: severe refractory disease • Recruitment dates: NR • Country: Iraq • Language: English • Number of centres: 1 • Trial registration number: ChiCTR2000033323 • Date of trial registration: 28 May 2020
Participants	<ul style="list-style-type: none"> • Age: 46 and 56 years • Gender: male • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 2 • Severity of disease: severe disease • Comorbidities: hypertension (patient 2) • Inclusion criteria: "COVID with convalescent plasma treatment" • Exclusion criteria: non-COVID patient • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): acetaminophen (paracetamol), amlodipine, antibiotics, antipyrol, azithromycin, enoxaparin, hydroxychloroquine, lopinavir, meropenem vial, noninvasive oxygen therapy, ritonavir, Tamiflu
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: 200 mL * Number of doses: 1 * Type of antibody test(s) and antibody-titre(s): NR * RT-PCR tested: NR

Abdullah 2020 (Continued)

- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody-negative: NR
 - * Severity of disease: moderate
 - * Timing from recovery from disease: NR
 - * RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severe within one 7 to 17 days since onset of illness
- For studies including a control group: comparator (type): not applicable
- Concomitant therapy: acetaminophen (paracetamol), amlodipine, antibiotics, antipyrol, azithromycin, enoxaparin, hydroxychloroquine, lopinavir, meropenem vial, noninvasive oxygen therapy, ritonavir, Tamiflu
- Duration of follow-up: NR
- Treatment cross-overs: none
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome: death rate
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: not applicable
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): nil
 - * Number of participants with SAEs: nil
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: yes, up to discharge
 - * 30-day and 90-day mortality: not applicable
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: yes
 - * QoL: NR
 - * Virological response: yes
- Additional study outcomes: NR

Notes

- Sponsor/funding: NR
- COI: None to disclose
- Other: study approved by Arabic board of medical specialties - Ethical committee

Abolghasemi 2020

Study characteristics

Methods

- Trial design: non-randomised, parallel group
- Type of publication: journal publication
- Setting: moderate to severe disease
- Recruitment dates: 15 March 2020-April 2020
- Country: Iran
- Language: English
- Number of centres: 4
- Trial registration number: IRCT20200325046860N1

Abolghasemi 2020 (Continued)

	<ul style="list-style-type: none"> Date of trial registration: 30 March 2020
Participants	<ul style="list-style-type: none"> Age: CP group mean \pm SD 54.41 \pm 13.71, control group 56.83 \pm 14.98 Gender: CP group male 67 (58.3%), female 48 (41.7%); control group male 37 (50.0%), female 37 (50.0%) Ethnicity: NR Number of participants (recruited/allocated/evaluated): 189 patients (115 CP treatment group and 74 control group) Severity of disease: moderate to severe disease Comorbidities: hypertension, diabetes Inclusion criteria: <ul style="list-style-type: none"> Age \geq 18 years Confirmed COVID-19 infection through laboratory (RT-qPCR) and/or lung involvement confirmed with chest imaging (CT scan) Presence of some or all of disease clinical symptoms such as shortness of breath (dyspnoea), respiratory frequency \geq 20/min, fever and cough Hospitalised with a blood oxygen saturation (SPO₂) \leq 93% at rest on room air 5 \leq 7 days since illness onset Willingness to participate and sign the consent form Exclusion criteria: <ul style="list-style-type: none"> Intubated patients or patients on mechanical ventilation Severe liver or kidney disease Septic shock Physician decision that CP therapy is not in patients' best interest Patients with improving clinical conditions who meet hospital discharge criteria (defined as clinical recovery, i.e. return of body temperature, respiratory rate, oxygen saturation to normal and cough relief) Known hypersensitivity to plasma Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): routine antiviral therapy including lopinavir/ritonavir, hydroxychloroquine and an anti-inflammatory agent
Interventions	<ul style="list-style-type: none"> CP therapy or hyperimmune immunoglobulin therapy: CP therapy Details of CP: <ul style="list-style-type: none"> Type of plasma: CP, preparation details not described (guideline of Iran blood transfusion organisation criteria), max 650 mL collected Volume: 500 mL Number of doses: 1-2 Type of antibody test(s) and antibody-titre(s): donated plasma was tested by the semi-quantitative ELISA and rapid strip test (IgG 98% pos, IgM 75% pos) antibody identification test for COVID-19. Based on laboratory testing, donated plasmas contained antibody titre cut-off index > than 1.1 RT-PCR tested: yes Details of donors: <ul style="list-style-type: none"> CP for treatment was collected from 40 donors. The median age was 42.0 years (IQR 32.5-49 years). 18–60 years old Gender: both, females with history of pregnancy were excluded HLA and HNA antibody-negative: NR Severity of disease: NR Timing from recovery from disease: additionally, all donors should have no remaining symptoms of COVID-19 infection at least 14 days prior to donation. RT-PCR tested: yes Treatment details, including time of plasma therapy (e.g. early stage of disease): moderate to severe within 1 week since onset of illness For studies including a control group: comparator (type): conventional treatment (matched for age, gender and presence of hypertension and diabetes)

Abolghasemi 2020 (Continued)

- Concomitant therapy: conventional treatment including routine antiviral therapy including lopinavir/ritonavir, hydroxychloroquine and an anti-inflammatory agent
- Duration of follow-up: NR
- Treatment cross-overs: none
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome
 - * Mortality
 - * Length of hospital stay
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes (reduced all-cause mortality in treatment group compared with control group (14.8% vs 24.3%))
 - * Time to death: yes
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): nil
 - * Number of participants with SAEs: nil
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: yes - 8 participants (7%) in CP group required intubation while this value was 20% in control group
 - * 30-day and 90-day mortality: yes (no follow-up period stated)
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: yes 98 (98.2%) of participants who received CP were discharged from hospital which is substantially higher compared to 56 (78.7%) participants in control group. Length of hospital stay was significantly lower (9.54 days) in CP group compared with that of control group (12.88 days)
 - * QoL: NR
 - * Virological response: NR
- Additional study outcomes: NR

Notes

- Sponsor/funding: Darmanara Co, Iran Blood Transfusion Organization
- COI: none to disclose
- Other: nil

Bradfute 2020

Study characteristics

Methods

- Trial design: single-arm
- Type of publication: journal publication
- Setting: hospitalised patients
- Country: USA
- Language: English
- Number of centres: 1
- Trial registration number: NCT04434131
- Date of registration: 16 June 2020

Participants

- Age: median age was 52 years (range: 39-91)
- Gender: 12 participants (8 male and 4 female)
- Ethnicity: 11 participants of American Indian/Alaska Native (AI/AN) descent, 1 white

Bradfute 2020 (Continued)

- Number of participants (recruited/allocated/evaluated): 12
- Severity of disease: severe
- Comorbidities: obesity
- Inclusion criteria:
 - * Patients must be ≥ 18 years
 - * Hospitalised with COVID-19 respiratory symptoms and confirmation via COVID-19 SARS-CoV-2 RT-PCR testing. If COVID-19 test results are pending or done at enrolment, test results must be positive prior to administration of CP
 - * Patient (or LAR) is willing and able to provide written informed consent and comply with all protocol requirements
 - * For patients unable to consent, consent by the LAR may be obtained by phone
- Exclusion criteria:
 - * Women with positive pregnancy test or breastfeeding
 - * Receipt of pooled immunoglobulin in past 30 days
 - * Contraindication to transfusion or history of prior severe allergic reactions to transfused blood products
 - * On ECMO or in refractory shock at entry
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): oxygen therapy (5 participants), mechanical ventilation (7 participants)

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: 200 mL
 - * Number of doses: 1
 - * Type of antibody test(s) and antibody-titre(s): antibodies against the S1 subunit of SARS-CoV-2 spike protein (AntiSARS-CoV-2 Total Reagent Pack and Calibrator, Ortho-Clinical Diagnostics) and neutralising antibody assessment. Plaques were counted for determination of 80% plaque reduction neutralisation titres (PRNT80). The minimal level of detection was 1:40
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: at least 28 days following positive test results, with complete recovery from COVID-19
 - * RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients, participants received CP a median of 8.5 days (range: 6-16) after the onset of symptoms and a median 3.5 days (range: 1-10) after hospitalisation
- For studies including a control group: comparator (type): not applicable
- Concomitant therapy: standard of care
- Duration of follow-up: 14 days
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome
 - * Correlation between the neutralising Ab (Nab) dose titre in the CP and change comparing pretreatment and day 1 NAb titres to inpatients with documented COVID-19 infection
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR

Bradfute 2020 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: none
 - * Number of participants with SAEs: none
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: reported
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: reported (days 1, 3, 7, and 14 after CP transfusion)
- Additional outcomes: nil

-
- Notes
- Sponsor/funding: University of New Mexico
 - COI: none to disclose
 - Other: nil
-

Donato 2020

Study characteristics

-
- Methods
- Trial design: single-arm intervention study
 - Type of publication: preprint article
 - Setting: inpatient
 - Recruitment dates: 15 April 2020-16 June 2020
 - Country: USA
 - Language: English
 - Number of centres: 1
 - Trial registration number: NCT04343755
 - Date of trial registration: 9 April 2020
-
- Participants
- Age: median age in track 2: 59 years (IQR 47-69); median age in track 3: 53 years (IQR 45-58)
 - Gender: 22 male/25 female
 - Ethnicity: Hispanic, white, black, Asian
 - Number of participants (recruited/allocated/evaluated): 48/47/47
 - Severity of disease: moderate to severe
 - Comorbidities: obesity, hypertension, diabetes, COPD, immunocompromised, active cancer, (pregnant)
 - Inclusion criteria:
 - * Recipients age > 18 years old, are assigned to 1 of 2 clinical tracks, track 2 or 3, based on COVID-19 disease severity
 - * Track 2:
 - hospitalised, moderate symptoms requiring medical care for COVID-19 infection
 - symptoms may include fever, dyspnoea, dehydration among others
 - hypoxaemia may be present but is not a requirement
 - * Track 3:
 - requiring mechanical ventilation for the care of COVID-19 infection

Donato 2020 (Continued)

- Exclusion criteria:
 - * History of severe transfusion reaction to plasma products
 - * Infusion of immune globulin within the previous 30 days
 - * AST or ALT > 10 x ULN
 - * Requirement for vasopressors
 - * COVID-19-associated acute kidney injury requiring dialysis
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): hydroxychloroquine, azithromycin, steroids, tocilizumab, remdesivir

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP:
 - * Type of plasma: fresh and frozen; choice based solely on the availability of product at the time of request
 - * Volume: 200-500mL
 - * Number of doses: 1
 - * Type of antibody test(s) and antibody-titre(s): neutralising IgG spike RBD > 1:500 were selected for plasma donation, with a preference for titres 1:1000-10,000 and >1:10,000
 - * RT-PCR tested: yes
- Details of donors:
 - * Gender: both
 - * HLA and HNA antibody-negative: yes
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
 - * RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): a single infusion of CP was administered at a rate < 250 mL per hour. Premedication with diphenhydramine 25 mg IV and hydrocortisone 100 mg IV with or without acetaminophen (paracetamol) was given. The use of fresh vs frozen plasma was based solely on the availability of product at the time of request
- For studies including a control group: comparator (type): not applicable
- Concomitant therapy: hydroxychloroquine, azithromycin, steroids, tocilizumab, remdesivir
- Duration of follow-up: 60 days
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome
 - * For participants hospitalised for COVID-19 but not intubated: mechanical ventilation rate at 7 days from starting treatment in hospitalised COVID-19 patients
 - * For participants with COVID-19 already intubated: mortality rate at 30 days from starting treatment for patients with COVID-19
- Primary review outcomes
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: yes (survival curve)

Donato 2020 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): nil, one grade 2 AE observed
 - * Number of participants with SAEs: nil
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days:
 - * 30-day and 90-day mortality: yes
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: yes (duration of hospital stay)
 - * QoL: NR
 - * Virological response: yes, at day 10, and 30
- Additional study outcomes: impact of donor neutralising antibody titre levels on the primary objectives, and recipient anti-SARS-CoV-2 titre levels pre-infusion and on days +3, +10, +30 and +60

Notes

- Sponsor/funding: "This work was supported the COVID Emergency Research Fund #61315, Hackensack University Medical Centre; by funds provided to the CDI by Activision Publishing Inc, Suez North America, and by NJ Stands Up to COVID."
- COI: none to disclose
- Other: nil

Duan 2020
Study characteristics

Methods

- Trial design: prospective single-arm pilot study
- Type of publication: journal publication
- Setting: inpatient
- Recruitment dates: 23 January 2020-19 February 2020
- Country: China
- Language: English
- Number of centres: 3
- Trial registration number: ChiCTR2000030046
- Date of trial registration: 21 February 2020

Participants

- Age: median age 52.5 years (IQR 45.0-59.5 years)
- Gender: 6 male, 4 female
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 10
- Severity of disease: severe
- Comorbidities: cardiovascular and/or cerebrovascular diseases and essential hypertension
- Inclusion criteria: 1 of the conditions 2-4 plus condition 1: 1) age \geq 18 years; 2) respiratory distress, respiratory rate \geq 30 breaths/min; 3) oxygen saturation level $<$ 93% in resting state; and 4) PaO₂/FiO₂ \leq 300 mmHg (1 mmHg = 0.133 kPa)
- Exclusion criteria: 1) previous allergic history to plasma or ingredients (sodium citrate); 2) cases with serious general conditions, such as severe organ dysfunction, who were not suitable for CP transfusion
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation):
 - * oxygen support (9/10 before CP therapy, 8/10 after CP therapy): mechanical ventilation, high-flow nasal cannula oxygenation, conventional low-flow nasal cannula oxygenation
 - * antiviral treatments (10/10): Arbidol 0.2 g every 8 h) by mouth, monotherapy or combination therapy with remdesivir 0.2 g/day IV or ribavirin 0.5 g/day IV or peramivir 0.3 g/day IV, or ribavirin

Duan 2020 (Continued)

0.5 g/day IV monotherapy, IFN- α 500 MIU/day inhalation, oseltamivir 75 mg every 12 h by mouth, peramivir 0.3 g/day IV

- * antibacterial or antifungal treatment (8/10): when participants had coinfection
- * corticosteroids 6/10): IV methylprednisolone (20 mg every 24 h)

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP:
 - * Type of plasma: apheresis plasma. Apheresis was performed using a Baxter CS 300 cell separator (Baxter). A 200- to 400-mL ABO-compatible plasma sample was harvested from each donor depending on age and body weight, and each sample was divided and stored as 200 mL aliquots at 4 °C without any detergent or heat treatment. The CP was then treated with methylene blue and light treatment for 30 min in the medical plasma virus inactivation cabinet (Shandong Zhongbaokang Medical Appliance Co, Ltd)
 - * Volume: 200 mL
 - * Number of doses: 1
 - * Type of antibody test(s) and antibody-titre(s): the neutralising activity against SARS-CoV-2 was evaluated by classical plaque reduction test using a recently isolated viral strain. Antibody titre: > 1:160
 - * Pathogen inactivated or not: methylene blue photochemistry
 - * RT-PCR tested: NR
- Details of donors:
 - * CP for treatment was collected from 40 donors. The median age was 42.0 years (IQR 32.5-49 years).
 - * Gender: NR
 - * HLA and HNA antibody-negative: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
 - * RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): administered between 10 and 20 days after admission (median: 16.5 days)
- For studies including a control group: comparator (type): historic control, matched by age, gender and severity of disease
- Concomitant therapy: mechanical ventilation, high-flow nasal cannula oxygenation, conventional low-flow nasal cannula oxygenation, Arbidol 0.2 g every 8 h by mouth, monotherapy or combination therapy with remdesivir 0.2 g/day IV or ribavirin 0.5 g/day IV or peramivir 0.3 g/day IV, or ribavirin 0.5 g/day IV monotherapy, IFN- α 500 MIU/day inhalation, oseltamivir 75 mg every 12 h by mouth, peramivir 0.3 g/day IV, antibacterial or antifungal treatment when participants had coinfection, IV methylprednisolone (20 mg every 24 h)
- Duration of follow-up: NR
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome
 - * The changes of clinical symptom, laboratory and radiological data 3 days after CP transfusion
- Primary review outcomes
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR

Duan 2020 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): only CP transfusion-related AEs reported (evanescent facial red spot)
 - * Number of participants with SAEs: reported, none occurred
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: reported; up to day 4
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: yes
- Additional study outcomes: lymphocyte count, CRP, ALT, AST, total bilirubin, SaO₂, clinical symptoms improvement, clinical outcome, defined as: death, stable, improved, discharged, neutralising anti-body titres, SARS-CoV-2 RNA by RT-PCR, reduction of pulmonary lesions on chest CT

Notes

- Sponsor/funding: this study was funded by Key projects of the Ministry of Science and Technology China 'Preparation of specific plasma and specific globulin from patients with a recovery period of COVID-19 infection' (Project 2020YFC0841800). This work was also supported by Shanghai Guangci Translational Medicine Development Foundation. We thank all patients and donors involved in this study.
- COIs: study authors declare no competing interests
- Other: "written informed consent according to the Declaration of Helsinki was obtained from each patient or legal relatives. This study was approved by the Ethics Committee of the China National Biotec Group Co., Ltd. (Approval number 2020-0001)."

Dulipsingh 2020

Study characteristics

Methods

- Trial design: single-arm intervention study
- Type of publication: preprint
- Setting: hospital
- Recruitment dates: 21 April 2020-8 June 2020
- Country: USA
- Language: English
- Number of centres: 1
- Trial registration number: NCT04343261
- Date of trial registration: 13 April 2020

Participants

- Age: NR
- Gender: NR
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 46 enrolled
- Severity of disease: severe or immediately life-threatening COVID-19
- Comorbidities: NR

Dulipsingh 2020 (Continued)

- Inclusion criteria
 - * All genders
 - * Age > 18 years and < 90 years
 - * Must have laboratory-confirmed COVID-19
 - * Must provide informed consent
 - * Must have severe or immediately life-threatening COVID-19
- Exclusion criteria
 - * No gender exclusion
 - * Age < 18 years and > 90 years
 - * COVID-19-negative
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
- Donor eligibility criteria: CP collected from donors recovered from COVID-19 between the ages 18 and 90 with a confirmed positive nasopharyngeal swab SARS CoV-2 RNA test within the previous 45 days and symptom-free for at least 2 weeks
- Donor exclusion criteria: no positive diagnosis of COVID-19 within the last 45 days; history of HIV, Hepatitis B or C; temperature > 37.5 °C; were pregnant or 6 weeks post-partum; donated blood within the previous six months; weighed < 50 kg

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP:
 - * type of plasma: CP
 - * volume: 200 mL
 - * number of doses: 2
 - * Type of antibody test(s) and antibody-titre(s): chemiluminescent SARS-CoV-2 IgM and IgG assays from Diazyme (Poway, CA)
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: both
 - * HLA and HNA antibody-negative: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: symptom-free for 2 weeks
 - * RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): average duration between positive test and receiving CP was 11.4 days
- For studies including a control group: comparator (type): none (single-arm)
- Concomitant therapy: NR
- Duration of follow-up: 7 days
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome: change in viral load, serum antibody titres in donors and recipients
- Primary review outcomes
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR

Dulipsingh 2020 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): reported (1 participant had a transfusion reaction, details not specified)
 - * Number of participants with SAEs: reported (1 participant had a transfusion reaction, details not specified)
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * Virological response: reported (viral load and antibody titres were measured immediately prior to receiving CP and again on days 3, 5, and 7 following transfusion)
 - * QoL: NR
- Additional outcomes: NR

Notes

- Sponsor/funding: Saint Francis Care
- COI: nil
- Other: nil

Gharbharan 2020

Study characteristics

Methods

- Trial design: RCT, open-label
- Type of publication: preprint
- Setting: inpatient
- Recruitment dates: 8 April 2020-10 June 2020
- Country: Netherlands
- Language: English
- Number of centres: 18
- Trial registration number: NCT04342182
- Date of trial registration: 10 April 2020

Participants

- Age: median age 61 (IQR 56-70) years in intervention group; 63 (IQR 55-77) years in control group
- Gender: 62 male, 24 female
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 204/86/86
- Severity of disease: moderate to severe
- Comorbidities: diabetes mellitus, hypertension, cardiac, pulmonary, cancer, immunodeficiency, chronic kidney disease, liver cirrhosis
- Inclusion criteria: PCR-confirmed COVID-19 disease, admitted to the hospital, most recent PCR-positive sample is < 96 h old, written informed consent by patient or LAR, age ≥ 18 years
- Exclusion criteria: participation in another intervention trial on the treatment of COVID-19 that falls under the Dutch law human research (WMO) and in which individual patients are randomised to different treatment options, known IgA deficiency, invasive ventilation for > 96 h already
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
- Donor eligibility criteria: donors with a history of COVID infection that was documented by PCR, known ABO-Resus(D) blood group, negative screening for irregular antibodies, asymptomatic for at least 24 h, written informed consent regarding the plasmapheresis procedure

Gharbharan 2020 (Continued)

	<ul style="list-style-type: none"> • Donor exclusion criteria: if age < 18 years and > 66 years, weight < 45 kg, medical history of heart failure, history of transfusion with red blood cells, platelets or plasma
<p>Interventions</p>	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: <ul style="list-style-type: none"> <input type="checkbox"/> serum samples of donors analysed for the presence of neutralising antibodies by performing a PRNT with the SARS-CoV-2 virus (German isolate; GISAID ID EPI_ISL 406862; European Virus Archive Global #026V-03883) <input type="checkbox"/> For each participant, we selected the plasma with the highest PRNT50 titre from the ABO compatible donor pool * Volume: 300 mL * Number of doses: 1; participants without a clinical response and a persistently positive RT-PCR could receive a second plasma unit after 5 days * Type of antibody test(s) and antibody-titre(s): antiSARS-CoV-2 neutralising antibodies confirmed by a SARS-COV-2 PRNT and a PRNT50 titre > 1:80 * Pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * CP for treatment was collected from 115 donors. The median age was 43 years (IQR 31-52 years) * Gender: 105 male (91%) * HLA and HNA antibody-negative: yes * Severity of disease: NR * Timing from recovery from disease: NR * RT-PCR tested: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): administered on the day of inclusion • For studies including a control group: comparator (type): standard of care; off-label use of EMA-approved drugs (e.g. chloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, anakinra) as a treatment for COVID-19 was allowed in hospitals where this was part of the standard of care • Concomitant therapy: NR • Duration of follow-up: NR; followed for at least 15 days after inclusion and 75 (87%) and 32 (37%) for at least 30 and 60 days respectively • Treatment cross-overs: not applicable • Compliance with assigned treatment: good (all compliant)
<p>Outcomes</p>	<ul style="list-style-type: none"> • Primary study outcome <ul style="list-style-type: none"> * Overall mortality until discharge from the hospital or a maximum of 60 days after admission whichever comes first • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes * Time to death: NR • Secondary review outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: reported * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: reported for day 15 * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR * Virological response: NR

Gharbharan 2020 (Continued)

- Additional study outcomes: NR

Notes

- Sponsor/funding: Erasmus Medical Center
- Collaborator: Sanquin Plasma Products BV
- COIs: authors declared to have no competing interests
 - * The trial was stopped early after enrolment of 86 participants
 - * "The study was reviewed and approved by the institutional review board of the Erasmus University Medical Center. Written informed consent was obtained from every patient or a legal patient representative. The DSMB reviewed the safety of the participants on a regular basis and recommended the study team regarding the further conduct of the study at predefined time point"

Hegerova 2020
Study characteristics

Methods

- Trial design: matched control study, retrospective
- Type of publication: journal publication, letter
- Setting: inpatient
- Recruitment dates: 13-26 April 2020
- Country: USA
- Language: English
- Number of centres: 5
- Trial registration number: NR
- Date of trial registration: not applicable

Participants

- Age: median age 60 years (range, 29-95) in intervention group; NR for control group
- Gender: NR
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 40
- Severity of disease: severe and critically ill
- Comorbidities: hypertension, diabetes, and obesity
- Inclusion criteria: severely and critically ill hospitalised COVID-19 patient
- Exclusion criteria: NR
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP:
 - * Type of plasma: ABO-compatible CP under an expanded access protocol (IND 19832; [Joyner 2020](#))
 - * Volume: NR
 - * Number of doses: 1
 - * Type of antibody test(s) and antibody-titre(s): NR
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * CP for treatment was collected from 8 donors. The age ranged from 29-79 years
 - * Gender: NR
 - * HLA and HNA antibody-negative: NR
 - * Severity of disease: all had symptoms of respiratory illness, muscle aches, and/or headache, but none required hospitalisation
 - * Timing from recovery from disease: > 28 days
 - * RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR

Hegerova 2020 (Continued)

- For studies including a control group: comparator (type): standard of care; half of the control patients received remdesivir
- Concomitant therapy: azithromycin, hydroxychloroquine, remdesivir or multiple combinations
- Duration of follow-up: 14 days
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome: NR
- Primary review outcomes
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes, venous thromboembolism
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: yes, day 7 and day 14
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: length of stay
 - * QoL: NR
 - * Virological response: NR
- Additional study outcomes: mechanical ventilation, duration of mechanical ventilation, extubated survivors, discharges, deaths

Notes

- Sponsor/funding: Barbara and Kent Chaplin, a US Department of Health and Human Services (HHS), Biomedical Advanced Research and Development Authority (BARDA) grant contract 75A50120C00096, National Institutes of Health, National Center for Advancing Translational Sciences (NCATS) grant UL1TR002377, Schwab Charitable Fund (Eric E Schmidt, Wendy Schimdt donors), United Health Group, National Basketball Association (NBA), Millennium Pharmaceuticals, Octapharma Octapharma USA, Inc, and the Mayo Clinic
- COIs: authors declared to have no competing interests
- Other:
 - * Participants in intervention group were treated under an expanded access protocol (IND 19832, [Joyner 2020](#))
 - * Study was approved by the Institutional Review Board of Providence St. Joseph Health

Jin 2020

Study characteristics

Methods

- Trial design: case series
- Type of publication: preprint
- Setting: hospital
- Recruitment dates: 2 February 2020-27 April 2020
- Country: China
- Language: English
- Number of centres: 1
- Inclusion/exclusion criteria: NR
- Trial registration no.: ChiCTR2000033056

Jin 2020 (Continued)

	<ul style="list-style-type: none"> Date of trial registration: 19 May 2020
Participants	<ul style="list-style-type: none"> Age: 51-75 Gender: 2 female, 4 male Ethnicity: NR Number of participants (recruited/allocated/evaluated): 6 Severity of disease: general, critical and severe critical Comorbidities: <ul style="list-style-type: none"> * Patient 1: coronary disease; diabetes mellitus; cerebral infarction * Patient 2: cardiac insufficiency; postoperative oesophageal cancer * Patient 3: none * Patient 4: none * Patient 5: hypertension; hyperlipidaemia; diabetes mellitus, cholecystectomy; hysterectomy; tonsillectomy * Patient 6: hypertension; coronary heart disease; cerebral haemorrhage; bilateral renal artery stenosis Inclusion criteria: (1) patients with positive laryngeal swab; (2) difficult to turn negative RT-PCR of COVID-19 infections and severe disease developed rapidly; (3) recurrent patients (patients whose throat swab became negative and then had a positive result) and worsening symptoms after empirically treated with antivirals. The enrolled patients were not allergic to plasma contents; negative for HBV, HCV, HIV; and not mixed with other bacterial infections. The patients continued to use antivirals while using CP therapy. Exclusion criteria: NR Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): oxygen therapy through nasal catheter, various antivirals, systemic steroids
Interventions	<ul style="list-style-type: none"> Intervention(s): CP therapy Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: 200 mL once * Number of doses: 1 * Type of antibody test(s) and antibody-titre(s): serum SARS-CoV-2-specific ELISA antibody titre > 1: 1000 and a neutralising antibody titre > 40 * Pathogen inactivated: NR * RT-PCR tested: NR Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody-negative: NR * Severity of disease: NR * Timing from recovery from disease: NR * RT-PCR tested: negative for SARS-CoV-2 nucleic acid for consecutive two RT-PCR tests Treatment details, including time of plasma therapy (e.g. early stage of disease): administered between day 22 and day 64 of hospitalisation Comparator: not applicable Concomitant therapy: oxygen therapy through nasal catheter, various antivirals, systemic steroids. Unclear whether these treatments were stopped before plasma transfusion or continuously given. Duration of follow-up: 49-64 days Treatment cross-overs: not applicable Compliance with assigned treatment: good
Outcomes	<ul style="list-style-type: none"> Primary study outcome(s): NR Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: reported (1 patient not discharged at study end) * Time to death: not applicable

Jin 2020 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: reported
 - * 30-day and 90-day mortality: not applicable
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: yes
- Additional study outcomes: chest CT, PaO₂/FiO₂; laboratory data, including lymphocyte count, CRP and IL-6; changes in complications and the time for the laryngeal swab to change from positive to negative

Notes

- Sponsor/funding: this study was supported by Science and Technology Support Plan of Guizhou Province in 2019 (Qian Ke He Support (2019) 2834) and Science and Technology Plan of Guizhou Province in 2020 (Qian Ke He Fundamental [2020] 1Z061)
- COIs: the authors have no potential conflicts of interest to disclose
- Other: this study was approved by the Biomedical Ethics Committee of Affiliated Hospital of Zunyi Medical University. We have obtained written informed consent from each participant. This study was registered at the Chinese Clinical Trial Register (CTTR number: ChiCTR2000033056, registered 19 May 2020). URL: www.chictr.org.cn/edit.aspx?pid=53859&htm=4

Joyner 2020a
Study characteristics

Methods

- Trial design: expanded access
- Type of publication: preprint publication
- Setting: hospital, 52.3% in ICU
- Recruitment dates: 4 April 2020 to 4 July 2020
- Country: USA
- Language: English
- Number of centres: 2807 acute care facilities in the USA and territories
- Trial registration number: NCT04338360
- Date of trial registration: 8 April 2020

Participants

- Age: 18 to > 80 years
- Gender: men 21,215 (60.2%), women 13,996 (39.7%) and people in other gender/sex categories 28 (0.1%)
- Ethnicity: Asian (4.2%), black (18.8%), white (50.4%), unknown (26.6%)
- Number of participants (recruited/allocated/evaluated): recruited: 47,047 patients; transfused: 36,226 patients; evaluated: the first 35,322 patients
- Severity of disease: hospitalised adults with severe or life-threatening COVID-19
- Comorbidities: NR

Joyner 2020a (Continued)

- Inclusion criteria:
 - * Age \geq 18 years
 - * Laboratory-confirmed diagnosis of infection with SARS-CoV-2
 - * Admitted to an acute care facility for the treatment of COVID-19 complications
 - * Severe or life-threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease. (Severe COVID-19 is defined by one or more of the following: dyspnoea, respiratory frequency \geq 30/min, blood oxygen saturation \leq 93%, PaO₂/FiO₂ < 300, lung infiltrates > 50% within 24-48 h. Life-threatening COVID-19 is defined as one or more of the following: multiple organ dysfunction or failure, septic shock, respiratory failure.)
 - * Informed consent provided by the patient or healthcare proxy
- Exclusion criteria: none
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP:
 - * Type of plasma: ABO-compatible COVID-19 CP
 - * Volume: approximately 200 mL
 - * Number of doses: \geq 1
 - * Type of antibody test(s) and antibody-titre(s): Ortho-Clinical IgG CLIA (qualitative assay)
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody-negative: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: symptom-free for 14 days
 - * RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): variable (day 0-day 11+)
- Comparator: none
- Concomitant therapy: NR
- Duration of follow-up: 4 h for safety (first version), 7 days for safety (second version), 30 days for mortality (third version)
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: NR

Outcomes

- Primary study outcome(s):
 - * Provide access to COVID-19 CP, assessed as the availability of CP
- Primary review outcomes
 - * All-cause mortality at hospital discharge: 7-day and 30-day mortality rate reported for third version
 - * Time to death: NR
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): serious transfusion-related AEs reported for 20,000 participants (second version)
 - * Number of participants with SAEs: reported for 20,000 participants (up to one week post transfusion in the second version)
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: reported for 30-day mortality in the third version.
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR

Joyner 2020a (Continued)

- * QoL: NR
- * Virological response: NR
- Additional study outcomes: none

Notes

- Sponsor/funding: US Department of Health and Human Services (HHS), Biomedical Advanced Research and Development Authority (BARDA) grant 75A50120C00096 (to MJJ), National Center for Advancing Translational Sciences (NCATS) grant UL1TR002377, National Heart, Lung, and Blood Institute (NHLBI) grant 5R35HL139854 (to MJJ), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) 5T32DK07352 (to JWS and CCW), Natural Sciences and Engineering Research Council of Canada (NSERC) PDF-532926-2019 (to SAK), National Institute of Allergy and Infectious Disease (NIAID) grants R21 AI145356 and R21 AI152318 (to DF), R01 AI152078 9 (to AC), National Heart Lung and Blood Institute R01 HL059842 (to AC), Schwab Charitable Fund (Eric E Schmidt, Wendy Schmidt donors), United Health Group, National Basketball Association (NBA), Millennium Pharmaceuticals, Octopharma USA, Inc, and the Mayo Clinic
- COIs: NR
- Other: preliminary analysis, study still ongoing

Li 2020

Study characteristics

Methods

- Trial design: RCT
- Type of publication: journal publication
- Setting: hospital
- Recruitment dates: 14 February 2020-1 April 2020
- Country: China
- Language: English
- Number of centres: 7
- Trial registration number: ChiCTR2000029757
- Date of registration: NR

Participants

- Age: median 70 years, IQR 62-78 years
- Gender: 60 male (58.3%), 43 female (41.7%)
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 103 (52 CP, 51 standard treatment)
- Severity of disease: severe or life-threatening
- Comorbidities: hypertension, cardiovascular disease, cerebrovascular disease, diabetes, liver disease, cancer, kidney disease
- Inclusion criteria:
 - * signed informed consent
 - * aged at least 18 years
 - * COVID-19 diagnosis based on PCR testing
 - * positive PCR result within 72 h prior to randomisation
 - * pneumonia confirmed by chest imaging
 - * clinical symptoms meeting the definitions of severe or life-threatening COVID-19
 - * acceptance of random group assignment
 - * hospital admission
 - * willingness to participate in all necessary research studies and be able to complete the study follow-up
 - * no participation in other clinical trials, such as antiviral trials, during the study period

Li 2020 (Continued)

- Exclusion criteria:
 - * pregnancy or lactation
 - * immunoglobulin allergy
 - * IgA deficiency
 - * pre-existing comorbidity that could increase the risk of thrombosis
 - * life expectancy < 24 h
 - * disseminated intravascular coagulation
 - * severe septic shock
 - * PaO₂/FIO₂ of < 100
 - * severe congestive heart failure
 - * detection of high titre of S protein–RBD-specific IgG antibody (≥ 1:640)
 - * other contraindications as determined by the patient’s physicians
 - * participation in any antiviral clinical trials for COVID-19 within 30 days prior to enrolment
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): antivirals, antibiotics, steroids, human Ig, Chinese herbal medicines, interferon

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP:
 - * Type of plasma: plasmapheresis
 - * Volume: 4-13 mL/kg of recipient body weight, median 200 mL, IQR 200-300 mL
 - * Number of doses: 1 (96%) or more
 - * Antibody test and antibody-titre: only the plasma units with an S-RBD-specific IgG titre of at least 1:640 were used correlating to serum neutralisation titre of 1:80
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: both, 18-55 years suitable for blood donation
 - * HLA and HNA antibody-negative: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: discharged from hospital > 2 weeks
 - * RT-PCR tested: lab-confirmed COVID-19 diagnosis, 2 negative PCR results from nasopharyngeal swabs at least 24 h apart prior to hospital discharge
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severe to life-threatening
- For studies including a control group: comparator (type): standard therapy
- Concomitant therapy: antivirals, antibiotics, steroids, human Ig, Chinese herbal medicines, interferon
- Duration of follow-up: 28 days
- Treatment cross-overs: none
- Compliance with assigned treatment: 1 participant in control arm received CP, 1 participant in CP arm discontinued study

Outcomes

- Primary study outcome(s): clinical improvement within 28 days (patient discharged alive or reduction of 2 points on a 6-point disease severity scale)
- Primary review outcomes
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported

Li 2020 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: reported
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: yes
- Additional study outcomes: rate of viral PCR to negative at up to 72 h

Notes

- Sponsor/funding: this work was supported by the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS) grants 2020-I2M-CoV19-006, 2016-I2M-3-024 (Dr Z. Liu), and 2017-I2M-1-009 (Dr L. Li) and the Nonprofit Central Research Institute Fund of Chinese Academy of Medical Sciences grant 2018PT32016 (Dr Z. Liu)
- COIs: Dr Liu reports holding a pending patent on COVID-19 testing. Dr Wu reports consulting for Verax Medical and Grifols, receiving royalties from UptoDate and AABB, and being a volunteer visiting professor and receiving travel support for giving medical education from the Chinese Institute of Blood Transfusion. No other disclosures were reported.
- Other: nil

Liu 2020
Study characteristics

Methods

- Trial design: matched control study
- Type of publication: preprint
- Setting: hospitalised patients
- Recruitment dates: 24 March 2020-8 April 2020
- Country: USA
- Language: English
- Number of centres: 1
- Trial registration number: NR
- Date of trial registration: NR

Participants

- Age: 55 (\pm 13) years
- Gender: 2/3rd male, 1/3rd female
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 45 recruited, 39 allocated and evaluated (matched retrospectively to controls)
- Severity of disease: severe or life-threatening disease and consented to therapy
- Comorbidities: 21 (54%) obese, 7 (18%) current or former history of tobacco use, 1 (3%) participant had end-stage renal disease requiring peritoneal dialysis, asthma in 3 (8%), cancer in 2 (5%), COPD in 1 (3%), diabetes in 8 (21%), OSA in 2 (5%)
- Inclusion criteria: severe or life-threatening disease and consented to therapy
- Exclusion criteria: NR improvement of disease (4 of the 45 recruited patients did not receive plasma transfusion because they improved)

Liu 2020 (Continued)

- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): azithromycin, broad-spectrum antibiotics, hydroxychloroquine, therapeutic anticoagulants, corticosteroids, directly acting antivirals, stem cells, and interleukin 1 and interleukin 6 inhibitors

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: plasmapheresis ABO-matched
 - * Volume: 250 mL each dose (500 mL total)
 - * Number of doses: 2, each unit infused over 1 to 2 h
 - * Type of antibody test(s) and antibody-titre(s): 2-step Spike protein-directed ELISA, anti-spike antibody titre of $\geq 1:320$ dilution
 - * Pathogen inactivated: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody-negative: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
 - * RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severe to life-threatening disease, median time between admission and transfusion was 4 (1 to 7) days
- Comparator: propensity score-matched cohort from the same hospital and calendar period matching was performed on the following variables: administration of hydroxychloroquine and azithromycin, intubation status and duration, length of hospital stay, oxygen requirement on the day of transfusion; control patients were matched to plasma recipients by length of stay prior to transfusion
- Concomitant therapy: azithromycin, broad-spectrum antibiotics, hydroxychloroquine, therapeutic anticoagulants, corticosteroids, directly acting antivirals, stem cells, and interleukin 1 and interleukin 6 inhibitors, oxygen therapy (87%), mechanical ventilation (10%), 69.2% were receiving high-flow oxygen
- Duration of follow-up: median follow-up time was 11 (1 to 28) days for the plasma group and 9 (0 to 31) 186 days for the control group
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome(s): supplemental oxygen requirements
- Primary review outcomes
 - * All-cause mortality at hospital discharge: reported (survival at 3 time points: days 1, 7, and 14 post-transfusion)
 - * Time to death: reported
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): reported; assessed every 15 minutes after transfusion
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: reported (supplemental oxygen requirements three time points: days 1, 7, and 14 post-transfusion)
 - * 30-day and 90-day mortality: NR (survival at 3 time points: days 1, 7, and 14 post-transfusion)
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR
- Additional study outcomes: none

Liu 2020 (Continued)

- Notes
- Sponsor/funding: Dr. Krammer reports that patent applications have been filed for the assay used to select plasma donors, and Mount Sinai has licensed its use to several companies. Dr. Aberg reports grants and personal fees from Gilead, grants and personal fees from Merck, grants and personal fees from Janssen, personal fees from Theratech, personal fees from Medicure, grants from Regeneron, grants and personal fees from Viiv, outside the submitted work. No external funding
 - COIs: all other study authors have nothing to disclose
 - Other: all necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.

Madariaga 2020

Study characteristics

- Methods
- Trial design: single-arm study
 - Type of publication: journal publication, preprint
 - Setting: hospitalised severe/life-threatening patients
 - Recruitment dates: 10 April 2020
 - Country: USA
 - Language: English
 - Number of centres: 1
 - Trial registration number: NCT04340050
 - Date of trial registration: 9 April 2020
- Participants
- Age: 9.6 (range 19-75)
 - Gender: 27% were female
 - Ethnicity: NR
 - Number of participants (recruited/allocated/evaluated): 10
 - Severity of disease: severe or life-threatening
 - Comorbidities: 1 participant had undergone bilateral lung transplantation for cystic fibrosis (R8), 1 participant had undergone stem cell transplant for myelodysplastic syndrome (R7) and 1 participant had end-stage renal disease on chronic haemodialysis (R10)
 - Inclusion criteria:
 - * Participants must be ≥ 18 years
 - * Must have laboratory-confirmed COVID-19
 - * Must have severe or immediately life-threatening COVID-19
 - Severe defined as dyspnoea, respiratory frequency ≥ 30 /min, blood oxygen saturation $\leq 93\%$, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 , and/or lung infiltrates $> 50\%$ within 24-48 h
 - Life-threatening defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure. Lower priority should be given to participants with septic shock or multiple organ dysfunction or failure since their disease may have progressed to a point where they are not able to benefit from CP therapy.
 - * Must be < 21 days from the start of illness
 - * Patient is willing and able to provide written informed consent and comply with all protocol requirements. If the patient is not able to consent, we will obtain consent from the power of attorney or a healthcare proxy for the patient as determined by the Illinois Healthcare Surrogate Act
 - * Patient, power of attorney or healthcare proxy agrees to storage of specimens for future testing
 - * Of note, eIND application for each recipient participant will need to be approved before administration of CP

Madariaga 2020 (Continued)

- Exclusion criteria:
 - * Women with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period
 - * Receipt of pooled immunoglobulin in past 30 days
 - * Contraindication to transfusion or history of prior reactions to transfusion blood products
 - * Patients currently enrolled in other drug trials that preclude investigational treatment with anti-SARS-CoV-2 CP
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): 2 recipients were on venovenous ECMO, 1 was mechanically ventilated, one was on high-flow nasal cannula and the remainder were on nasal cannula or room air. 5 had received anti-viral or anti-inflammatory treatments and 2 were immunosuppressed after lung and stem cell transplantation

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP
 - * Type of plasma: CP, age ≥ 18
 - * Volume: 300 mL
 - * Number of doses: 1
 - * Antibody test and antibody-titre: variable levels of anti-receptor binding domain (range 1:73-1:3892) and anti-spike (range 1:69-1:2921) antibody titre
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: yes
- Details of donors
 - * Gender: both, non pregnant women only
 - * HLA and HNA antibody-negative: NR
 - * Severity of disease: severe or life-threatening COVID-19 as defined by the USFDA
 - * Timing from recovery from disease: within 21 days from the start of illness and severe or life-threatening COVID-19 as defined by the USFDA
 - * RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severe or life-threatening
- For studies including a control group: comparator (type): not applicable
- Concomitant therapy: 2 recipients were on venovenous ECMO, 1 was mechanically ventilated, 1 was on high-flow nasal cannula and the remainder were on nasal cannula or room air. 5 had received anti-viral or anti-inflammatory treatments and 2 were immunosuppressed after lung and stem cell transplantation
- Duration of follow-up: 15 days
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: good

Outcomes

- Primary study outcome(s): feasibility and response
- Primary review outcomes
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported

Madariaga 2020 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): none
 - * Number of participants with SAEs: none
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: reported
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: nasopharyngeal SARS-CoV-2 at day 0, 1, 3, 7, 14 from transfusion, levels of anti-receptor binding domain (anti-RBD) and anti-spike antibodies were measured by ELISA in blood samples taken from plasma donors and plasma recipients
- Additional study outcomes: SOFA score, temperature, CRP

Notes

- Sponsor/funding: University of Chicago
- COIs: all study authors declare no competing interests
- Other: nil

Olivares-Gazca 2020
Study characteristics

Methods

- Trial design: pilot study, prospective, longitudinal, single-arm, and quasi-experimental
- Type of publication: journal publication
- Setting: hospitalised severe patients
- Recruitment dates:
- Country: Mexico
- Language: English
- Number of centres: 3
- Trial registration number: NCT04357106
- Date of trial registration: 22 April 2020

Participants

- Age: median age of 53 years (range 27-72)
- Gender: 2 female, 8 male
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 10
- Severity of disease: severe
- Comorbidities: diabetes, hypertension, obesity
- Inclusion criteria:
 - * severe pneumonia with rapid progression
 - * $\text{PaO}_2/\text{FiO}_2 < 300$, with or without mechanical ventilation support
 - * admitted to the ICU
 - * age > 18 years
 - * willing to participate and having signed the informed consent form – either participants or first-degree relatives
- Exclusion criteria:
 - * Patients treated with the following medications: azithromycin, ritonavir/lopinavir, remdesivir, interferons, ruxolitinib, tocilizumab (however, some included in final study)
 - * Patients with severe kidney failure who require replacement therapy

Olivares-Gazca 2020 (Continued)

	<ul style="list-style-type: none"> • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): steroids; hydroxychloroquine; azithromycin; tocilizumab; lopinavir/ritonavir, oxygen therapy, ventilation
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP therapy • Details of CP <ul style="list-style-type: none"> * Type of plasma: ABO-matched, apheresis procedures were conducted in all donors with an Amicus machine (Fresenius Kabi, Deerfield, IL, USA) or a Spectra Optia machine (Terumo BCT, Lakewood, CO, USA) and following the Spin-Nebraska protocol * Volume: 200 mL, the mandatory pre-donation tests in Mexico were also required to be negative and included: hepatitis B virus, hepatitis C virus, HIV, <i>Brucella</i> sp., and syphilis * Number of doses: 1 * Antibody test and antibody-titre: immunoglobulin G (IgG) and IgM anti-coronavirus antibodies were determined by rapid lateral flow immunoassay * Pathogen inactivated or not: NR * RT-PCR tested: RT-PCR of the upper respiratory tract secretions obtained by swab test, positive at diagnosis • Details of donors <ul style="list-style-type: none"> * Gender: both * HLA and HNA antibody-negative: NR * Severity of disease: NR * Timing from recovery from disease: negative RT-PCR test 10 days after the disappearance of symptoms of the disease, performed twice with a difference of 24 h * RT-PCR tested: RT-PCR of the upper respiratory tract secretions obtained by swab test, positive at diagnosis • Treatment details, including time of plasma therapy (e.g. early stage of disease): severe • For studies including a control group: comparator (type): not applicable • Concomitant therapy: steroids; hydroxychloroquine; azithromycin; tocilizumab; lopinavir/ritonavir, oxygen therapy, ventilation • Duration of follow-up: 8 days • Treatment cross-overs: not applicable • Compliance with assigned treatment: good
Outcomes	<ul style="list-style-type: none"> • Primary study outcome(s): safety and clinical outcomes • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: reported (2 deaths) * Time to death: reported • Secondary review outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): none * Number of participants with SAEs: none * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: reported * 30-day and 90-day mortality: reported * Admission on the ICU: yes (all admitted at baseline) * Length of stay on the ICU: reported * Time to discharge from hospital: NR * QoL: NR * Virological response: NR • Additional study outcomes: body temperature, PaO₂/FiO₂, sequential organ failure assessment (SOFA) score, complete blood cell count, liver and kidney function tests, C-reactive protein (CRP), D-dimer, and chest imaging studies.
Notes	<ul style="list-style-type: none"> • Sponsor/funding: this study was funded by the <i>Consejo de Ciencia y Tecnología del Estado de Puebla</i> (CONCYTEP).

Olivares-Gazca 2020 (Continued)

- COIs: all study authors declare no competing interests
- Other: nil

Perotti 2020
Study characteristics

Methods	<ul style="list-style-type: none"> • Trial design: single-arm, open-label • Type of publication: preprint • Setting: hospital • Recruitment dates: 25 March 2020-21 April 2020 • Country: Italy • Language: English • Number of centres: 3 • Trial registration number: NCT 04321421 • Date of registration: 25 March 2020
Participants	<ul style="list-style-type: none"> • Age: mean 63 years (SD 12) • Gender: 28 male (61%), 18 female (39%) • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): planned sample size: 49, recruited: 46 • Severity of disease: moderate to severe • Comorbidities: 19 (41%) had ≥ 2 comorbidities, including diabetes, hypertension, cancer • Inclusion criteria: <ul style="list-style-type: none"> * Age ≥ 18 years * Positive SARS-CoV-2 RT-PCR on nasal swab or deep respiratory sample * Moderate-severe ARDS for ≤ 10 days as per Berlin definition * Increase in the PCR value of approximately 3.5 times the upper reference limit or above 1.8 mg/dL * Need for mechanical ventilation and/or CPAP * Patients who signed the informed consent. If there is no possibility of obtaining informed consent for the clinical condition (e.g. patients sedated and treated for acute respiratory failure and consequent mechanical ventilation), the patient's consent will be assumed until manifestly stated otherwise. • Exclusion criteria: <ul style="list-style-type: none"> * Diagnosis of moderate-severe ARDS >10 days * Proven hypersensitivity or allergic reaction to blood products or immunoglobulin * Manifest willingness to participate • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): antibiotics (84%), hydroxychloroquine (86%), antivirals (42%), anticoagulants (98%), oxygen therapy (CPAP (70%), intubation (16%), high-flow (12%), low-flow (2%))
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP therapy • Details of CP <ul style="list-style-type: none"> * Type of plasma: plasma collection was performed with the latest generation cell separator (Trima Accel – Terumo BCT and Amicus – Fresenius Kabi) devices. A plasma volume of about 660 mL was collected during each procedure and immediately equally divided into 2 bags using a sterile tubing welder. The collected units were stored at a controlled temperature ranging from -40 to -25 °C. ABO-compatible * Volume: approx 330 mL * Number of doses: up to 3 over 5 days (1 (49%), 2 (49%), 3 (2%)) * Antibody test and antibody-titre: 1:80-1:640. Neutralising antibodies (NT-Abs) titres against SARS-CoV2 was defined according to the following protocol. Briefly, 50 μL of sample from each patient, starting from 1:10 in a serial fourfold dilution series, were added in two wells of a flat bottom tis-

Perotti 2020 (Continued)

sue culture micro titre plate (COSTAR, Corning Incorporated, NY 14831, USA), mixed with an equal volume of 50 TCID₅₀ of a SARS-CoV-2 strain isolated from a symptomatic patient. Neutralising titre was the maximum dilution with the reduction of 90% of CPE. A positive titre was $\geq 1/10$. Positive and negative controls were included in all tests run.

- * Pathogen inactivated or not: yes, by INTERCEPT processing system (Cerus Europe BV) or the Mirasol PRT System (Terumo BCT, Lakewood, CO, USA)
- * RT-PCR tested: negative novel coronavirus nucleic acid test
- Details of donors
 - * Gender: both, females with no previous pregnancy included, age ≥ 18
 - * HLA and HNA antibody-negative: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: 2 consecutive negative nasopharyngeal swabs performed 7-30 days before
 - * RT-PCR tested: 2 consecutive negative nasopharyngeal swabs performed 7-30 days before tested by RT-PCR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): moderate to severe
- For studies including a control group: comparator (type): not applicable
- Concomitant therapy: antibiotics (84%), hydroxychloroquine (86%), antivirals (42%), anticoagulants (98%), oxygen therapy (CPAP; 70%), intubation (16%), high-flow (12%), low-flow (2%)
- Duration of follow-up: 7 days
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: good

Outcomes

- Primary study outcome: 7-day mortality
- Primary review outcomes
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: reported
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR
- Additional study outcomes: laboratory parameters (CRP, ferritin, LDH, viral load), radiological changes (chest X-ray)

Notes

- Sponsor/funding: no funding received
- COIs: all study authors declare no competing interests
- Other: nil

Rasheed 2020
Study characteristics

Methods

- Trial design: interventional study with matched control group
- Type of publication: journal, preprint server

Rasheed 2020 (Continued)

- Setting: hospitalised patients
- Recruitment dates: 3 April 2020-1 June 2020
- Country: Iraq
- Language: English
- Number of centres: 1
- Trial registration number: [NCT04441424](#)
- Date of trial registration: 22 June 2020

Participants

- Age: mean 47.82 years in control group, mean 55.67 years in CP group
- Gender: CP group consisted of 57.1% men and 42.86% women
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 49 (21 received CP, 28 in control group)
- Severity of disease: hospitalised patients, early stage critically ill patients in RCU
- Comorbidities: NR
- Inclusion criteria:
 - * 49 critically-ill COVID-19 patients included
 - * All had pneumonia and resided in RCU
 - * Age \geq 18 years
 - * With dyspnoea and oxygen saturation $<$ 90% in resting state
 - * At their first 3 days in RCU either receiving O₂ therapy, CPAP, or on ventilators
 - * All participants were residing in infectious diseases wards before being transferred to RCU
- Exclusion criteria:
 - * Previous allergic history to plasma or its ingredients such as sodium citrate
 - * Cases with serious general conditions, such as severe organ dysfunction, that are not suitable for transfusion
 - * Very late stage ARDS where CP has proved to be of low therapeutic benefit
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): standard therapy including oxygen therapy, ventilation; azithromycin, hydroxychloroquine

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: NR
 - * Volume: 400 mL
 - * Number of doses: 1
 - * Type of antibody test(s) and antibody-titre(s): a rapid immunochromatographic test, COVID-19 IgG/IgM test was used to screen the donors and the recipients for the presence of anti-SARS-CoV-2 IgM antibodies. SARS-CoV-2 IgG index $>$ 1, the donors with IgG index \geq 1.25 were selected
 - SARS-CoV-2 IgG antibody ELISA kit DEIASL019 (Creative Diagnostics, USA) and rapid test COVID-19 IgG/IgM test (Biozek, Netherlands)
 - * Pathogen inactivated: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: both, age $<$ 50 years
 - * HLA and HNA antibody-negative: NR (pregnant women excluded)
 - * Severity of disease: moderate
 - * Timing from recovery from disease: NR
 - * RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients (early stage of critically ill patients, within first 3 days in RCU either receiving O₂ therapy or on ventilators)
- Comparator: hospitalised patients (early stage of critically ill patients, within first 3 days in RCU either receiving O₂ therapy or on ventilators.) The CP group was compared to the age- and sex- matched control group in terms of recovery time from critical illness (RTCI), days of infection before inclusion to the study, and the whole duration of infection.

Rasheed 2020 (Continued)

- Concomitant therapy: standard therapy (including hydroxychloroquine and azithromycin)
- Duration of follow-up: up to 8 weeks, safety observed for 3 h
- Treatment cross-overs: nil
- Compliance with assigned treatment: good

Outcomes

- Primary study outcome(s): safety, duration of viral shedding, mortality
- Primary review outcomes
 - * All-cause mortality at hospital discharge: reported (8% in control group to only 4.8% in CP group)
 - * Time to death: reported
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): none
 - * Number of participants with SAEs: none
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: recovery time from critical illness in CP group, 4.52 ± 2.3 days, was lower than that in control group, 8.45 ± 1.8 days
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: reported (SARS-CoV-2 RT-PCR by nasopharyngeal swabs at days 2, 3, 5, SARS-CoV-2 antibody levels by using SARS-CoV-2 IgG antibody ELISA kit DEIASL019 at days 0, 3)
- Additional study outcomes: nil

Notes

- Sponsor/funding: Alkarkh Health Directorate-Baghdad
- COIs: the study authors have no potential conflicts of interest to disclose
- Other: nil

Salazar 2020a
Study characteristics

Methods

- Trial design: prospective, propensity score-matched study
- Type of publication: journal article
- Setting: hospitalised patients
- Recruitment dates: 28 March 2020-6 July 2020
- Country: USA
- Language: English
- Number of centres: 1
- Trial registration number: IND
- Date of trial registration: NR

Participants

- Age: < 30 to > 80
- Gender: male 136 (60.7%), female, 88 (39.3%) for secondary matched participants transfused within 72 h; male 39 (42.4), female 53 (57.6%) for secondary matched participants transfused after 72 h
- Ethnicity: white, black, Asian, Hispanic, unknown
- Number of participants (recruited/allocated/evaluated): 316 participants transfused, of these 136 analysed for primary outcome and compared to 251 controls
- Severity of disease: severe and/or life-threatening COVID-19 disease

Salazar 2020a (Continued)

- Comorbidities: COPD, chronic kidney disease, hyperlipidaemia, coronary disease, hypertension, diabetes
- Inclusion criteria: severe and/or life-threatening COVID-19 disease
 - * Severe disease was defined as one or more of the following: shortness of breath (dyspnoea), respiratory rate ≥ 30 /min, blood oxygen saturation $\leq 93\%$ (on room air), PaO₂:FiO₂ ratio < 300 , and/or pulmonary infiltrates $> 50\%$ within 24-48 h (of screening assessment)
 - * Life-threatening disease was defined as one or more of the following: respiratory failure, septic shock, and/or multiple organ dysfunction or failure
- Exclusion criteria: history of prior severe reactions to transfusion of blood products with imputability of probable or definite, as defined by the CDC NHSN Hemovigilance Module26; they had underlying uncompensated and untreated end-stage disease; and/or patients had fluid overload or other condition that would contraindicate administration of plasma.
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): standard therapy including oxygen therapy, ventilation, ECMO, steroids, azithromycin, tocilizumab, antivirals

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: NR
 - * Volume: NR
 - * Number of doses: 1-2
 - * Type of antibody test(s) and antibody-titre(s): anti-RBD IgG titre. For first unit of CP, anti-RBD IgG titre of $\geq 1:1350$ (284/316; 90%); 22 participants received an initial or sole unit of CP with an anti-RBD IgG titre $> 1:150$ but $< 1:1350$
 - * Pathogen inactivated: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: both
 - * HLA and HNA antibody-negative: donors were documented to be negative for anti-HLA antibodies
 - * Severity of disease: NR
 - * Timing from recovery from disease: asymptomatic for > 14 days
 - * RT-PCR tested: tested negative for SARS-CoV-2 at the time of plasmapheresis
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severe/life-threatening disease
- Comparator: standard of care
- Concomitant therapy: standard therapy including oxygen therapy, ventilation, ECMO, steroids, azithromycin, tocilizumab, antivirals
- Duration of follow-up: 28 days
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome(s): 28-day mortality
- Primary review outcomes
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: reported

Salazar 2020a (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: reported
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR
- Additional study outcomes: inflammatory markers, D dimer, fibrinogen, CRP, ferritin

Notes

- Sponsor/funding: this study was supported by the Fondren Foundation, Houston Methodist Hospital and Research Institute (to JMM)
- COIs: ES is the local principal investigator for a clinical trial sponsored by Regeneron assessing an investigational therapy for COVID-19
- Other: nil

Xia 2020

Study characteristics

Methods

- Trial design: retrospective, matched, controlled study
- Type of publication: journal article
- Setting: hospitalised patients
- Recruitment dates: 4 February 2020-30 March 2020
- Country: China
- Language: English
- Number of centres: 1
- Trial registration number: NR
- Date of trial registration: NR

Participants

- Age: median 63 (54-71) years
- Gender: male 50.8%, female 49.2%
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 1568 (138 received CP, 1430 in control group)
- Severity of disease: hospitalised patients, severe/critically ill
- Comorbidities: hypertension, diabetes, cardiovascular disease, cerebrovascular disease, malignancy, COPD, chronic kidney disease, chronic liver disease, immunodeficiency
- Inclusion criteria: hospitalised patients
- Exclusion criteria: NR
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): standard therapy including oxygen therapy, ventilation, ECMO

Interventions

- Intervention(s): CP therapy

Xia 2020 (Continued)

- Details of CP:
 - * Type of plasma: NR
 - * Volume: 200-1200 mL
 - * Number of doses: NR
 - * Type of antibody test(s) and antibody-titre(s): NR
 - * Pathogen inactivated: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody-negative: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
 - * RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients (severe/critically ill)
- Comparator: hospitalised patients (severe/critically ill)
- Concomitant therapy: standard therapy
- Duration of follow-up: up to 20 April
- Treatment cross-overs: nil
- Compliance with assigned treatment: not applicable

Outcomes

- Primary study outcome(s): NR
- Primary review outcomes
 - * All-cause mortality at hospital discharge: 3 participants (2.2%) died in the CP group up to 20 April, reducing approximately 50% of the mortality rate when compared to that in the standard-treatment group (4.1%)
 - * Time to death: reported
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): none
 - * Number of participants with SAEs: none
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: 126 non-ICU patients before CCP therapy, 3 patients (2.4%) were admitted to ICU, as compared to 72 out of 1,403 (5.1%) ICU admissions in the standard-treatment group
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: reported (SARS-CoV-2 viral load of nasopharyngeal swabs, SARS-CoV-2 antibody levels)
- Additional study outcomes: lymphocyte count, routine blood and biochemistry examinations, CRP, lactate dehydrogenase (LDH), type B natriuretic peptide (BNP), urea nitrogen, procalcitonin, and glucose

Notes

- Sponsor/funding: nil reported
- COIs: the study authors have no potential conflicts of interest to disclose
- Other: nil

Zeng 2020

Study characteristics

Methods	<ul style="list-style-type: none"> • Trial design: retrospective matched controlled study • Type of publication: journal online, ahead of print • Setting: ICU • Recruitment dates: NR • Country: China • Language: English • Number of centres: 2 • Trial registration number: NR • Date of trial registration: NR
Participants	<ul style="list-style-type: none"> • Age: median 61.5 years in CP group, median 73 years in control group • Gender: 5 male, 1 female in CP group; 11 males, 4 females in control group • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 21 (6 received CP, 15 in control group) • Severity of disease: critical (admitted to ICU) • Comorbidities: pregnancy, diabetes, hypertension, cardiovascular disease (CP group) • Inclusion criteria: critically ill patients • Exclusion criteria: NR • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): antibiotics (100%), antiviral therapy (67%), traditional Chinese medicine (50%), IVIG (83%), steroid therapy (67%), high-flow oxygen therapy (100%), mechanical ventilation (83%), renal replacement therapy (33%), ECMO (67%) in the CP group
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: median 300 mL (range 200-600 mL) * Number of doses: 1-2 * Type of antibody test(s) and antibody-titre(s): Gold immunochromatography for SARS-CoV-2 IgM and IgG tests were performed using blood sample (New Coronavirus [2019-nCoV] Antibody Detection Kit, Shanghai Outdo Biotech and Tangshan Innovita Biotech). * Pathogen inactivated: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody-negative: NR * Severity of disease: NR * Timing from recovery from disease: NR * RT-PCR tested: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): critically ill patients • Comparator: Not applicable • Concomitant therapy: antibiotics (100%), antiviral therapy (67%), traditional Chinese medicine (50%), IVIG (83%), steroid therapy (67%), high-flow oxygen therapy (100%), mechanical ventilation (83%), renal replacement therapy (33%), ECMO (67%) in the CP group. Unclear whether these treatments were stopped before plasma transfusion or continuously given • Duration of follow-up: NR • Treatment cross-overs: Not applicable • Compliance with assigned treatment: good (all compliant)
Outcomes	<ul style="list-style-type: none"> • Primary study outcome(s): survival

Zeng 2020 (Continued)

- Primary review outcomes
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): none
 - * Number of participants with SAEs: none
 - * Improvement of clinical symptoms, assessed with or convertible to the WHO Clinical Progression Scale (WHO 2020e) at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: reported (all admitted)
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: reported (1 discharged)
 - * QoL: NR
 - * Virological response: yes
- Additional study outcomes: duration of viral shedding

Notes

- Sponsor/funding: supported by The National Natural Science Foundation of China (No. 81970517), Zhongyuan (Henan) Thousands Outstanding Talents Plan (No. ZYQR201912179), Foundation for Distinguished Young Talents of Zhengzhou University Medical School (No.2020ZQLMS), and The Key Scientific Research Project of Henan Higher Education Institutions of China (No. 20B320028).
- COIs: the authors have no potential conflicts of interest to disclose.
- Other: written informed consents were obtained from all the family members of patients who received plasma.

AE: adverse event; **ALT:** alanine transaminase; **ARDS:** acute respiratory distress syndrome; **AST:** aspartate transaminase; **BAL:** bronchoalveolar lavage; **BAT:** best available therapy; **BMI:** body mass index; **CDC:** Centers for Disease Control and Prevention; **COI:** conflict of interest; **COPD:** chronic obstructive pulmonary disease; **CP:** convalescent plasma; **CPAP:** continuous positive airway pressure; **CPK:** creatine phosphokinase; **CRP:** C-reactive protein; **CT:** computed tomography; **DFPP:** double-filtration plasmapheresis; **DSMB:** Data and Safety Monitoring Board; **DVT:** deep vein thrombosis; **ECMO:** extracorporeal membrane oxygenation; **ED:** emergency department; **ELISA:** enzyme-linked immunosorbent assay; **FDA:** US Food and Drug Administration; **FiO2:** fractional inspired oxygen; **GFR:** glomerular filtration rate; **HBV/HCV:** hepatitis B/C; **HCPOA:** healthcare power of attorney; **HLA:** human leukocyte antigen; **HNA:** human neutrophil antigens; **ICU:** intensive care unit; **IgA (B/G/M):** immunoglobulin A (B/G/M); **IL-6:** interleukin-6; **IQR:** interquartile range; **IV:** intravenous; **IVIG:** intravenous immunoglobulin; **LAR:** legal authorised representative; **LDH:** lactate dehydrogenase; **NR:** not reported; **NYHA:** New York Heart Association; **PaO2:** arterial blood oxygen partial pressure; **PCR:** polymerase chain reaction; **PE:** pulmonary embolism; **PRNT:** plaque reduction neutralisation test; **QoL:** quality of life; **RCT:** randomised controlled trial; **RCU:** respiratory care unit; **RNA:** ribonucleic acid; **RT-PCR:** reverse transcription polymerase chain reaction; **SAE:** serious adverse event; **SARS:** severe acute respiratory syndrome; **SC:** subcutaneous; **SOFA:** Sequential Organ Failure Assessment; **SpO2:** peripheral capillary oxygen saturation; **TACO:** transfusion-associated circulatory overload; **TAD:** transfusion-associated dyspnoea; **TB:** tuberculosis; **TRALI:** transfusion-related acute lung injury; **TTP:** thrombotic thrombocytopenic purpura; **UIP:** usual interstitial pneumonia; **ULN:** upper limit of normal; **WBC:** white blood count; **WHO:** World Health Organization

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ahn 2020	Single-arm study; not pre-registered in a clinical study registry
Anderson 2020	Single-arm study; not pre-registered in a clinical study registry
Bao 2020b	Single-arm study; not pre-registered in a clinical study registry
Bobek 2020	Single-arm study; not pre-registered in a clinical study registry

Study	Reason for exclusion
Brasil Ministerio 2020	Standard operating procedure
Budhai 2020	Feasibility of plasma collection only
Cantore 2020	Single-arm study compared to published cases; not pre-registered in a clinical study registry
Cao 2020a	Ineligible intervention
Chen 2020b	Ineligible intervention
Chen 2020c	Ineligible intervention
ChiCTR2000030312	Study cancelled before starting recruitment
ChiCTR2000030381	Study cancelled before starting recruitment
ChiCTR2000030442	Study cancelled before starting recruitment
Clark 2020	Single-arm study; not pre-registered in a clinical study registry
de Assis 2020	Ineligible indication
Díez 2020	Ineligible intervention
Enzmann 2020	Single-arm study; not pre-registered in a clinical study registry
Erkurt 2020	Single-arm study; not pre-registered in a clinical study registry
Fan 2020	Single-arm study; not pre-registered in a clinical study registry
Figlerowicz 2020	Single-arm study; not pre-registered in a clinical study registry
Franchini 2020	Standard operating procedure
Grisolia 2020	Single-arm study; not pre-registered in a clinical study registry
Hashim 2020	Feasibility of plasma collection only
Hu 2020	Ineligible intervention
Im 2020	Single-arm study; not pre-registered in a clinical study registry
ISRCTN86534580	Ineligible intervention
Jamous 2020	Single-arm study; not pre-registered in a clinical study registry
Jiang 2020a	Single-arm study; not pre-registered in a clinical study registry
Jiang 2020b	Ineligible intervention
Karatras 2020	Single-arm study; not pre-registered in a clinical study registry
Kong 2020	Single-arm study; not pre-registered in a clinical study registry
Lin 2020	Ineligible intervention

Study	Reason for exclusion
Liu 2020a	Single-arm study; not pre-registered in a clinical study registry
Martinez-Resendez 2020	Single-arm study; not pre-registered in a clinical study registry
McCuddy 2020	Single-arm study; not pre-registered in a clinical study registry
Ministerio de Salud 2020	Standard operating procedure
Mira 2020	Single-arm study; not pre-registered in a clinical study registry
NCT04261426	Ineligible intervention
NCT04323800	Ineligible participant population (participants exposed to COVID-19)
NCT04325672	Study cancelled before starting recruitment
NCT04344015	Feasibility of plasma collection only
NCT04344379	Ineligible intervention
NCT04344977	Feasibility of plasma collection only
NCT04350580	Ineligible intervention
NCT04360278	Feasibility of plasma collection only
NCT04368013	Ineligible intervention
Niu 2020	Single-arm study; not pre-registered in a clinical study registry
Pei 2020	Single-arm study; not pre-registered in a clinical study registry
Peng 2020	Single-arm study; not pre-registered in a clinical study registry
Qiu 2020	No use of convalescent plasma. Reporting on generalised collection of information about COVID-19 infection relating to aetiology, pathology, symptoms, clinical presentation and some generalised pharmacological treatment methods. The papers do not contain patient data that we required. Article translated by Rujan Shrestha and Ya-Ying Wang via Cochrane TaskExchange
Robbiani 2020	Ineligible intervention
Salazar 2020b	Single-arm study; not pre-registered in a clinical study registry
Shen 2020	Single-arm study; not pre-registered in a clinical study registry
Shi 2020	Ineligible intervention
Soleimani 2020	Single-arm study; not pre-registered in a clinical study registry
Taher 2020	Single-arm study; not pre-registered in a clinical study registry
Tan 2020	Single-arm study; not pre-registered in a clinical study registry

Study	Reason for exclusion
Tu 2020	No use of convalescent plasma. Reporting on generalised collection of information about COVID-19 infection relating to aetiology, pathology, symptoms, clinical presentation and some generalised pharmacological treatment methods. The papers do not contain patient data that we required. Article translated by Rujan Shrestha and Ya-Ying Wang via Cochrane TaskExchange
Wang 2020	Single-arm study; not pre-registered in a clinical study registry
Wright 2020	Single-arm study; not pre-registered in a clinical study registry
Xie 2020	Ineligible intervention
Xu 2020b	Single-arm study; not pre-registered in a clinical study registry
Yang 2020	Single-arm study; not pre-registered in a clinical study registry
Ye 2020	Single-arm study; not pre-registered in a clinical study registry
Zhang 2020a	Single-arm study; not pre-registered in a clinical study registry
Zhang 2020b	Single-arm study; not pre-registered in a clinical study registry
Zhang 2020c	Single-arm study; not pre-registered in a clinical study registry
Çınar 2020	Single-arm study; not pre-registered in a clinical study registry

Characteristics of studies awaiting classification *[ordered by study ID]*

[Agarwal 2020](#)

Methods	<ul style="list-style-type: none"> • Trial design: RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 22 April 2020-14 July 2020 • Country: India • Language: English • Number of centres: 39 • Trial registration number: CTRI/2020/04/024775 • Date of trial registration: 12 April 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Patients admitted with RT-PCR-confirmed COVID-19 illness * Age > 18 years * Has any of the 2: <ul style="list-style-type: none"> <input type="checkbox"/> PaO₂/FiO₂: 200-300 <input type="checkbox"/> Respiratory rate > 24/min and SaO₂ < 93% on room air * Availability of matched donor plasma at the point of enrolment

Agarwal 2020 (Continued)

- Exclusion criteria
 - * Pregnant or breastfeeding women
 - * Known hypersensitivity to blood products
 - * Receipt of pooled immunoglobulin in last 30 days
 - * Critically ill patients:
 - P/F ratio < 200 (moderate - severe ARDS)
 - Shock
 - * Participating in any other clinical trial
 - * Clinical status precluding infusion of blood product

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - * type of plasma: used from 262 donors (male (94.3%), with mean (SD) age of 34.3 (9.3) years)
 - * volume: 200 mL
 - * number of doses: 2 doses
 - * antibody-titre: median (IQR) titre of 1:40 (1:30 to 1:80)
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): median (IQR) time since symptom onset: 8 (6-11)
- For studies including a control group: comparator (type): randomised 1:1 to CP and standard of care vs standard of care including any drugs that are being used in clinical practice
- Concomitant therapy: standard of care for COVID-19 disease
- Treatment cross-overs: none

Outcomes

- Primary study outcome:
 - * Composite measure of progress to severe disease (PaO₂/FiO₂ ratio < 100) any time within 28 days of enrolment
 - * All-cause mortality at 28 days
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes
 - * Mortality (time to event): NR
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes, transfusion-related AEs only
 - * Number of participants with SAEs: yes (transfusion-related mortality)
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: assessed, but NR
 - * 30-day and 90-day mortality: NR (up to 28 days)
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * Virological response:
 - * QoL: NR

Agarwal 2020 (Continued)

- Additional review outcomes
 - * Time to symptom resolution at 1, 3, 5, 7, and 14 days
 - Fever
 - Shortness of breath
 - Fatigue
 - * Duration of respiratory support required
 - Duration of invasive mechanical ventilation
 - Duration of non-invasive
 - * Change in oxygen requirement post-transfusion, at 0, 1, 3, 5, 7 and 14 days
 - * Change in SOFA pre- and post-transfusion, at 0, 1, 3, 5, 7 and 14 days
 - * Correlation between IgG antibody in donor plasma and recipient plasma after transfusion, at 0, 1, 3 and 7 days
 - * Correlation between viral neutralisation titre and ELISA antibody assay in donor plasma
 - * Length of hospital stay
 - * Levels of bio-markers (CRP, IL6, ferritin) pre- and post-transfusion, at 0 and 3 days
 - * Need of vasopressor use
 - * Pre- and post-transfusion antibody titres (IgG) in recipient plasma, at 0, 3 and 7 days
 - * Radiological improvement, at 0, 3 and 7 days
 - * Change in RNA levels (Ct values) of SARS-CoV-2 from RT-PCR transfusion, at 0, 3 and 7 days

Notes

- Preprint published on 10 September 2020
- Sponsor/funding: this multicentric study was funded by ICMR, an autonomous Government-funded medical research council

Avendano-Sola 2020

Methods

- Trial design: multicentre, RCT
- Sample size: 278 planned, 81 randomised (interim analysis)
- Setting: hospital
- Country: Spain
- Language: English
- Number of centres: 9
- Trial registration: [NCT04345523](https://www.clinicaltrials.gov/ct2/show/study/NCT04345523)

Participants

- Inclusion criteria
 - * Written informed consent prior to performing study procedures. Witnessed oral consent will be accepted in order to avoid paper handling. Written consent by participant or representatives will be obtained as soon as possible
 - * Male or female adult patient ≥ 18 years of age at time of enrolment
 - * Laboratory-confirmed SARS-CoV-2 infection as determined by PCR in naso/oropharyngeal swabs or any other relevant specimen
 - * Patients requiring hospitalisation for COVID-19 without mechanical ventilation (invasive or non-invasive) or high-flow oxygen devices and at least 1 of the following:
 - radiographic evidence of pulmonary infiltrates by imaging (chest X-ray, CT scan, etc.), or
 - clinical assessment (evidence of rales/crackles on exam) and SpO₂ $\leq 94\%$ on room air that requires supplemental oxygen
 - * Not > 12 days between the onset of symptoms (fever or cough) and treatment administration day

Avendano-Sola 2020 (Continued)

- Exclusion criteria
 - * Requiring mechanical ventilation (invasive or non-invasive) or high-flow oxygen devices
 - * > 12 days since symptoms (fever or cough)
 - * Participation in any other clinical trial of an experimental treatment for COVID-19
 - * In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 h, irrespective of the provision of treatments
 - * Any incompatibility or allergy to the administration of human plasma
 - * Stage 4 severe chronic kidney disease or requiring dialysis (i.e. estimated GFR < 30)

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - * type of plasma: prepared approximately 140-200 CP donors
 - * volume: NR
 - * number of doses: NR
 - * antibody-titre: NR
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage within 12 days
- For studies including a control group: comparator (type): randomised 1:1 to CP and standard of care vs standard of care including any drugs that are being used in clinical practice (e.g. lopinavir/ritonavir; darunavir/cobicistat; hydroxy/chloroquine, tocilizumab, etc.), other than those used as part of another clinical trial
- Concomitant therapy: standard of care as specified above
- Treatment cross-overs: none

Outcomes

- Primary study outcome: category changes in ordinal scale (time frame: 15 days) (for categories: see additional outcomes)
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes
 - mortality of any cause at 15 days (time frame: 15 days)
 - mortality of any cause at 29 days (time frame: 29 days)
 - * Time to death: yes (up to 29 days)
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: NR (up to 29 days)
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR

Avendano-Sola 2020 (Continued)

- Additional review outcomes
 - * Category changes in ordinal scale (time frame: 15 days)
 - proportion of participants in categories 5, 6 or 7 of the 7-point ordinal scale at day 15 ordinal scale:
 - not hospitalised, no limitations on activities
 - not hospitalised, limitation on activities
 - hospitalised, not requiring supplemental oxygen
 - hospitalised, requiring supplemental oxygen
 - hospitalised, on non-invasive ventilation or high-flow oxygen devices
 - hospitalised, on invasive mechanical ventilation or ECMO
 - death
 - * Time to category 5, 6 or 7 of the ordinal scale (time frame: 29 days)
 - time to change from baseline category to worsening into 5, 6 or 7 categories of the ordinal scale
 - * Oxygenation-free days (time frame: 29 days)
 - * Ventilator-free days
 - * Change in biological parameters (time frame: days 1, 3, 5, 8, 11 and 29) - serum levels of CRP, lymphocyte count, LDH, D Dimer, IL-6, coagulation tests at baseline and days 3, 5, 8, 11, 15 and 29
 - * Antibodies levels in CP donors recovered from COVID-19 (time frame: 3 months)
 - quantitative total antibodies and neutralising antibody activity against SARS-CoV-2 in the sera from donors and participants using viral pseudotypes
 - * Viral load (time frame: days 1, 3, 5, 8, 11 and 29)
 - change in PCR for SARS-CoV-2 in naso/oropharyngeal swabs and blood at baseline and on days 3, 5, 8, 11 (while hospitalised); and days 15 and 29 (if able to return to clinic or still hospitalised)

Notes

- Interim analysis after randomisation of 81 participants
- First published: 1 September 2020
- Sponsor/funding: "This research is funded by the Government of Spain, Ministry of Science and Innovation, Instituto de Salud Carlos III, grant number COV20/00072 (Royal Decree-Law 8/2020, of 17 March, on urgent extraordinary measures to deal with the economic and social impact of COVID-19), co-financed by the European Regional Development Fund (FEDER) A way to make Europe."

CTRI/2020/04/024706

Methods	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Participants	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Interventions	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Outcomes	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Notes	

CTRI/2020/04/024804

Methods	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Participants	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Interventions	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Outcomes	no information available, as the study register was not available
Notes	

CTRI/2020/04/024915

Methods	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Participants	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Interventions	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Outcomes	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Notes	

CTRI/2020/05/025209

Methods	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Participants	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Interventions	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Outcomes	
Notes	

CTRI/2020/05/025299

Methods	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
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CTRI/2020/05/025299 *(Continued)*

Participants	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Interventions	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Outcomes	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Notes	

CTRI/2020/05/025328

Methods	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Participants	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Interventions	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Outcomes	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Notes	

CTRI/2020/05/025346

Methods	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Participants	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Interventions	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Outcomes	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Notes	

CTRI/2020/06/025803

Methods	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Participants	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)

CTRI/2020/06/025803 (Continued)

Interventions	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Outcomes	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Notes	

CTRI/2020/06/026123

Methods	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Participants	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Interventions	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Outcomes	No information available, as the study register was not available for several days (at least 25 August 2020-28 August 2020)
Notes	

AE: adverse event; **ARDS:** acute respiratory distress syndrome; **C AP:** community-acquired pneumonia; **COPD:** chronic obstructive pulmonary disease; **CP:** convalescent plasma; **CRP:** C-reactive protein; **CT:** computed tomography; **ECMO:** extracorporeal membrane oxygenation; **ELISA:** enzyme-linked immunosorbent assay; **FIO₂:** fractional inspired oxygen; **GFR:** glomerular filtration rate; **HLA:** human leukocyte antigen; **HNA:** human neutrophil antigens; **ICU:** intensive care unit; **IgA (B/G/M):** immunoglobulin A (B/G/M); **IL-6:** interleukin-6; **IQR:** interquartile range; **IV:** intravenous; **LDH:** lactate dehydrogenase; **NR:** not reported; **PaO₂:** arterial blood oxygen partial pressure; **PCR:** polymerase chain reaction; **QoL:** quality of life; **RCT:** randomised controlled trial; **RT-PCR:** reverse transcription polymerase chain reaction; **SAE:** serious adverse event; **SD:** standard deviation; **SOFA:** Sequential Organ Failure Assessment; **TACO:** transfusion-associated circulatory overload; **TAD:** transfusion-associated dyspnoea; **TRALI:** transfusion-related acute lung injury

Characteristics of ongoing studies [ordered by study ID]

ChiCTR2000029850

Study name	Efficacy and safety of convalescent plasma treatment for severe patients with novel coronavirus pneumonia (COVID-19): a prospective cohort study
Methods	<ul style="list-style-type: none"> • Trial design: prospective cohort study, controlled • Sample size: 10 in each arm (20) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Laboratory-confirmed diagnosis of COVID-19 infection by RT-PCR * Aged > 18 years * Written informed consent given by the patient or next-of-kin * Clinical deterioration despite conventional treatment that required intensive care

ChiCTR2000029850 (Continued)

	<ul style="list-style-type: none"> • Exclusion criteria <ul style="list-style-type: none"> * Hypersensitive to immunoglobulin * IgA deficiency
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: NR <ul style="list-style-type: none"> * type of plasma: NR * volume: NR * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): standardised comprehensive treatment • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: fatality rate • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes (fatality rate) * Time to death: NR • Secondary review outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR * 30-day and 90-day mortality: yes * Admission on the ICU: NR * Length of stay on the ICU: yes * Time to discharge from hospital: hospital stay duration * QoL: NR • Additional study outcomes <ul style="list-style-type: none"> * Viral titres in respiratory samples * Incubation period * PaO₂/FiO₂ * Cytokines/chemokines
Starting date	15 February 2020
Contact information	<p>Liang Yu</p> <p>The First Affiliated Hospital of Zhejiang University, State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Disease, 79 Qingchun Road, Shangcheng District, Hangzhou, Zhejiang, 310003, yu-liang@zju.edu.cn</p> <p>Xiaowei Xu</p> <p>79 Qingchun Road, Shangcheng District, Hangzhou, Zhejiang, China, 310003, xxw69@126.com</p>
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 15 February 2022 • Sponsor/funding: The First Affiliated Hospital of Zhejiang University School of Medicine, Key Research and Development Project of Zhejiang Province

ChiCTR2000030010

Study name	A randomized, double-blind, parallel-controlled, trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia patients (COVID-19)
Methods	<ul style="list-style-type: none"> • Trial design: randomised, double-blind, parallel-controlled trial • Sample size: 50 in each arm (100) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Aged 18-70 years old, inpatients, male or female * Patients with severe novel coronavirus infection: according to the "Pneumonitis Diagnosis and Treatment Guideline for the Novel Coronavirus Infection (Trial Version 5)", clinically diagnosed cases (suspected cases with pneumonia imaging features) or suspected cases. Severe patients must also meet any of the following: 1) respiratory distress, respiratory rate ≥ 30 times/min; 2) In the resting state, the oxygen saturation is $\leq 93\%$; 3) $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg (1 mm Hg = 0.133 kPa) * Participants and/or legal guardians of the participants volunteered to participate in the study and voluntarily signed informed consent • Exclusion criteria <ul style="list-style-type: none"> * The clinical classification of patients with severe novel coronavirus infection is to meet any of the following: 1) respiratory failure occurs and requires mechanical ventilation; 2) shock occurs; 3) combined failure of other organs requires ICU monitoring and treatment * Those who are allergic to blood products or plasma components and auxiliary materials (sodium citrate) * There is multiple organ failure, and the estimated survival time is < 3 days * Those who tested positive for HIV antibodies before enrolment * Women who are pregnant or breastfeeding or have a birth plan within the past year * Participants in other clinical trials within 3 months before screening * Poor adherence or other conditions that the study author believes are not suitable for inclusion (such as poor physical condition)
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: Anti-SARS-CoV-2 virus inactivated plasma • Details of CP: <ul style="list-style-type: none"> * type of plasma: NR * volume: NR * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: yes • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): ordinary plasma • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: improvement of clinical symptoms (clinical improvement is defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital) • Primary outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: 14- and 28-day all-cause mortality * Time to death: NR

ChiCTR2000030010 (Continued)

- Secondary outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: 14- and 28-day all-cause mortality
 - * Admission on the ICU
 - * Length of stay on the ICU: ICU hospitalisation days
 - * Time to discharge from hospital
 - * QoL: NR
- Additional study outcomes
 - * Improvement of clinical symptoms (clinical improvement is defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital)
 - * Main clinical manifestations subsided or significantly improved (fever, dry cough, fatigue, etc.)

Starting date	19 February 2020
Contact information	<p>Liu Ying</p> <p>Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital) , 1 Yintan Road, Dongxihu District, Wuhan, Hubei, China , 430023, whsjytyy_gcp@163.com</p> <p>Zhang Dingyu</p> <p>1 Yintan Road, Dongxihu District, Wuhan, Hubei, China, 430023, 1813886398@qq.com</p>
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 31 May 2020 • Sponsor/funding: Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital), Sinopharm Wuhan Blood Products Co., Ltd., Sinopharm Wuhan Blood Products Co., Ltd

ChiCTR2000030039

Study name	Clinical study for infusing convalescent plasma to treat patients with new coronavirus pneumonia (COVID-19)
Methods	<ul style="list-style-type: none"> • Trial design: non-randomised controlled study • Sample size: 30 experimental, 60 control group • Setting: inpatient • Country: China • Language: translated into English • Number of centres: 8
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Diagnosis conforms to the diagnostic criteria of "pneumonia diagnosis and treatment program for new coronavirus infection (trial version 5)" * Clinical classification is normal, severe or critical * Patient aged \geq 18 years old * Patient or his/her legal guardian will participate voluntarily and sign the informed consent • Exclusion criteria <ul style="list-style-type: none"> * Highly allergic constitution or history of severe allergy, especially plasma allergy * Doctor believes that there are other reasons not to include the patient

ChiCTR2000030039 (Continued)

Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP <ul style="list-style-type: none"> * type of plasma: CP * volume: 200-500 mL * number of doses: 2 infusions are recommended * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): conventional therapy • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: SARS-CoV-2 DNA, antibody levels • Primary outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR • Secondary outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR • Additional study outcomes <ul style="list-style-type: none"> * SARS-CoV-2 DNA: infusion day 1 and recheck according to the participant's condition * SARS-CoV-2 antibody levels: infusion day 1 and recheck according to the participant's condition * CRP: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge * IL-6: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge * LDH: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge * CPK: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge * Liver function: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge * Renal function: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge * Respiratory rate: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge * SiO₂: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge * Thoracic spiral CT: hospitalised day 1, day 3, day 7, day 14, infusion day 1, day 2, 14 days after discharge
Starting date	1 February 2020
Contact information	<p>Liping Wang</p> <p>Affiliated Hospital of Xuzhou Medical University, 9 Kunpeng Road, Gulou District, Xuzhou, Jiangsu, 163wangliping@163.com China</p> <p>Xuebing Yan</p>

ChiCTR2000030039 (Continued)

9 Kunpeng Road, Gulou District, Xuzhou, Jiangsu, China, yxbxuzhou@126.com

Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 1 February 2020 • Sponsor/funding: Affiliated Hospital of Xuzhou Medical University, Affiliated Hospital of Xuzhou Medical University, the working unit
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ChiCTR2000030179

Study name	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19)
Methods	<ul style="list-style-type: none"> • Trial design: randomised controlled trial • Sample size: 50 in each arm (100) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Confirmed participant (or legal guardian) agrees to participate in the study and signs the informed consent form * Aged 18-65 years * Real-time fluorescent RT-PCR of respiratory specimens or blood specimens to detect patients positive for novel coronavirus * Patients diagnosed as severe and critically ill and with rapid disease progression according to the "Diagnosis and Treatment Program for Pneumonia of New Coronavirus Infection (Trial Version 6)" • Exclusion criteria <ul style="list-style-type: none"> * Any situation where the solution cannot be carried out safely * Allergic constitution, allergic to plasma or drugs * Being too old, with severe underlying diseases that affect survival, including uncontrolled clinically significant heart, lung, kidney, digestive, haematological, neuropsychiatric, immune, metabolic, or malignant tumours, severe malnutrition, etc * Patients with severe respiratory failure, heart failure, and multiple organ failure * Participants in other clinical trials
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: routine treatment + plasma treatment • Details of CP <ul style="list-style-type: none"> * type of plasma: NR * volume: NR * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): routine treatment • Concomitant therapy: no • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcomes: cure rate, mortality • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: mortality * Time to death: NR

ChiCTR2000030179 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: mortality
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: length of stay
- Additional study outcomes: cure rate

Starting date	24 February 2020
Contact information	<p>Liu Wei</p> <p>The First Affiliated Hospital of Nanchang University, 17 Yongwai Main Street, Nanchang, Jiangxi, China, 330006, cdyfyliuwei@163.com</p> <p>Le Aiping</p> <p>17 Yongwai Main Street, Nanchang, Jiangxi, China, 330006, leaiping@126.com</p>
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 24 April 2020 • Sponsor/funding: The First Affiliated Hospital of Nanchang University, raised independently

ChiCTR2000030627

Study name	Study on the application of convalescent plasma therapy in severe COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 15 in each arm (30) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Patients who were diagnosed as COVID-19 by nucleic acid test and were in accordance with the clinical classification of severe or critically illness. (Refer to the clinical classification criteria in the pneumonia diagnosis and treatment program of novel coronavirus infection, General Office of the National Health Commission (trial version 4)) • Exclusion criteria <ul style="list-style-type: none"> * Patients with hypersensitivity to plasma products; patients with severe transfusion reactions in the past; patients with acute pulmonary oedema, congestive heart failure, PE, malignant hypertension, polycythaemia vera, extreme renal failure and other diseases
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP

ChiCTR2000030627 (Continued)

- Details of CP: NR
 - * type of plasma: NR
 - * volume: NR
 - * number of doses: NR
 - * antibody-titre: NR
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): routine treatment
- Concomitant therapy: no
- Treatment cross-overs: no

Outcomes

- Primary study outcomes: temperature, virus nucleic acid detection
- Primary review outcomes
 - * All-cause mortality at hospital discharge: mortality rate
 - * Time to death
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): incidence of AEs in blood transfusion
 - * Number of participants with SAEs
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: yes
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: length of admission
 - * QoL: NR
- Additional study outcomes
 - * Laboratory examination

Starting date

1 February 2020

Contact information

Guojun Zhang

The First Affiliated Hospital of Zhengzhou University, 1 Jianshe Road East, Zhengzhou, He'nan, China, zlgj-001@126.com

Guojun Zhang

1 Jianshe Road East, Zhengzhou, He'nan, China, zlgj-001@126.com

Notes

- Recruitment status: recruiting
- Prospective completion date: 30 May 2020
- Sponsor/funding: The First Affiliated Hospital of Zhengzhou University, Science and Technology Department of He'nan Province

ChiCTR2000030702
Study name

Convalescent plasma for the treatment of common COVID-19: a prospective RCT

Methods

- Trial design: open-label, RCT
- Sample size: 25 in each arm (50)
- Setting: inpatient
- Country: China

ChiCTR2000030702 (Continued)

	<ul style="list-style-type: none"> • Language: translated to English • Number of Centres: 4
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Patient signed an informed consent form to participate in the study of CP therapy * Patient age ≥ 18 years old * COVID-19 patients diagnosed by PCR * Nucleic acid positive within 72 h before blood transfusion * Pneumonia confirmed by imaging * Hospitalisation for fever (axillary temperature ≥ 36.7 °C, or oral temperature ≥ 38.0 °C, or anal or ear temperature ≥ 38.6 °C) and respiratory rate > 24 breaths/min or cough (at least 1 of the 2) * Severe clinical warning indicators: such as a progressive decrease in peripheral blood lymphocytes, a progressive increase in peripheral blood inflammatory factors, a progressive increase in lactic acid, and rapid progress of lung lesions in the short term, et al * Accept random grouping into any group * Hospitalised before the end of the clinical study * Willing to participate in all necessary research directions and be able to participate in follow-up * During the period of participating in this study, they will no longer participate in clinical trials such as other antiviral drugs • Exclusion criteria <ul style="list-style-type: none"> * Doctor believes that the patient is not suitable to participate in this trial, including those who may not co-operate, do not comply with the requirements of the procedure, or participating in this trial may put the patient in an unsafe situation * Pregnant or lactation periods women * Immunoglobulin allergy * IgA deficiency * Clinical symptoms are mild (no pneumonia on imaging) * Clinical symptoms are severe or critical where severe patients meet any of the following: 1) respiratory distress, respiratory rate ≥ 30 breaths/min; 2) in resting state, oxygen saturation $\leq 93\%$; 3) partial PaO₂/FiO₂ ≤ 300 mmHg (1 mmHg = 0.133 kPa); and critically ill patients meet any of the following: 1) respiratory failure and need mechanical ventilation; 2) shock; 3) patients with other organ failure need ICU monitoring treatment * Diseases that may increase the risk of thrombosis, such as cold globulinaemia, severe refractory hypertriglyceridaemia, clinically defined monoclonal gamma globulinaemia, etc * Detection of high titre of anti-novel coronavirus antibody RBDIgG (> 1) * Received any experimental treatment for novel coronavirus infection within 30 days before screening * Researchers judged that the patients had the following life-threatening conditions, including, but not limited to, Phammer F < 100 mmHg, near-death state or expected survival time < 24 h, severe septic shock or DIC), etc * Severe congestive heart failure, or other relative contraindications for plasma transfusion determined by study authors
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: conventional treatment and CP therapy • Details of CP: <ul style="list-style-type: none"> * type of plasma: NR * volume: NR * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: conventional treatment • Concomitant therapy: symptomatic treatment, antiviral treatment, and antibacterial treatment • Treatment cross-overs: NR

ChiCTR2000030702 (Continued)

Outcomes	<ul style="list-style-type: none"> • Primary study outcome: time to clinical recovery after randomisation • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: 28-day mortality * Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes (cumulative incidence of AEs (AE), grades 3 and 4 AE): cumulative incidence of severe AEs, incidence of adverse plasma transfusion reactions * Number of participants with SAEs: cumulative incidence of severe AEs (SAE) * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection: 28-day assisted oxygen therapy or non-invasive mechanical ventilation rate * 30-day and 90-day mortality: 28-day mortality * Admission on the ICU: yes * Length of stay on the ICU: yes (ICU hospitalisation) * Time to discharge from hospital: yes (hospitalisation time) * QoL: NR • Additional study outcomes <ul style="list-style-type: none"> * Incidence of breathing exacerbations * Time for conscious cough relief during infection (cough present when enrolled) * Time to remission of conscious dyspnea during infection (existed dyspnea upon enrolment) * Proportion of viral nucleic acid negative
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Starting date	15 February 2020
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Contact information	<p>Liu Zhong</p> <p>Institute of Blood Transfusion, Chinese Academy of Medical Sciences, 26 Huacai Road, Chenghua District, Chengdu, Sichuan, China, 610000, Liuz@ibt.pumc.edu.cn</p> <p>Cao Bin</p> <p>2 Yinghua Street East, Chaoyang District, Beijing, China, 100029, caobin_ben@163.com</p>
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Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 15 August 2020 • Sponsor/funding: China-Japan friendship hospital, Beijing, Institute of Blood Transfusion, Chinese Academy of Medical Sciences, Beijing, Government
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ChiCTR2000030929

Study name	A randomized, double-blind, parallel-controlled trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia (COVID-19)
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Methods	<ul style="list-style-type: none"> • Trial design: randomised, double-blind, parallel-controlled trial • Sample size: 30 in each arm (60) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1
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ChiCTR2000030929 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Aged 18-70 years old, inpatients, male or female * Patients with severe COVID-19: confirmed cases shall be in compliance with guideline of "Diagnosis and Treatment Plan for COVID-19 (Version 7)" or updated versions. * Confirmed cases can be defined if suspected cases have characteristic of following pathogeny or serology <ul style="list-style-type: none"> <input type="checkbox"/> detect nucleic acid of novel coronavirus positive by real-time fluorescent RT-PCR <input type="checkbox"/> have highly homologous to known novel coronavirus by sequencing <input type="checkbox"/> detect sero-specific IgM- and IgG-positive; IgG-specific against new coronavirus positive conversion or the titre of IgG is 4 times higher in convalescent period than in acute period * Adult patients with severe COVID-19 shall meet any of the following: <ul style="list-style-type: none"> <input type="checkbox"/> respiratory distress, respiratory rate ≥ 30 times/minute <input type="checkbox"/> in the resting state, oxygen saturation is $\leq 93\%$ <input type="checkbox"/> for lung radiology, the lesion has obtained $> 50\%$ obvious improvement within 24-48 h <input type="checkbox"/> $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg (1 mmHg = 0.133 kPa) * Patients and/or their legal guardians volunteered to participate in the study and voluntarily signed informed consent. • Exclusion criteria <ul style="list-style-type: none"> * Clinical classification of patients with severe novel coronavirus infection is to meet any of the following: <ul style="list-style-type: none"> <input type="checkbox"/> respiratory failure occurs and requires mechanical ventilation; <input type="checkbox"/> shock occurs; <input type="checkbox"/> combined failure of other organs requires ICU monitoring and treatment * Those who are allergic to blood products or plasma components and auxiliary materials (sodium citrate) * Multiple organ failure, and the estimated survival time is < 3 days * Those who tested positive for HIV antibodies before enrolment * Women who are pregnant or breastfeeding or have a birth plan within the past year * Participants in other clinical trials within 1 month before screening * Poor adherence or other conditions that the study author believes are not suitable for inclusion (such as poor physical condition)
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: anti-SARS CoV virus inactivated plasma * volume: NR * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: yes • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type) - ordinary plasma • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: improvement of clinical symptoms (clinical improvement is defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital) • Primary review outcomes reported: <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes (at 14- and 28-day) * Time to death: NR

ChiCTR2000030929 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: Invasive mechanical ventilation during infection; ECMO duration during infection: NR
 - * 30-day and 90-day mortality: 28-day mortality
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: ICU hospitalisation days
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional study outcomes
 - * Improving time of main clinical symptoms (wheezing, cough, sputum, etc)

Starting date	17 March 2020
Contact information	Lianghao Zhang 11443556@qq.com Sinopharm Wuhan Blood Products Co., Ltd. 1 Golden Industrial Park Road, Zhengdian, Jiangxia District, Wuhan, Hubei, China
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 16 June 2020 • Sponsor/funding: Renmin Hospital of Wuhan University, 99 Zhang-Zhi-Dong Road, Wuchang District, Wuhan, Hubei, China

ChiCTR2000031501

Study name	The efficacy of convalescent plasma in patients with critical novel coronavirus pneumonia (COVID-19): a pragmatic, prospective cohort study
Methods	<ul style="list-style-type: none"> • Trial design: prospective cohort study, controlled • Sample size: 10 in each arm (20) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Severe or critical patients with COVID-19 pneumonia confirmed by novel coronavirus diagnosis and treatment plan (7th Edition) * 18-85 years old * Obtaining informed consent

ChiCTR2000031501 (Continued)

- Exclusion criteria
 - * Participating in clinical trials of other drugs
 - * Pregnant or lactating women
 - * ALT/AST > 5-fold ULN, neutrophil < 0.5 x 10⁹/L, platelet < 50 x 10⁹/L
 - * Diagnosis of rheumatic immune-related diseases was clear
 - * Long-term oral anti-rejection drugs or immunomodulatory drugs
 - * Hypersensitive reaction to mAb or any adjuvant
 - * Active TB patients with definite bacterial and fungal infection
 - * Patients with organ transplantation history within 3 months
 - * History of percutaneous coronary intervention in the past 60 days;
 - * COPD with end-stage chronic diseases, including heart failure above NYHA grade III, chronic kidney disease with creatinine clearance < 40 mL/min or requiring family oxygen therapy

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - * type of plasma: NR
 - * volume: NR
 - * number of doses: NR
 - * antibody-titre: NR
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): routine treatment
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome: hospital mortality
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: yes
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection: new receipt of high-flow oxygen absorption, new receipt of non-invasive mechanical ventilation, new receipt of continuous renal replacement therapy, new receipt of ECMO
 - * 30-day and 90-day mortality: hospital mortality, day 90 mortality
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: ICU hospitalisation days
 - * Time to discharge from hospital: NR
 - * QoL: NR

ChiCTR2000031501 (Continued)

- Additional study outcomes
 - * Time to COVID-19 RT-PCR-negative in surviving patients
 - * Time of medical imaging improvement
 - * Lymphocyte count
 - * CRP
 - * IL-6
 - * New onset organ failure
 - * Incidence of secondary bacterial infection
 - * Incidence of secondary fungal infection
 - * Incidence of critical illness in severe patients
 - * Day 90 readmission for COVID-19 pneumonia

Starting date	17 March 2020
Contact information	Weiqin Li liweiqindr@vip.163.com Eastern Theater General Hospital 305 Zhongshandong road, Xuanwu district, Nanjing, Jiangsu, China
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 17 July 2020 • Sponsor/funding: Eastern Theater General Hospital, 305 Zhongshan Road East, Xuanwu District, Nanjing, Jiangsu, China

ChiCTR2000033798

Study name	The efficacy and safety of convalescent plasma therapy in novel coronavirus pneumonia (COVID-19): a medical records based retrospective cohort study
Methods	<ul style="list-style-type: none"> • Trial design: factorial • Sample size: 150 • Setting: hospitalised patients • Country: China • Language: Chinese/English • Number of centres: 1 • Trial registration: ChiCTR2000033798 • Date of registration: 2020-06-12
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Meets COVID-19 diagnosis criteria of WHO • Exclusion criteria <ul style="list-style-type: none"> * age < 18 years; * pregnant; * length of hospital stay < 24 hours; * insufficient clinical information; * serious complications not directly related to COVID-19 (including but not limited to surgical emergencies, intracranial haemorrhage, multiple injuries, etc.) * dead within 24 h after admission • Donor eligibility criteria: NR • Donor exclusion criteria: NR

ChiCTR2000033798 (Continued)

Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: CP * volume: NR * number of doses: NR * Antibody test and antibody-titre: NR * pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody: NR * Severity of disease: NR * Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients • Comparator (type): standard of care • Concomitant therapy: standard of care • Duration of follow-up: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * All-cause in-hospital mortality • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes * Time to death: yes • Secondary review outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR * WHO ordinal scale: NR * 30-day and 90-day mortality: reported * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR * Virological response: serum SARS-CoV-2 RNA load, serum antibody titers of IgG and IgM • Additional outcomes: nil
Starting date	12 December 2020
Contact information	Yi Bian, bianyi2526@163.com
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 2021-06-11 • Sponsor/funding: nil

EUCTR2020-001310-38

Study name	A randomized, prospective, open label clinical trial on the use of convalescent plasma compared to best supportive care in patients with severe COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: open-label, RCT • Sample size: 120 • Setting: inpatient • Country: Germany • Language: English • Number of centres: 5
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Patients with SARS-CoV-2 infection * Age \geq 18 years and \leq 75 years * SARS-CoV-2 infection confirmed by PCR (BAL, sputum, nasal and/or pharyngeal swab) * Severe disease defined by at least 1 of the following: <ul style="list-style-type: none"> <input type="checkbox"/> respiratory rate \geq 30 breaths/minute under ambient air <input type="checkbox"/> requirement of any type of ventilation support <input type="checkbox"/> needs ICU treatment * Written informed consent by patient or legally authorised representative • Exclusion criteria <ul style="list-style-type: none"> * Accompanying diseases other than COVID-19 with an expected survival time of $<$ 12 months * In the opinion of the clinical team, progression to death is imminent and inevitable within the next 48 h, irrespective of the provision of treatment * Interval $>$ 72 h since start of ventilation support * Not considered eligible for extracorporeal oxygenation support (even in case of severe ARDS according to Berlin classification with Horovitz-Index $<$ 100 mg Hg) * Chronic obstructive lung disease (COPD), stage 4 * Lung fibrosis with UIP pattern in CT and severe emphysema * Chronic heart failure NYHA \geq 3 and/or pre-existing reduction of left ventricular ejection fraction to \leq 30% * Cardiovascular failure requiring \geq 0.5 μg/kg/min noradrenaline (or equivalent) or requiring $>$ 2 types of vasopressor medication * Liver cirrhosis Child C * Liver failure: bilirubin $>$ 5 x ULN and elevation of ALT or AST ($>$ 10 x ULN) * Any history of adverse reactions to plasma proteins * Known deficiency of IgA * Pregnancy * Breastfeeding women * Volume overload until sufficiently treated * Pulmonary oedema * Participation in another clinical trial for treatment of COVID-19
Interventions	<p>Interventions</p> <ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: FFP with marketing authorisation in Germany issued by Paul-Ehrlich-Institut * volume: NR * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): within 72 hours of start of ventilation support

EUCTR2020-001310-38 (Continued)

- For studies including a control group: comparator (type): randomised 1:1 to CP and best supportive care
- Concomitant therapy: NR
- Treatment cross-overs: cross-over allowed for patients with progressive COVID-19

Outcomes

- Primary study outcome: composite endpoint of survival no longer fulfilling criteria of severe COVID-19 within 21 days after randomisation
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes
 - Survival
 - * Time to death: yes
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: case fatality rate at 21, 35, 60 days
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional outcomes
 - * Time to clinical improvement on WHO R&D Blueprint seven-category ordinal scale by 2
 - * Time until negative SARS-CoV-2 PCR
 - * Predictive value of comorbidities and inflammation markers
 - * Feasibility of collection of plasma units
 - * Kinetics of anti-SARS-CoV-2 antibodies in plasma of participants = plasma donors who recovered from a SARS-CoV-2 infection
 - * Titre of anti-SARS-CoV-2 in transfused plasma units
 - * Impact of donor characteristics on anti-SARS-CoV-2 humoral response
 - * Course of anti-SARS-CoV-2 titre in participants
 - * Effect of timing of plasma transfusions on outcome

Starting date 6 April 2020

Contact information Sixten Körper, IKT Ulm, 89081 Ulm, Germany; s.koerper@blutspende.de

 Notes

- Recruitment status: ongoing
- Prospective completion date: NR
- Sponsor/funding: DRK-Bluspendendienst Baden-Württemberg - Hessen gGmbH, Germany

IRCT20150808023559N21

Study name The effect of convalescent plasma therapy on the outcomes of patients with 19-COVID

 Methods

- Trial design: RCT
- Sample size: 60
- Setting: hospitalised patients
- Country: Iran
- Language: English

IRCT20150808023559N21 (Continued)

- Number of centres: 1
- Trial registration: IRCT20150808023559N21
- Date of registration: 2020-05-09

Participants

- Inclusion criteria
 - * Blood oxygenation saturation < 90%
 - * Abnormal lung CT scan
 - * Significant shortness of breath
 - * Fever
 - * Not improving in the next 48 h
 - * There is no possibility of discharge of patient in the next 48 h
 - * Patient consent
- Exclusion criteria
 - * The patient should not be connected to a ventilator
 - * The patient has not given consent
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - * type of plasma: CP
 - * volume: 500 mL
 - * number of doses: 1
 - * Antibody test and antibody-titre: NR
 - * pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator (type): standard of care
- Concomitant therapy: standard of care
- Duration of follow-up: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome:
 - * Reduction in all-cause mortality
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: yes

IRCT20150808023559N21 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: nil

Starting date	12 May 2020
Contact information	Somaieh Matin, s.matin@arums.ac.ir
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 2020-08-22 • Sponsor/funding: Ardabil University of Medical Sciences

IRCT20151228025732N53

Study name	Therapeutic effects of plasma of recovered people from COVID-19 on hospitalized patients with this disease
Methods	<ul style="list-style-type: none"> • Trial design: non-randomised, parallel group • Sample size: 12 (6 control 6 intervention) • Setting: inpatient • Country: Iran • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Patients admitted to the ICU who receive mechanical invasive or non-invasive ventilation, PaO₂/FiO₂ ratio < 300 mmHg (93%). Currently receiving IV vasoactive medications to maintain mean arterial pressure > 65 mmHg; respiratory frequency ≥ 30/min; laboratory-confirmed COVID-19 infection (by real-time PCR) • Exclusion criteria <ul style="list-style-type: none"> * Negative real-time PCR from respiratory secretions or blood within 48 h prior to CP transfusion * History of allergic reaction to blood or plasma products * Known IgA deficiency
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune globulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: CP, prepared from recovered patients * volume: 2 units * number of doses: 2 * antibody-titre: > 1:320 * pathogen inactivated or not: NR

IRCT20151228025732N53 (Continued)

- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised participants
- For studies including a control group: comparator (type): conventional treatment
- Concomitant therapy: conventional treatment
- Treatment cross-overs: none

Outcomes

- Primary study outcome: checking the amount of ventilation, white blood cell count, CRP, percentage of CD8+ T cells in peripheral blood, percentage of CD4+ T cells in peripheral blood
- Primary review outcomes
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (30 min after intervention and daily)
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes: white blood cell count, CRP, percentage of CD8+ T cells in peripheral blood, percentage of CD4+ T cells in peripheral blood

Starting date

20 April 2020

Contact information

Alireza Emadi Semnan University of Medical Sciences, Semnan, Iran

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are20935@semums.ac.ir

Notes

- Recruitment status: recruiting
- Prospective completion date: 20 June 2020 (recruitment end date)
- Sponsor/funding: Semnan University of Medical Sciences

IRCT20200310046736N1

Study name

Comparison of the therapeutic effect of convalescent plasma and plasma-derived immunoglobulin-enriched solution on COVID-19 patients

Methods

- Trial design: a hospital-based, parallel-group, single-blind, RCT
- Sample size: 45
- Setting: inpatient
- Country: Iran
- Language: English
- Number of centres: 1

IRCT20200310046736N1 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * COVID-19 patients who have the clinical signs of COVID-19 infection such as fever, cough, sputum production, sore throat, and so on * Positive CT scan * Declare informed consent for this study * Age: 20-45 years • Exclusion criteria <ul style="list-style-type: none"> * Pregnant women (based on WHO protocol) * Lactating women (based on WHO protocol) * Individuals who exhibit specific allergic reactions to IV administration * History of dangerous underlying diseases such as IgA deficiency * History of dangerous diseases such as cardiovascular and or haematological disorders (haemophilia, thalassaemia, leukaemia) * History of underlying diseases such as liver and kidney disease * Smokers
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: obtained from fully recovered patients according to inclusion criteria * volume: 200 cc/day IV administration for 1-4 h * number of doses: for 1-4 days * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): randomised (3 arms): CP, plasma-derived immunoglobulin-enriched solution and best supportive care or routine care without any new therapeutic interventions • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: complete remission of clinical signs of disease (about 1 week after starting the treatment), negative result for COVID-19 RT-PCR test (7-14 days after starting the treatment), normal CT scan (7-14 days after starting the treatment) • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR • Secondary review outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR • Additional outcomes <ul style="list-style-type: none"> * Negative result for COVID-19 RT-PCR test * Normal CT scan * Recovery and normal levels of biomarkers associated with COVID-19

IRCT20200310046736N1 (Continued)

Starting date	24 March 2020
Contact information	Parastoo Moradi Choghakabodi, Iran (Islamic Republic of); parastoomoradi40@yahoo.com
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 24 July 2020 • Sponsor/funding: Ahvaz University of Medical Sciences, 61357-15794 Ahvaz, Iran

IRCT20200404046948N1

Study name	Efficacy and safety of convalescent plasma in the treatment of COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: open-label, RCT • Sample size: 60 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 4
Participants	<p>Participants</p> <ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Laboratory-confirmed COVID-19 by PCR * Aged 18-70 years old * Inpatients * Clinical severe or immediately life-threatening COVID-19 (severe patients meet any of the following: dyspnoea, respiratory frequency \geq 30/min, blood oxygen saturation \leq 93% (in resting state), PaO₂/FiO₂ < 300, and/or lung infiltrates > 50% within 24-48 h * Life-threatening disease is defined as: respiratory failure and need mechanical ventilation, septic shock, and/or multiple organ dysfunction or failure * Patient or his/her legal guardian will sign the informed consent and participate voluntarily * Accepting randomised allocation (allocating into any group) * Being hospitalised before the end of the clinical trial and available for any follow-up • Exclusion criteria <ul style="list-style-type: none"> * History of allergy to blood products or plasma components and auxiliary materials (sodium citrate) * Critical conditions like multiple organ failure, and the estimated survival time is < 3 days * Severe congestive heart failure, or any other conditions in which plasma transfusion is contraindicated decided by study authors * Any risk factor that may increase the risk of thrombosis * Pregnant or breastfeeding women * Participation in another clinical trial * Taking any other medicine for COVID 19 treatment out of the protocol * Doctor believes that the patient is not suitable to participate in this trial
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: NR * volume: 200-500 mL * number of doses: 2 IV infusions during 2 consecutive days * antibody-titre: NR * pathogen inactivated or not: NR

IRCT20200404046948N1 (Continued)

- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): conventional therapy and CP or conventional therapy only
- Concomitant therapy: conventional therapy
- Treatment cross-overs: NR

Outcomes

- Primary study outcome: clinical improvement within 14 days of admission
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes
 - Mortality in 2 groups during 14 days
 - * Time to death: NR, 14 days only
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional outcomes
 - * Proportion of PCR-negative (3 and 7 days after transfusion)
 - * Clinical characteristics including fever, respiratory frequency and PaO₂/FiO₂

Starting date

13 April 2020

Contact information

Ramin Hamidi Farahani, Artesh University of Medical Sciences, Tehran, Iran; Amir.salarian@gmail.com

Notes

- Recruitment status: recruiting
- Prospective completion date: 20 June 2020
- Sponsor/funding: Artesh University of Medical Sciences, 1411718541 Tehran, Iran

IRCT20200409047007N1

Study name

Effect of COVID 19 survivors plasma in COVID 19 patients with ARDS

Methods

- Trial design: open-label, RCT
- Sample size: 32
- Setting: hospitalised patients
- Country: Iran
- Language: English
- Number of centres: 1

Participants

- Inclusion criteria
 - * PaO₂/FiO₂ ratio < 300 despite receiving standard treatment
 - * Patient should be 50-75 years old
 - * Normal IgA level
 - * < 1 week has passed since the patient entered the ICU

IRCT20200409047007N1 (Continued)

	<ul style="list-style-type: none"> • Exclusion criteria <ul style="list-style-type: none"> * Uncontrolled hypertension * Advanced heart failure * Systolic blood pressure < 90 mm Hg * COPD * Patient is intubated * Chronic renal failure with GFR < 30
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: NR * volume: 500 cc each time * number of doses: up to 3 times/day * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): this treatment is started as soon as possible after the patient enters the ICU and within a week • For studies including a control group: comparator (type): in the control group, patients benefit from all available supportive and specific therapies based on existing standards • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: mortality rate in first month from the time of entry into the study • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes <ul style="list-style-type: none"> <input type="checkbox"/> mortality rate in first month from the time of entry into the study * Time to death: NR, first month only • Secondary review outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR * 30-day and 90-day mortality: yes * Admission on the ICU: NR * Length of stay on the ICU: yes * Time to discharge from hospital: NR * QoL: NR • Additional study outcomes: NR
Starting date	13 April 2020
Contact information	Dr Mohsen Seddigh Shamsi, Mashhad University of Medical Sciences, Department of Internal Medicine, Taqi Abad Square, Mashhad, Iran
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 15 August 2020 • Sponsor/funding: Mashhad University of Medical Sciences, Mashhad, Iran

IRCT20200413047056N1

Study name	Comparison between the efficacy of intravenous immunoglobulin and convalescent plasma in improving the condition of patients with COVID-19: a randomized clinical trial
Methods	<ul style="list-style-type: none"> • Trial design: randomised, clinical trial • Sample size: 15 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * 18-50 years old * RT-PCR * Confirm the infection in the throat swab or sputum or lower respiratory tract samples * Signed informed consent form on a voluntary basis * Meet any of the following criteria for severe or critical ill conditions: <ul style="list-style-type: none"> <input type="checkbox"/> respiratory rate ≥ 30/min; or <input type="checkbox"/> rest SpO₂ $\leq 90\%$; or <input type="checkbox"/> PaO₂/FiO₂ ≤ 300 mmHg; or <input type="checkbox"/> respiratory failure and needs mechanical ventilation; or <input type="checkbox"/> multiple organ failure and needs ICU monitoring • Exclusion criteria <ul style="list-style-type: none"> * NR
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: NR * volume: 200 cc each time * number of doses: 2 * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): 3 arms: CP; IV immunoglobulin (400 mg/kg/d); this group will receive common national protocol • Concomitant therapy: common national protocol • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: lung involvement in X-ray and CT-scan, SpO₂, LDH enzyme, viral load, acute phase protein, white blood cell count, erythrocyte sedimentation rate, length of hospital stay, duration of mechanical ventilation • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR

IRCT20200413047056N1 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional outcomes
 - * Lung involvement in X-ray and CT-scan
 - * SpO₂
 - * LDH enzyme
 - * Viral load
 - * Acute phase protein
 - * White blood cell count
 - * Erythrocyte sedimentation rate

Starting date	18 April 2020
Contact information	Malihe Zangoue, Birjand University of Medical Sciences, Birjand, Iran; mzungoue@yahoo.com
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 15 August 2020 • Sponsor/funding: Birjand University of Medical Sciences, Birjand, Iran

IRCT20200525047562N1

Study name	Treatment of COVID-19 patients with convalescent plasma
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 100 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 4 • Trial registration: IRCT20200525047562N1 • Date of registration: 6 May 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Symptomatic COVID-19 patients who are hospitalised and have score > 4 in terms of WHO Progression Scale will enter the study. COVID-19 patients who have score < 4 in terms of WHO Progression Scale and > 24 h passed from the hospitalisation, won't enter the study • Exclusion criteria <ul style="list-style-type: none"> * Control group: the control group is a patient who is hospitalised with suspicion of COVID-19 but either not in randomisation or not satisfied with receiving plasma • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP

IRCT20200525047562N1 (Continued)

- Details of CP:
 - * type of plasma: CP
 - * volume: 500 cc
 - * number of doses: 1-2
 - * Antibody test and antibody-titre: NR
 - * pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator (type): no CP
- Concomitant therapy: standard of care
- Duration of follow-up: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome:
 - * WHO progression scale: reduce at least 2 points on clinical signs or score < 3, each earlier
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: reported
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: reported
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: nil

Starting date 25 May 2020

Contact information Peyman Eshghi, p.eshghi@ibto.ir

- Notes
- Recruitment status: recruitment complete
 - Prospective completion date: 2020-07-26
 - Sponsor/funding: High Educational and Research Institute of Transfusion Medicine

ISRCTN85216856

Study name Using blood plasma to develop passive immunity to coronavirus in Ecuador

ISRCTN85216856 (Continued)

Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 200 • Setting: hospitalised patients • Country: Ecuador • Language: English • Number of centres: 1 • Trial registration: ISRCTN85216856 • Date of registration: 6 May 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Aged \geq 18 years * Clinical, molecular (using IgM/IgG or RT-PCR), or lung imaging diagnosis of COVID-19 * Deterioration of previously normal lung function defined as SaO₂ of < 90% in 0.5 FiO₂, and/or a higher requirement of O₂ than in the previous 24 h * A score of 5-7 on the early warning scale for COVID-19 patients or a SOFA score between 2 and 10 * Informed consent provided by participants or their representatives • Exclusion criteria <ul style="list-style-type: none"> * Diagnosis and/or treatment for cancer * HIV infection * Currently receiving immunosuppressants for a condition other than SARS-CoV2 infection * Superimposed systemic infections * Liver or kidney failure * COPD, previous pulmonary fibrosis, and/or restrictive lung disease * Have received previous transfusions • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: CP * volume: 5 mL of plasma/kg of body weight IV * number of doses: 1 * Antibody test and antibody-titre: NR * pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody: NR * Severity of disease: NR * Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients • Comparator (type): standard plasma • Concomitant therapy: standard of care • Duration of follow-up: 21 days • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Case fatality rate assessed through data collected from the follow-up instrument and medical record at 21 and 28 days • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes (up to day 21) * Time to death: NR

ISRCTN85216856 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: reported
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes:
 - * SOFA, thoracic X-ray and/or tomography if possible will also be documented at discharge
 - * Demographic information, including age and sex will be collected using the specific instrument created to screen potential patients at baseline
 - * Time of initiation of treatment in relation to the evolution of the disease assessed using the follow-up instrument, which is completed daily from baseline to 21 days)
 - * Sequelae at discharge (liver, kidney functions, pulmonary, cardiac and neurological) assessed by the follow-up instrument at discharge

Starting date	March 2020
Contact information	Dr Manuel Baldeon manuel.baldeon@ute.edu.ec
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: December 2020 • Sponsor/funding: SalvarVidasEC (Ecuador)

NCT02735707

Study name	Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP)
Methods	<ul style="list-style-type: none"> • Trial design: randomised multifactorial adaptive platform (REMAP) • Sample size: 7100 • Setting: patients in ICU • Country: international (Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, NZ, Portugal, Romania, Spain, UK, USA) • Language: English • Number of centres: 90 • Trial registration: NCT02735707 • Date of registration: 13 April 2016

NCT02735707 (Continued)

Participants

- Inclusion criteria
 - * Adult patient admitted to an ICU for severe CAP within 48 h of hospital admission with:
 - symptoms or signs or both that are consistent with lower respiratory tract infection AND
 - radiological evidence of new onset consolidation (in patients with pre-existing radiological changes, evidence of new infiltrate)
 - * Up to 48 h after ICU admission, receiving organ support with one or more of:
 - non-invasive or Invasive ventilatory support;
 - receiving infusion of vasopressor or inotropes or both
 - * COVID inclusion criteria:
 - Adult patients (≥ 18 years) admitted to hospital with acute illness due to suspected or proven pandemic infection
- Exclusion criteria
 - * Healthcare-associated pneumonia:
 - prior to this illness, is known to have been an inpatient in any healthcare facility within the last 30 days
 - Resident of a nursing home or long-term care facility
 - * Death is deemed to be imminent and inevitable during the next 24 h AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment
 - * Previous participation in this REMAP within the last 90 days
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - * type of plasma: CP
 - * volume: NR
 - * number of doses: 1-2
 - * Antibody test and antibody-titre: NR
 - * pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): patients in ICU
- Comparator (type): multi-platform adaptive trial
 - * corticosteroid domain: hydrocortisone
 - * antibiotic domain: multiple
 - * antiviral against influenza: 10-day course of oseltamivir, 5-day course of oseltamivir, nil
 - * antiviral domain: lopinavir/ritonavir, hydroxychloroquine + lopinavir/ritonavir, hydroxychloroquine, nil
 - * antiinflammatory: tocilizumab, anakinra, sarilumab, hydrocortisone, nil
 - * thromboprophylaxis domain: standard care vs therapeutic anticoagulation
 - * simvastatin: simvastatin vs nil
 - * Vitamin C: vitamin C vs nil
 - * Ig domain: CP (1-2 units) vs nil
 - * ventilation: protocolised invasive mechanical ventilation strategy vs clinician-preferred
- Concomitant therapy: NR
- Duration of follow-up: 6 months
- Treatment cross-overs: NR

NCT02735707 (Continued)

Outcomes

- Primary study outcome:
 - * All-cause mortality (time frame: Day 90)
 - * Days alive and not receiving organ support in ICU
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes (up to day 28)
 - * Time to death: NR
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: reported
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: reported, EQ5D-5L and WHODAS 2.0 (not completed in all regions)
 - * Virological response: serial detection of SARS-CoV-2 in upper or lower respiratory tract specimens (using only specimens collected for routine clinical testing) (time frame: Day 90, censored at hospital discharge)
- Additional outcomes
 - * COVID-19 Antiviral Domain and COVID-19 Immune Modulation Domain specific endpoint
 - * Occurrence of multi-resistant organism colonisation/infection (time frame: Day 90, censored at hospital discharge)
 - * Occurrence clostridium difficile (time frame: Day 90, censored at hospital discharge)
 - * Occurrence of serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death (time frame: Day 90, censored at hospital discharge)
 - * Change from baseline influenza virus levels in upper and lower respiratory tract specimens (time frame: Day 3, up to Day 7), characterised as home, rehabilitation hospital, nursing home or long-term care facility, or another acute hospital
 - * Proportion of intubated patients who receive a tracheostomy (time frame: Day 28)
 - * Destination at time of hospital discharge (time frame: Day 90)
 - * Readmission to the index ICU during the index hospitalization (time frame: Day 90)
 - * Ventilator free days (time frame: Day 28)
 - * Organ failure-free days (time frame: Day 28)

Starting date	11 April 2016
Contact information	<ul style="list-style-type: none"> • Cameron Green info@remapcap.org • Wilma Van Bentum-Puijk, MSc+31 (0) 88 755 5555 prepare_icu@umcutrecht.nl
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: December 2023 • Sponsor/funding: MJM Bonten

NCT04264858

Study name	An exploratory clinical study on the treatment of acute severe 2019-nCoV pneumonia with immunoglobulin from cured 2019-nCoV pneumonia patients
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NCT04264858 (Continued)

Methods	<ul style="list-style-type: none"> • Trial design: non-randomised, parallel-assigned, open trial • Sample size: 10 • Setting: inpatient • Country: China • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Volunteers who have understood and signed the informed consent * Age ≥ 18 years, gender unlimited * Patients diagnosed with acute severe COVID-19 pneumonia <ul style="list-style-type: none"> <input type="checkbox"/> laboratory (RT-PCR)-confirmed infection with COVID-19 <input type="checkbox"/> lung involvement confirmed with pulmonary CT scan <input type="checkbox"/> at least 1 of the following conditions should be met: respiratory distress, respiratory rate ≥ 30 times/min; oxygen saturation ≤ 93% in resting state; PaO₂/FiO₂ ≤ 300 mmHg; respiratory failure and mechanical ventilation are required; shock occurs; ICU monitoring and treatment is required in combination with other organ failure • Exclusion criteria <ul style="list-style-type: none"> * Viral pneumonia with other viruses besides COVID-19 * Patients are not suitable for immunoglobulin therapy * Participation in other studies * Other circumstances in which the investigator determined that the patient is not suitable for the clinical trial
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: immunoglobulin of cured patients • Details of CP: <ul style="list-style-type: none"> * type of plasma: immunoglobulin * volume: 0.2 g/kg * number of doses: daily for 3 doses * antibody-titre: NA * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): gamma globulin 0.2 g/kg • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: time to clinical improvement, defined as the time (in days) from initiation of study treatment (active or placebo) until a decline of 2 categories from admission status on a six-category ordinal scale of clinical status which ranges from 1 (discharged) to 6 (death) (for categories ordinal scale, see Additional outcomes). • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes (up to day 28) * Time to death: NR

NCT04264858 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes
 - * Time to clinical improvement using 6 category ordinal scale (time frame: up to 28 days)
 - 6. Death;
 - 5. ICU, requiring ECMO and/or IMV;
 - 4. ICU/hospitalization, requiring NIV/ HFNC therapy;
 - 3. Hospitalization, requiring supplemental oxygen (but not NIV/ HFNC);
 - 2. Hospitalization, not requiring supplemental oxygen;
 - 1. Hospital discharge.
 - * Clinical status assessed by the ordinal scale (on days 7, 14, 21, and 28)
 - * The differences in oxygen intake methods (time frame: up to 28 days)
 - no need for supplemental oxygenation
 - nasal catheter oxygen inhalation
 - mask oxygen inhalation
 - noninvasive ventilator oxygen supply
 - invasive ventilator oxygen supply
 - * Duration (days) of supplemental oxygenation (time frame: up to 28 days)
 - * Duration (days) of mechanical ventilation (time frame: up to 28 days)
 - * Mean PaO₂/FiO₂ (time frame: up to 28 days)
 - * Lesions of the pulmonary segment numbers involved in pulmonary CT (every 7 days) (time frame: up to 28 days)
 - * Time to COVID-19 RT-PCR negativity in respiratory tract specimens (every 3 days) (time frame: up to 28 days)
 - * Dynamic changes of COVID-19 antibody titre in blood (time frame: up to 28 days)
 - * Length of hospital stay (days) (time frame: up to 28 days)

Starting date	17 March 2020
Contact information	Xiang Cheng Department of Cardiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology Wuhan, Hubei, China, 430022
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 31 May 2020 • Sponsor/funding: Wuhan Union Hospital, China

NCT04292340

Study name	The efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of novel coronavirus pneumonia patient (COVID-19): an observational study
Methods	<ul style="list-style-type: none"> • Trial design: prospective single-arm intervention study • Sample size: 15 • Setting: inpatient • Country: China • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Participants were diagnosed as COVID-19 * Participants received anti-SARS-CoV-2 inactivated CP * Written informed consent • Exclusion criteria <ul style="list-style-type: none"> * Participants lacked detailed medical history
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: NR * volume: NR * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): not applicable • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: Virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 1, day 3 and day 7, numbers of participants with different clinical outcomes • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes * Time to death: NR • Secondary review outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: yes * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR • Additional outcomes <ul style="list-style-type: none"> * Virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 1, day 3 and day 7 (time frame: 1 day/3 days/7 days after receiving plasma transmission) * Numbers of participants with different clinical outcomes (time frame: from receiving plasma transmission to 4 weeks) <ul style="list-style-type: none"> <input type="checkbox"/> clinical outcomes include death, critical illness, recovery

NCT04292340 (Continued)

Starting date	1 February 2020
Contact information	Hongzhou Lu, Ph.D+86-021-37990333 ext 3222 luhongzhou@fudan.edu.cn Shanghai Public Health Clinical Center Shanghai, Shanghai, China, 201508
Notes	<ul style="list-style-type: none"> Recruitment status: recruiting Prospective completion date: 31 July 2020 Sponsor/funding: Shanghai Public Health Clinical Center

NCT04327349

Study name	Investigating effect of convalescent plasma on COVID-19 patients outcome: a clinical trial
Methods	<ul style="list-style-type: none"> Trial design: single-arm intervention study Sample size: 30 Setting: inpatient Country: Iran Language: English Number of centres: 1
Participants	<ul style="list-style-type: none"> Inclusion criteria <ul style="list-style-type: none"> * COVID-19 patients * Consent to attend the study * Age 30-70 years * Not intubated * PaO₂/FiO₂ is > 200 or SpO₂ is > 85% Exclusion criteria <ul style="list-style-type: none"> * History of hypersensitivity to blood transfusions or its products * History of IgA deficiency * Heart failure or any other factor that prevents the transmission of 500 mL plasma * Entering the intubation stage
Interventions	<ul style="list-style-type: none"> CP therapy or hyperimmune immunoglobulin therapy: CP therapy Details of CP: <ul style="list-style-type: none"> * type of plasma: NR * volume: NR * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: NR Treatment details, including time of plasma therapy (e.g. early stage of disease): NR For studies including a control group: comparator (type): not applicable Concomitant therapy: NR Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> Primary study outcome: mortality changes (day 10 and day 30), changes of CRP (day 1, day 3 and day 7), IL-6 (day 1, day 3 and day 7), tumour necrosis factor-α (day 1, day 3 and day 7), PaO₂/FiO₂ (day 1, day 3 and day 7)

NCT04327349 (Continued)

- Primary review outcomes
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: yes (30-day mortality)
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes
 - * Changes of CRP
 - * Changes of IL-6
 - * Changes of tumour necrosis factor- α
 - * Changes of PaO₂/FiO₂
 - * Changes of CD4, CD8, CD4/CD8 ratio
 - * Changes of lymphocyte count
 - * Changes of leukocyte count
 - * Changes of ALT/AST
 - * Changes of alkaline phosphatase (ALP)
 - * Changes of LDH
 - * Changes of CPK
 - * Changes of CPK-MB
 - * Changes of specific IgG
 - * Radiological findings by CT scan and chest X-ray

Starting date	28 March 2020
Contact information	NR
Notes	<ul style="list-style-type: none"> • Recruitment status: enrolling by invitation • Prospective completion date: 30 September 2020 • Sponsor/funding: NR

NCT04332380

Study name	Convalescent plasma for patients with COVID-19: a pilot study (CP-COVID-19)
Methods	<ul style="list-style-type: none"> • Trial design: single-arm intervention study • Sample size: 10 • Setting: hospital • Country: Colombia • Language: English • Number of centres: 1

NCT04332380 (Continued)

Participants

- Inclusion criteria
 - * Aged 18-60 years, male or female
 - * Hospitalised participants with diagnosis for COVID 19 by RT-PCR
 - * Without treatment
 - * Moderate cases according to the official guideline 'Pneumonia Diagnosis and Treatment Scheme for Novel Coronavirus Infection (Trial Version 6)'
 - * Confusion, urea, respiratory rate, blood pressure-65 score (CURB-65 score) ≥ 2
 - * SOFA < 6
 - * Ability to understand and willing to sign a written informed consent document
- Exclusion criteria
 - * Pregnant or breastfeeding
 - * Prior allergic reactions to transfusions
 - * Critically ill patients in ICUs
 - * Patients with surgical procedures in the last 30 days
 - * Patients with active treatment for cancer (radiotherapy or chemotherapy)
 - * HIV diagnosed patients with viral failure (detectable viral load > 1000 copies/mL persistent, 2 consecutive viral load measurements within a 3-month interval, with medication adherence between measurements after at least 6 months of starting a new regimen antiretrovirals)
 - * Patients who have suspicion or evidence of co-infections
 - * End-stage chronic kidney disease (GFR < 15 mL/min/1.73 m²)
 - * Child Pugh C stage liver cirrhosis
 - * High cardiac output diseases
 - * Autoimmune diseases or IgA nephropathy
 - * Patients have any condition that in the judgement of the Investigators would make the person inappropriate for entry into this study

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP:
 - * type of plasma: NR
 - * volume: 500 mL total
 - * number of doses: 2
 - * antibody-titre: NR
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): not applicable
- Concomitant therapy: NR
- Treatment cross-overs: not applicable

Outcomes

- Primary study outcome: change in viral load (time frame: days 0, 4, 7, 14 and 28), change in IgM COVID-19 antibodies titres (time frame: days 0, 4, 7, 14 and 28), change in IgG COVID-19 antibodies titres (time frame: days 0, 4, 7, 14 and 28)
- Primary review outcomes
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR

NCT04332380 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional outcomes
 - * Change in viral load
 - * Change in IgM COVID-19 antibodies titres
 - * Change in IgG COVID-19 antibodies titres
 - * Clinical status assessed according to the WHO guideline

Starting date	1 April 2020
Contact information	Juan M Anaya Cabrera, MD, PhD ; +57 321 233 9828; anayajm@gmail.com Manuel E Rojas Quintana, MD, MSc; +57 315 459 9951; manuel_9316@hotmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 31 December 2020 • Sponsor/funding: NR

NCT04332835

Study name	Convalescent plasma for patients with COVID-19: a randomized, open label, parallel, controlled clinical study (CP-COVID-19)
Methods	<ul style="list-style-type: none"> • Trial design: randomised, open-label, parallel-controlled trial • Sample size: 40 in each arm (80) • Setting: hospital • Country: Colombia • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Aged 18-60 years, male or female * Hospitalised participants with diagnosis of COVID 19 by RT-PCR * Moderate cases according to the official guideline 'Pneumonia Diagnosis and Treatment Scheme for Novel Coronavirus Infection (Trial Version 6)' * Confusion, urea, respiratory rate, blood pressure-65 score (CURB-65 score) ≥ 2 * SOFA < 6 * Ability to understand and the willingness to sign a written informed consent document

NCT04332835 (Continued)

- Exclusion criteria
 - * Pregnant or breastfeeding
 - * Prior allergic reactions to transfusions
 - * Critically ill patients in ICUs
 - * Patients with surgical procedures in the last 30 days
 - * Patients with active treatment for cancer (radiotherapy or chemotherapy)
 - * HIV-diagnosed patients with viral failure (detectable viral load > 1000 copies/mL persistent, 2 consecutive viral load measurements within a 3-month interval, with medication adherence between measurements after at least 6 months of starting a new regimen antiretrovirals)
 - * Suspicion or evidence of co-infections
 - * End-stage chronic kidney disease (GFR < 15 mL/min /1.73 m²)
 - * Child Pugh C stage liver cirrhosis
 - * High cardiac output diseases
 - * Autoimmune diseases or IgA nephropathy
 - * Any condition that in the judgement of the Investigators would make the patient inappropriate for entry into this study

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP:
 - * type of plasma: NR
 - * volume: 500 mL total
 - * number of doses: 2
 - * antibody-titre: NR
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): azithromycin (500 mg daily) and hydroxychloroquine (400 mg every 12 h) for 10 days
- Concomitant therapy: azithromycin (500 mg daily) and hydroxychloroquine (400 mg every 12 h) for 10 days
- Treatment cross-overs: not applicable

Outcomes

- Primary study outcome: change in viral load, change in immunoglobulin M COVID-19 antibodies titres, change in immunoglobulin G COVID-19 antibodies titres
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes (7, 14, 28 day mortality)
 - * Time to death: NR
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional outcomes
 - * Change in viral load
 - * Change in immunoglobulin M COVID-19 antibodies titres
 - * Change in immunoglobulin G COVID-19 antibodies titres
 - * Clinical status assessed according to the WHO guideline

NCT04332835 (Continued)

Starting date	1 May 2020
Contact information	Juan M Anaya Cabrera, MD, PhD; +57 321 233 9828; anayajm@gmail.com Manuel E Rojas Quintana, MD, MSc; +57 315 459 9951; manuel_9316@hotmail.com
Notes	<ul style="list-style-type: none"> Recruitment status: not yet recruiting Prospective completion date: 31 December 2020 Sponsor/funding: Universidad del RosarioFundación Universitaria de Ciencias de la SaludCES UniversityInstituto Distrital de Ciencia Biotecnología e Innovacion en Salud

NCT04333251

Study name	Evaluating convalescent plasma to decrease coronavirus associated complications. A phase I study comparing the efficacy and safety of high-titer anti-SARS-CoV-2 plasma versus best supportive care in hospitalized patients with interstitial pneumonia due to COVID-19
Methods	<ul style="list-style-type: none"> Trial design: open-label, phase I, parallel-RCT Sample size: 115 Setting: hospital Country: USA Language: English Number of centres: 1
Participants	<ul style="list-style-type: none"> Inclusion criteria <ul style="list-style-type: none"> * ≥ 18 years * Must have been hospitalised with COVID-19 respiratory symptoms within 3-7 days from the beginning of illness * Patient and/or LAR willing to provide informed consent * Patient agrees to storage of specimens for future testing Exclusion criteria <ul style="list-style-type: none"> * ≤ 18 years * Receipt of pooled immunoglobulin in past 30 days * Contraindication to transfusion or history or prior reactions to transfusion blood products * Women who are identified as donors must not be pregnant Donor eligibility criteria <ul style="list-style-type: none"> * ≥ 18 years * Must have been hospitalised with COVID-19 respiratory symptoms and confirmation via COVID-19 SARS-CoV-2 RT-PCR testing but are now PCR-negative by 2 nasopharyngeal testing * Women of child-bearing potential must have a negative serum pregnancy test * Donor and/or LAR willing to provide informed consent * Donor agrees to storage of specimens for future testing
Interventions	<ul style="list-style-type: none"> CP therapy or hyperimmune immunoglobulin therapy: CP therapy Details of CP: <ul style="list-style-type: none"> * type of plasma: NR * volume: NR * number of doses: 1-2 units * antibody-titre > 1:64 * pathogen inactivated or not: NR Treatment details, including time of plasma therapy (e.g. early stage of disease): NR For studies including a control group: comparator (type): best supportive care

NCT04333251 (Continued)

	<ul style="list-style-type: none"> Concomitant therapy: oxygen therapy Treatment cross-overs: not applicable
Outcomes	<ul style="list-style-type: none"> Primary study outcome: reduction in oxygen and ventilation support (time frame: through study completion, an average of 4 weeks) Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR Secondary review outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR Additional outcomes: NR
Starting date	1 April 2020
Contact information	NR
Notes	<ul style="list-style-type: none"> Recruitment status: not yet recruiting Prospective completion date: 31 December 2022 Sponsor/funding: NR

NCT04333355

Study name	Phase 1 study to evaluate the safety of convalescent plasma as an adjuvant therapy in patients with SARS-CoV-2 infection
Methods	<ul style="list-style-type: none"> Trial design: single-arm, phase I, intervention study Sample size: 20 Setting: hospital Country: Mexico Language: English Number of centres: 1

NCT04333355 (Continued)

Participants

- Inclusion criteria
 - * Patients \geq 18 years
 - * Confirmed SARS-CoV-2 infection by RT-PCR
 - * Serious or life-threatening infection defined as:
 - serious: dyspnoea; respiratory rate \geq 30 cycles/min; blood oxygen saturation \leq 93% with an oxygen supply $>$ 60%; PaO₂/FiO₂ $<$ 300; 50% increase in pulmonary infiltrates defined by CT scans in 24-48 h
 - life-threatening infection: respiratory failure; septic shock; dysfunction or multiple organ failure
 - * Refractory to treatment with azithromycin/hydroxychloroquine or chloroquine/ritonavir/lopinavir defined as: 48 h with no improvement in the modified parameters such as serious or clinically imminent infection
 - * Signed informed consent by the patient or by the person responsible for the patient in the case of critically ill patients (spouse or parents)
- Exclusion criteria
 - * Patients with a history of allergic reaction to any type of previous transfusion
 - * Heart failure patients at risk of volume overload
 - * Patients with a history of chronic kidney failure in the dialysis phase
 - * Patients with previous haematological diseases (anaemia $<$ 10 g of haemoglobin, platelets $>$ 100,000/ μ L)
 - * Any case where the study author decides that the patient is not suitable for the protocol

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP:
 - * type of plasma: apheresis plasma
 - * volume: 500 mL total
 - * number of doses: 2
 - * antibody-titre: NR
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): not applicable
- Concomitant therapy: supportive standard care
- Treatment cross-overs: not applicable

Outcomes

- Primary study outcomes: possible adverse effects (time frame: 14 days)
- Primary review outcomes
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR

NCT04333355 (Continued)

- Additional outcomes
 - * Heart failure
 - * Pulmonary oedema
 - * Lung infiltrates by thorax CT
 - * Viral load of SARS-CoV-2 by RT-PCR

Starting date	15 April 2020
Contact information	Servando Cardona-Huerta, MD., Ph.D; +5218112121946; servandocardona@tec.mx Sylvia De la Rosa, MD; +5218111832730; sylvia.delarosa@tec.mx
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 30 April 2021 • Sponsor/funding: Hospital San Jose Tec de MonterreyTecnologico de Monterrey

NCT04338360

Study name	Expanded access to convalescent plasma for the treatment of patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: expanded access • Sample size: NR • Setting: hospital • Country: USA • Language: English • Number of centres: 12
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age \geq 18 years * Laboratory-confirmed diagnosis of infection with SARS-CoV-2 * Admitted to an acute care facility for the treatment of COVID-19 complications * Severe or life-threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease. (Severe COVID-19 is defined by one or more of the following: dyspnoea, respiratory frequency \geq 30/min, blood oxygen saturation \leq 93%, PaO₂/FiO₂ < 300, lung infiltrates > 50% within 24-48 h. Life-threatening COVID-19 is defined as one or more of the following: multiple organ dysfunction or failure, septic shock, respiratory failure) * Informed consent provided by the patient or healthcare proxy • Exclusion criteria: none
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP therapy • Details of CP: <ul style="list-style-type: none"> * type of plasma: * volume: NR * number of doses: 1 * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): not applicable • Concomitant therapy: NR • Treatment cross-overs: not applicable
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: NR

NCT04338360 (Continued)

- Primary review outcomes
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital
 - * QoL: NR
- Additional outcomes: NR

Starting date	NR
Contact information	Michael Joyner, MD; 507-255-4288; USCOVIDplasma@mayo.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: expanded access available • Prospective completion date: NR • Sponsor/funding: Mayo Clinic

NCT04344535

Study name	Convalescent plasma versus standard plasma for COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: randomised phase 1/2 • Sample size: 500 • Setting: hospital • Country: USA • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Adults \geq 18 years * Hospitalised with PCR+ COVID-19 infection * If female must not be pregnant and/or breastfeeding • Exclusion criteria <ul style="list-style-type: none"> * Unable to randomise patient within 14 days of admission to Stony Brook Hospital (or any other hospital if a transfer to Stony Brook Hospital) * In the treating physician's opinion, the patient cannot tolerate a 450-550 mL infusion of plasma over up to 8 h (4 h max per unit), even if prophylaxed with IV diuretic * Contraindication to transfusion or history of prior reactions to blood transfusions • Inclusion criteria for plasma recipients <ul style="list-style-type: none"> * Adults \geq 18 years * Hospitalised with PCR-positive COVID-19 infection * If female must not be pregnant and/or breastfeeding
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP

NCT04344535 (Continued)

- Details of CP:
 - * type of plasma: CP, specific preparation NR
 - * volume: 450-550 mL
 - * number of doses: 2
 - * antibody-titre: ideally > 1:320, but meeting minimum titre per FDA Guidelines for CP
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): within 14 days of hospitalisation
- For studies including a control group: comparator (type): 450-550 mL of plasma with low titre to anti-SARS-CoV-2 antibodies (standard plasma)
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome: number of days patient remains ventilator-free (up to 28 days)
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes (90-day all-cause mortality)
 - * Time to death: yes
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: yes
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes: number of days patient remains ventilator-free (up to 28 days)

Starting date

8 April 2020

Contact information

Contact information not shared

Responsible party: Elliott Bennett-Guerrero, Professor of Anesthesiology, Stony Brook University

Notes

- Recruitment status: enrolling by invitation
- Prospective completion date: 31 August 2021
- Sponsor/funding: Stony Brook University

NCT04345289

Study name

Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia (CCAP)

Methods

- Trial design: investigator-initiated, multicentre, randomised, double-blinded, placebo-controlled, multi-stage trial (Phase 3)
- Sample size: 1500
- Setting: multicentre sites
- Country: Denmark
- Language: English
- Number of centres: 12

NCT04345289 (Continued)

Participants

- Inclusion criteria
 - * ≥ 18 years of age
 - * Confirmed COVID-19 infection by presence of SARS-CoV-2 nucleic acid by PCR
 - * Evidence of pneumonia given by at least 1 of the following: SpO₂ $\leq 93\%$ on ambient air or PaO₂/FiO₂ < 300 mmHg/40 kPa or radiographic findings compatible with COVID-19 pneumonia
 - * Onset of first experienced symptom, defined as 1 respiratory symptom or fever, not > 10 days before admission
 - * For women of childbearing potential: negative pregnancy test and willingness to use contraceptive (consistent with local regulations) during study period
 - * Signed informed consent form by any participant capable of giving consent, or, when the participant is not capable of giving consent, by his or her LAR
- Exclusion criteria
 - * In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 h, irrespective of the provision of treatment
 - * History of allergic reaction to study drug (as judged by the site investigator)
 - * Participating in other drug clinical trials (participation in COVID-19 antiviral trials may be permitted if approved by sponsor)
 - * Pregnant or breastfeeding, positive pregnancy test in a pre-dose examination or patients family planning within 3 months after receiving study agent
 - * Estimated GFR < 30 mL/min
 - * Severe liver dysfunction (Child Pugh score C)
 - * Known history of the following medical conditions: active or latent TB or history of incompletely treated TB; chronic hepatitis B or C infection; retinopathy or maculopathy; neurogenic hearing impairment
 - * Presence of any of the following abnormal laboratory values at screening: absolute neutrophil count (ANC) < 1000 mm³ ($= 1.0 \times 10^9$ /L); ALT $> 5 \times$ ULN; platelet count $< 50,000$ per mm³ ($= 50 \times 10^9$ /L)
 - * Immunosuppression, defined as following: treatment with immunosuppressive agents, chemotherapy or immunomodulatory drugs within 30 days prior to inclusion; use of chronic oral corticosteroids for a non-COVID-19-related condition in a dose $>$ prednisolone 20 mg or equivalent per day for 4 weeks; ongoing chemotherapy
 - * Any serious medical condition or abnormality of clinical laboratory tests that, in the study author's judgment, precludes the patient's safe participation in and completion of the study

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: randomised 1:1:1:1:1 to parallel treatment arms: CP, sarilumab, hydroxychloroquine, baricitinib, IV and SC placebo, or oral placebo
- Details of CP:
 - * type of plasma: preparation method NR
 - * volume: 600 mL
 - * number of doses: 2 x 300 mL given in single infusion
 - * antibody-titre: NR
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): sarilumab, hydroxychloroquine, baricitinib, IV and SC placebo, or oral placebo
- Concomitant therapy: placebo treatment with saline 0.9% (1.14 mL) as a single SC injection, in addition to standard care
- Treatment cross-overs

Outcomes

- Primary study outcome:
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes (up to 90 days)
 - * Time to death: yes

NCT04345289 (Continued)

- Secondary review outcomes:
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: yes
 - * Admission on the ICU
 - * Length of stay on the ICU
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional outcomes
 - * composite endpoint of all-cause mortality or need of invasive mechanical ventilation (up to 28 days)
 - * Ventilator-free days (time frame: 28 days)
 - * Organ failure-free days (time frame: 28 days)
 - * Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status (time frame: 90 days)
 - number of days to improvement of at least 2 categories relative to baseline on the ordinal scale. Categories are as follows: death; hospitalised, in ICU requiring ECMO or mechanical ventilation; hospitalised, on non-invasive ventilation or high-flow oxygen device; hospitalised, requiring supplemental oxygen; hospitalised, not requiring supplemental oxygen; not hospitalised, limitation on activities and/or requiring home oxygen; not hospitalised, no limitations on activities

Starting date	20 April 2020
Contact information	Contact: Thomas Benfield, MD, DMSc+45 38622302 thomas.lars.benfield@regionh.dk
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 15 June 2021 • Sponsor/funding: Thomas Benfield

NCT04345523

Study name	Convalescent plasma therapy versus SOC for the treatment of COVID19 in hospitalized patients (ConPlas-19)
Methods	<ul style="list-style-type: none"> • Trial design: multicentre, randomised, clinical trial • Sample size: 278 • Setting: hospital • Country: Spain • Language: English • Number of centres: 9

NCT04345523 (Continued)

Participants

- Inclusion criteria
 - * Written informed consent prior to performing study procedures. Witnessed oral consent will be accepted in order to avoid paper handling. Written consent by patient or representatives will be obtained as soon as possible
 - * Male or female adult patient ≥ 18 years of age at time of enrolment
 - * Laboratory-confirmed SARS-CoV-2 infection as determined by PCR in naso/oropharyngeal swabs or any other relevant specimen
 - * Patients requiring hospitalisation for COVID-19 without mechanical ventilation (invasive or non-invasive) or high-flow oxygen devices and at least 1 of the following:
 - radiographic evidence of pulmonary infiltrates by imaging (chest X-ray, CT scan, etc.), or
 - clinical assessment (evidence of rales/crackles on exam) and SpO₂ $\leq 94\%$ on room air that requires supplemental oxygen
 - * Not > 12 days between the onset of symptoms (fever or cough) and treatment administration day
- Exclusion criteria
 - * Requiring mechanical ventilation (invasive or non-invasive) or high-flow oxygen devices
 - * > 12 days since symptoms (fever or cough)
 - * Participation in any other clinical trial of an experimental treatment for COVID-19
 - * In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 h, irrespective of the provision of treatments
 - * Any incompatibility or allergy to the administration of human plasma
 - * Stage 4 severe chronic kidney disease or requiring dialysis (i.e. estimated GFR < 30)

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - * type of plasma: prepared approximately 140-200 CP donors
 - * volume: NR
 - * number of doses: NR
 - * antibody-titre: NR
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage within 12 days
- For studies including a control group: comparator (type): randomised 1:1 to CP and standard of care vs standard of care including any drugs that are being used in clinical practice (e.g. lopinavir/ritonavir; darunavir/cobicistat; hydroxy/chloroquine, tocilizumab, etc.), other than those used as part of another clinical trial
- Concomitant therapy: standard of care as specified above
- Treatment cross-overs: none

Outcomes

- Primary study outcome: category changes in ordinal scale (time frame: 15 days) (for categories: see additional outcomes)
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes
 - mortality of any cause at 15 days (time frame: 15 days)
 - mortality of any cause at 29 days (time frame: 29 days)
 - * Time to death: yes (up to 29 days)

NCT04345523 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: NR (up to 29 days)
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional review outcomes
 - * Category changes in ordinal scale (time frame: 15 days)
 - proportion of patients in categories 5, 6 or 7 of the 7-point ordinal scale at day 15 ordinal scale:
 - not hospitalised, no limitations on activities
 - not hospitalised, limitation on activities
 - hospitalised, not requiring supplemental oxygen
 - hospitalised, requiring supplemental oxygen
 - hospitalised, on non-invasive ventilation or high-flow oxygen devices
 - hospitalised, on invasive mechanical ventilation or ECMO
 - death
 - * Time to category 5, 6 or 7 of the ordinal scale (time frame: 29 days)
 - time to change from baseline category to worsening into 5, 6 or 7 categories of the ordinal scale
 - * Oxygenation-free days (time frame: 29 days)
 - * Ventilator-free days
 - * Change in biological parameters (time frame: days 1, 3, 5, 8, 11 and 29) - serum levels of CRP, lymphocyte count, LDH, D Dimer, IL-6, coagulation tests at baseline and days 3, 5, 8, 11, 15 and 29
 - * Antibodies levels in CP donors recovered from COVID-19 (time frame: 3 months)
 - quantitative total antibodies and neutralising antibody activity against SARSCoV-2 in the sera from donors and patients using viral pseudotypes
 - * Viral load (time frame: days 1, 3, 5, 8, 11 and 29)
 - change in PCR for SARS-CoV-2 in naso/oropharyngeal swabs and blood at baseline and on days 3, 5, 8, 11 (while hospitalised); and days 15 and 29 (if able to return to clinic or still hospitalised)

Starting date	3 April 2020
Contact information	Cristina Avendaño Solá, MD, PhD +34 91 191 64 79 cavendano@salud.madrid.org
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting (1 site, the rest not yet recruiting) • Prospective completion date: July 2020 • Sponsor/funding: Cristina Avendaño Solá

NCT04345679

Study name	Anti COVID-19 convalescent plasma therapy
Methods	<ul style="list-style-type: none"> • Trial design: phase 1, single-arm study • Sample size: 20

NCT04345679 (Continued)

	<ul style="list-style-type: none"> • Setting: hospital • Country: Hungary • Language: English • Number of centres
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age: > 18 years * Admitted to hospital due to SARS CoV-2 infection * Written informed consent • Exclusion criteria <ul style="list-style-type: none"> * Age: < 18 years * Female patients who are pregnant or breastfeeding * Patients with prior allergic reaction to transfusion * Patients who received in the past 30 days immunoglobulin therapy • Inclusion criteria for blood donors <ul style="list-style-type: none"> * Age: > 18 and < 60 years * Body weight: > 50 kg * Confirmed previous SARS CoV-2 infection * 2 negative SARS CoV-2 test results * Written informed consent * Neutralising antibody titre min 1:120 • Exclusion criteria for blood donors <ul style="list-style-type: none"> * Age: < 18 or > 60 years * Female patients who are pregnant * HIV1/2 hepatitis B/C or syphilis infection
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: plasmapheresis donation of 400 mL will be performed in participants who recovered from COVID-19 and who are otherwise eligible for plasma donation, blood-type matched * volume: 200 mL * number of doses: 1 * antibody-titre: NR * pathogen inactivated or not: > level of 1:320 • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): none (single-arm) • Concomitant therapy: NR • Treatment cross-overs: none (single-arm)
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: changing of viral load of SARS-CoV2 • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes <ul style="list-style-type: none"> <input type="checkbox"/> mortality (time frame: day 7, 12, 28) * Time to death: yes (up to 28 days)

NCT04345679 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (duration of mechanical ventilation up to 28 days)
 - * 30-day and 90-day mortality: NR (up to 28 days)
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional outcomes
 - * Changing of viral load of SARS-CoV2 (time frame: day 1,3, 7, 12)
 - * Clinical status (time frame: day 7, 12, 28)
 - clinical status assessed according to the WHO guideline
 - * Changes in immunoglobulin G COVID-19 antibody titre (time frame: 12 days)
 - * Changes at the cytokine pattern (time frame: 12 days)

Starting date	14 April 2020
Contact information	<ul style="list-style-type: none"> • Eszter Fodor, medical doctor; +36306640494; eszter.fodor@orthosera.com • Zsombor Lacza, MD, PhD; +36305249554; zsombor.lacza@orthosera.com
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 1 April 2021 • Sponsor/funding: Orthosera Kft

NCT04345991

Study name	Efficacy of convalescent plasma to treat COVID-19 patients, a nested trial in the CORIMUNO-19 cohort
Methods	<ul style="list-style-type: none"> • Trial design: randomised, parallel-assignment • Sample size: 120 (60 in each arm) • Setting: early-stage disease • Country: France • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Patients included in the CORIMUNO-19 cohort * Onset of COVID-19 functional signs < 8 days (plasma transfusion may occur up to day 10 of onset) * Mild severity as described in the WHO scale • Exclusion criteria <ul style="list-style-type: none"> * Pregnancy * Current documented and uncontrolled bacterial infection * Prior severe (grade 3) allergic reactions to plasma transfusion
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune globulin therapy: CP

NCT04345991 (Continued)

- Details of CP:
 - * type of plasma: details of preparation not described
 - * volume: 200-220 mL
 - * number of doses: 2-4
 - * antibody-titre: NR
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage (within 10 days of symptom onset)
- For studies including a control group: comparator (type): standard of care
- Concomitant therapy: standard of care
- Treatment cross-overs: not applicable

Outcomes

- Primary study outcome: survival without needs of ventilator utilisation, WHO progression scale \geq 6 at day 4 of randomisation
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: yes
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: no (up to 28 days)
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional outcomes
 - * WHO progression scale (time frame: at 4, 7 and 14 days after randomisation)
 - * Survival without needs of ventilator utilisation (time frame: at 4, 7 and 14 days after randomisation)
 - * Survival without use of immunomodulatory drugs (time frame: at day 14 after randomisation)

Starting date 14 April 2020

 Contact information Karine LACOMBE, PU-PH +33 149283196 karine.lacombe2@aphp.fr

 Notes

- Recruitment status: not yet recruiting
- Prospective completion date: 1 June 2020
- Sponsor/funding: Assistance Publique - Hôpitaux de Paris

NCT04346446

Study name Efficacy of convalescent plasma therapy in severely sick COVID-19 patients: a pilot randomized controlled trial

 Methods

- Trial design: randomised, clinical trial
- Sample size: 20
- Setting: hospital
- Country: India
- Language: English

NCT04346446 (Continued)

	<ul style="list-style-type: none"> • Number of centres: 2
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Severe COVID-19 infections defined as WHO Interim Guidance and the Guideline of Diagnosis and Treatment of COVID-19 of National Health Commission of China (version 5.0) with confirmation by RT-PCR assay with severe disease i.e. meeting any 2 of the following criteria: <ul style="list-style-type: none"> <input type="checkbox"/> respiratory distress, respiratory rate ≥ 30 breaths/min <input type="checkbox"/> oxygen saturation level $< 93\%$ in resting state <input type="checkbox"/> $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg <input type="checkbox"/> lung infiltrates $> 50\%$ within 24-48 h • Exclusion criteria <ul style="list-style-type: none"> * Donors who gave negative consent to participate in the study * Aged < 18 years or > 65 years * Known comorbid diseases (cardiopulmonary disease-structural or valvular heart disease, coronary artery disease, COPD, chronic liver disease, chronic kidney disease) * Multi-organ failure or requiring mechanical ventilation * Pregnancy * HIV or hepatitis * BMI > 35 kg/m² * Extremely moribund patients with an expected life expectancy of < 24 h * Failure to give informed consent from the patient or family members * Haemodynamic instability requiring vasopressors * Previous allergic history to plasma * $\text{PaO}_2/\text{FiO}_2 < 150$ * Donors who were recovered with use of steroids during treatment
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: NR, up to 500 mL collected * volume: 200-600 mL * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): randomised 1:1 to CP or random plasma and best supportive care • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: proportion of participants remaining free of mechanical ventilation • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes <ul style="list-style-type: none"> <input type="checkbox"/> mortality in both groups (time frame: day 28) * Time to death: NR

NCT04346446 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional outcomes
 - * Improvement in PaO₂/FiO₂ ratio in both groups (time frame: day 2)
 - * Improvement in PaO₂/FiO₂ ratio in both groups (time frame: day 7)
 - * Improvement in SOFA score in both groups (time frame: day 2)
 - * Improvement in SOFA score in both groups (time frame: day 7)
 - * Requirements of vasopressor in both groups (time frame: day 28)
 - * Days free of dialysis in both groups (time frame: day 28)

Starting date	14 April 2020
Contact information	Dr Meenu Bajpai, MD, Institute of Liver and Biliary Sciences, India mailto:meenubajpai%40hot-mail.com?subject=NCT04346446 , ILBS-COVID-02, Efficacy of Convalescent Plasma Therapy in Severely Sick COVID-19 Patients
Notes	<ul style="list-style-type: none"> • Recruitment status: completed • Prospective completion date: 20 June 2020 • Sponsor/funding: Institute of Liver and Biliary Sciences, India

NCT04346589

Study name	Convalescent antibodies infusion in critically ill COVID 19 patients
Methods	<ul style="list-style-type: none"> • Trial design: interventional (single-arm) • Sample size: 10 • Setting: critically ill patients • Country: Italy • Language: English • Number of centres: 5
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * > 18-years, men and women * COVID-19 pneumonia diagnosed by standard criteria * Need of ventilator support * Informed consent for participation in the study (critically ill patients will be unable to provide consent. Consent will be oral if a written consent will be impossible. If the patient is incapable of giving an informed consent and an authorised representative is not available without a delay that would, in the opinion of the Investigator, compromise the potential life-saving effect of the treatment this can be administered without consent. Consent to remain in the research should be sought as soon as the conditions of the patient will allow it). * < 48 h of mechanical ventilation

NCT04346589 (Continued)

	<ul style="list-style-type: none"> Exclusion criteria <ul style="list-style-type: none"> * Patient being treated with other anti-COVID-19 experimental treatments
Interventions	<ul style="list-style-type: none"> CP therapy or hyperimmune immunoglobulin therapy: CP Details of CP: <ul style="list-style-type: none"> * type of plasma: anti-coronavirus antibodies obtained with double-filtration plasmapheresis (DFPP) from convalescent patients * volume: convalescent antibodies will be obtained with one DFPP procedure from consenting donors * number of doses: 1 * antibody-titre: NR * pathogen inactivated or not: NR Treatment details, including time of plasma therapy (e.g. early stage of disease): critically ill mechanically ventilated patients (< 48 h mechanical ventilation) For studies including a control group: comparator (type): none (single-arm) Concomitant therapy: NR Treatment cross-overs: none (single-arm)
Outcomes	<ul style="list-style-type: none"> Primary study outcome: number of mechanical ventilation days Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes (up to 6 months) * Time to death: yes Secondary review outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: yes * Admission on the ICU: yes * Length of stay on the ICU: yes * Time to discharge from hospital: NR * QoL: NR Additional outcomes <ul style="list-style-type: none"> * Number of mechanical ventilation days * Shift to CPAP ventilation
Starting date	April 2020
Contact information	Piero Luigi Ruggenti, MD; 0039 035 267 ext 3814; pruggenti@asst-pg23.it
Notes	<ul style="list-style-type: none"> Recruitment status: not yet recruiting Prospective completion date: July 2020 Sponsor/funding: A.O. Ospedale Papa Giovanni XXIII, Aferetica - Italy (BO)

NCT04347681

Study name	Potential efficacy of convalescent plasma to treat severe COVID-19 and patients at high risk of developing severe COVID-19
Methods	<ul style="list-style-type: none"> Trial design: non-randomised, parallel assignment Sample size: 40 (all receiving intervention)

NCT04347681 (Continued)

	<ul style="list-style-type: none"> • Setting: hospital • Country: Saudi Arabia • Language: English • Number of centres: 10
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * ≥ 18 years * COVID 19 confirmed as per case definition of CDC or Ministry of Health/Waqayah * Must have been requiring ICU care or severe or immediately life-threatening care: 1. patient requiring ICU admission; 2. severe disease, defined as: <ul style="list-style-type: none"> <input type="checkbox"/> dyspnoea <input type="checkbox"/> respiratory frequency ≥ 30/min <input type="checkbox"/> blood oxygen saturation ≤ 93% <input type="checkbox"/> PaO₂/FiO₂ < 300, and/or lung infiltrates > 50% within 24-48 h * 3. Life-threatening disease is defined as: <ul style="list-style-type: none"> <input type="checkbox"/> respiratory failure <input type="checkbox"/> septic shock, and/or <input type="checkbox"/> multiple organ dysfunction or failure • Exclusion criteria <ul style="list-style-type: none"> * Negative or non-conclusive test COVID-19 RT-PCR test for SARS-CoV-2 * Mild symptoms * Hospitalisation not requiring ICU admission
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune globulin therapy: CP therapy • Details of CP: <ul style="list-style-type: none"> * type of plasma: NR * volume: 10-15 mL/kg body weight of recipient * number of doses: 1-5 (up to 5 times daily) * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): none • Concomitant therapy: NR • Treatment cross-overs: none (single-arm)
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: ICU length of stay, safety and serious adverse reactions • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes (up to 12 weeks) * Time to death: yes (up to 12 weeks) • Secondary review outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes * Number of participants with SAEs: yes * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: yes * Admission on the ICU: yes * Length of stay on the ICU: yes * Time to discharge from hospital: NR * QoL: NR

NCT04347681 (Continued)

- Additional outcomes
 - * Days to clinical recovery, defined as number of days to symptoms resolution and COVID 19 negative PCR (by nasopharyngeal swab) (time frame: time from signing consent to recovery, up to 12 weeks)

Starting date	12 April 2020
Contact information	Hani AL-Hashmi, MD; 00966564773377; hanih.hashmi@kfsh.med.sa Mahammad Awadallah, MSc; 00966545032312; mahammad.awadalla@kfsh.med.sa
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting in 1 site • Prospective completion date: 11 April 2021 • Sponsor/funding: King Fahad Specialist Hospital Dammam

NCT04348656

Study name	Convalescent plasma for hospitalized adults with COVID-19 respiratory illness (CONCOR-1)
Methods	<ul style="list-style-type: none"> • Trial design: randomised, clinical trial • Sample size: 1200 • Setting: hospital • Country: Canada • Language: English • Number of centres: 27
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * ≥ 16 years old * Admitted to hospital with confirmed COVID-19 respiratory illness * Receiving supplemental oxygen * 500 mL of ABO-compatible CP is available • Exclusion criteria <ul style="list-style-type: none"> * Onset of symptoms > 12 days prior to randomisation * Intubated or plan in place for intubation * Plasma is contraindicated (e.g. history of anaphylaxis from transfusion) * Decision in place for no active treatment
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * volume: 500 mL of CP (from 1 single-donor unit of 500 mL or 2 units of 250 mL from 1-2 donations) collected by apheresis from donors who have recovered from COVID-19 and frozen (1 year expiration date from date of collection) * number of doses: when administering 2 units of 250 mL, the 2nd unit will be administered after the first, and no longer than 12 h later * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): randomised 1:1 to CP and standard care • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: endpoint of the need for intubation or patient death in hospital

NCT04348656 (Continued)

- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes
 - intubation or death in hospital (time frame: day 30)
 - * Time to death: yes
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: yes
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional outcomes
 - * Need for renal replacement therapy (time frame: day 30)
 - * Development of myocarditis (time frame: day 30)

Starting date	27 April 2020
Contact information	Donald M Arnold, MD, McMaster University, Hamilton, Canada arnold@mcmaster.ca
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 31 December 2020 • Sponsor/funding: Hamilton Health Sciences Corporation, Canada

NCT04348877

Study name	Plasma rich antibodies from recovered patients from COVID19 (PRA-001)
Methods	<ul style="list-style-type: none"> • Trial design: single-arm, interventional • Sample size: 20 • Setting: critically ill patients • Country: Egypt • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * 18-80 years old * Laboratory-confirmed COVID-19 * Severe or immediately life-threatening COVID-19 (severe disease is defined as: dyspnoea, respiratory frequency ≥ 30/min, blood oxygen saturation $\leq 93\%$, PaO₂/FiO₂ < 300, and/or lung infiltrates $> 50\%$ within 24-48 h. Life-threatening disease is defined as: respiratory failure, septic shock, and/or multiple organ dysfunction or failure) * Must provide informed consent by patient or his/her legal guardian or professional legal representative

NCT04348877 (Continued)

- Exclusion criteria
 - * Mild or moderate COVID-19
 - * Participation in any investigational clinical study, other than observational, within the past 30 days; or plans to participate in such a study at any time from the day of enrolment until 30 days post-treatment in the current study

Interventions

- CP therapy or hyperimmune globulin therapy: CP therapy
- Details of CP:
 - * type of plasma: other details not specified
 - * volume: 400 mL
 - * number of doses: NR
 - * antibody-titre: NR
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): none
- Concomitant therapy: standard of care (antiviral, hydroxychloroquine and antibiotics)
 - * (oseltamivir (75 mg/12 h for 5-10 days) and hydroxychloroquine (400 mg twice in first day, 200 mg twice for 4-9 days) ± azithromycin 500 mg daily for 5 days
- Treatment cross-overs: none

Outcomes

- Primary study outcome: viral COVID-19 clearance
- Primary review outcomes
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes
 - * Viral COVID-19 clearance (time frame: 14 days)
 - * Radiological improvement (time frame: 14 days)
 - * Clinical improvement in form of normal body temperature for 48 h (time frame: 14 days)

Starting date

20 April 2020

Contact information

Hossam Fahmy, Professor of Faculty of Medicine, Ain Shams University

Notes

- Recruitment status: not yet recruiting
- Prospective completion date: December 2020
- Sponsor/funding: Ain Shams University

NCT04352751

Study name	Experimental use of convalescent plasma for passive immunization in current COVID-19 pandemic in Pakistan in 2020
Methods	<ul style="list-style-type: none"> • Trial design: single-arm, interventional • Sample size: 2000 • Setting: moderate-severe cases • Country: Pakistan • Language: English • Number of centres: 1 reported
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Informed consent must have been obtained * Confirmed COVID-19 cases confirmed by RT-PCR laboratory tests * Moderately severe or severe life-threatening COVID-19 related features: <ul style="list-style-type: none"> <input type="checkbox"/> moderately severe disease as defined by the following features: shortness of breath; respiratory rate \geq 30/min; arterial blood oxygen saturation \leq 92%; and/or lung infiltrates $>$ 25% within 24-48 h <input type="checkbox"/> severe life-threatening disease as defined by the presence of any of the following features: respiratory failure; shock; multiple organ dysfunction • Exclusion criteria <ul style="list-style-type: none"> * Allergy history of plasma, sodium citrate and methylene blue * For patients with history of autoimmune system diseases or selective IgA deficiency, the application of CP should be evaluated cautiously by clinicians * Patients having evidence of uncontrolled cytokine release syndrome leading to end-stage multiorgan failure
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune globulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: standard apheresis plasma collection protocol using Haemonetics MCS+ intermittent blood flow system or Terumo Optia, Cobe-Spectra, Trima or Fresenius continuous flow system to be used. 900-1000 mL collected each time * volume <ul style="list-style-type: none"> <input type="checkbox"/> children: 15 mL/kg over 4-6 h once in patients under 35 kg body weight <input type="checkbox"/> adults: maximum 450-500 mL over 4-6 h once in all adult patients * number of doses: 1 * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): none • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: change in COVID-19 severity status (for categories: see additional outcomes) • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR

NCT04352751 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes (information will be recorded)
 - * Number of participants with SAEs: yes (information will be recorded)
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (up to 4 weeks post-treatment)
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes
 - * Change in COVID-19 severity status (time frame: up to 9 days). Improvement in disease severity will be regarded as a shift from critical to severe or from severe to mild disease category. The various disease categories are defined as following:
 - mild COVID-19, defined by the absence of features given in criteria for moderate and severe disease
 - severe COVID-19, defined by the presence of any of the following features: shortness of breath; respiratory rate ≥ 30 /min; arterial blood oxygen saturation $\leq 93\%$; lung infiltrates $> 50\%$ within 24-48 h
 - critical COVID-19, defined by the presence of any of the following features: respiratory failure; shock; multiple organ dysfunction

Starting date	April 2020
Contact information	Contact: Dr. Arshi Naz, PhD, Diplab; 00923232234376; labarshi@yahoo.com Contact: Dr. Neeta Maheshwary, MBBS M.Phil; 00923208247773; drneeta@hiltonpharma.com
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: April 2021 • Sponsor/funding: Hilton Pharma

NCT04353206

Study name	Convalescent plasma in ICU patients with COVID-19-induced respiratory failure
Methods	<ul style="list-style-type: none"> • Trial design: single-arm, interventional • Sample size: 90 • Setting: ICU • Country: USA • Language: English • Number of centres: 3
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * ≥ 18 years * Respiratory failure requiring mechanical ventilation due to COVID-19-induced pneumonia with confirmation via SARS-CoV-2 RT-PCR testing * PaO₂/FiO₂ ratio < 300 (or SpO₂/FiO₂ < 315) * Bilateral pulmonary infiltrates

NCT04353206 (Continued)

- Exclusion criteria
 - * Contraindication to transfusion (severe volume overload, history of anaphylaxis to blood products)
 - * In the opinion of the site investigator or primary clinical care team, anticipated to die within 48 h
 - * Acute or chronic disease/illness that, in the opinion of the site investigator, has an expected life expectancy of < 28 days unrelated to COVID-19-induced pneumonia (e.g. stage IV malignancy, neurodegenerative disease, anoxic brain injury, etc.)
 - * Use of home oxygen at baseline
 - * Use of home mechanical ventilation at baseline (CPAP or bi-level positive airway pressure without need for oxygen is NOT an exclusion)
 - * Respiratory failure caused by illness other than SARS-CoV-2
 - * Other documented uncontrolled infection
 - * > 72 h have elapsed since first meeting inclusion criteria
 - * Severe DIC, TTP, or antithrombin III deficiency needing factor replacement, fresh-frozen plasma, cryoprecipitate
 - * On warfarin and deemed necessary to maintain therapeutic international normalised ratio (because the CP will reverse the warfarin effect)
 - * On dialysis at the time enrolment is considered
 - * Active intracranial bleeding
 - * Clinically significant myocardial ischaemia
 - * Prisoner or incarceration
 - * Pregnancy or active breast feeding
 - * Has already received CP for COVID-19 infection during current admission
 - * Current participation in another interventional research study
 - * Inability or unwillingness of subject or legal surrogate/representative to give written informed consent

Interventions

- CP therapy or hyperimmune globulin therapy: CP therapy
- Details of CP:
 - * type of plasma: as per FDA guidelines
 - * volume: NR
 - * number of doses: 1-6 (1-2 units day 0, 3, 6)
 - * antibody-titre: NR
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): not > 72 h have elapsed since first meeting inclusion criteria
- For studies including a control group: comparator (type): none
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome: proportion of participants who consent to the study and receive at least one dose of CP
- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes (up to 60 days)
 - * Time to death: yes (up to 60 days)

NCT04353206 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: yes (up to 60 days)
 - * Admission on the ICU: yes (all in ICU)
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes
 - * Proportion of participants who consent to the study and receive at least one dose of CP (time frame: 60 days)
 - * Respiratory status and overall clinical status will be reviewed during follow-up (on days 14, 28, and 60)

Starting date	May 2020
Contact information	Noah Merin, MD PhD; 310-423-1160; Noah.Merin@cshs.org David Hager, MD PhD; dhager1@jhmi.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: May 2021 • Sponsor/funding: Noah Merin, Johns Hopkins University, University of Pittsburgh Medical Center

NCT04354831

Study name	A study evaluating the efficacy and safety of high-titre anti-SARS-CoV-2 plasma in hospitalised patients with COVID-19 infection
Methods	<ul style="list-style-type: none"> • Trial design: non-randomised • Sample size: 106 • Setting: hospital • Country: USA • Language: English • Number of centres: NR
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age ≥ 18 years * Hospitalised as an inpatient with positive COVID-19 test by PCR * Presence of respiratory symptoms with any of severe features as below: <ul style="list-style-type: none"> <input type="checkbox"/> respiratory rate ≥ 24/min <input type="checkbox"/> oxygen support > 3 L/min by nasal cannula <input type="checkbox"/> new onset or worsening of respiratory symptoms with radiologic confirmation of bilateral ground glass opacities that cannot be attributed to another cause * Patient/HCPA must agree to storage of blood specimens for future testing * Patient/HCPA is willing and able to provide electronic informed consent and comply with all protocol requirements. If patient is unable to consent due to incapacity, HCPA should be defined and able to consent for the patient * Allowed to receive all standard of care. Co-enrolment in other clinical trials is permitted

NCT04354831 (Continued)

- Exclusion criteria
 - * Women of childbearing potential with positive pregnancy test (mandatory)
 - * Breastfeeding
 - * Receipt of pooled immunoglobulin (e.g. IVIG or other hyperimmune globulin products) in past 14 days. This does not apply to monoclonal antibodies
 - * Mechanical ventilation for > 14 days
 - * Days from symptom onset > 21 days
 - * Expected survival < 72 h
 - * Contraindication to transfusion or history of prior reactions to transfusion blood products including any proven history of TRALI
 - * Patients who were previously admitted to ICU cannot be enrolled in the non-ICU cohort. These patients could need ICU-level care subsequently and at that time point could be considered for ICU cohort.

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP:
 - * type of plasma: SARS-CoV-2 CP
 - * volume: 1-2 units; ~200-400 mL maximum dose as 7 mL/kg adjusted ideal body weight
 - * number of doses: study drug will be administered as a single IV infusion
 - * antibody-titre: NR
 - * pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): NR
- Concomitant therapy: NR
- Treatment cross-overs: not applicable

Outcomes

- Primary study outcome: overall mortality within 60 days
- Primary review outcomes
 - * All-cause mortality at hospital discharge: overall mortality within 60 days
 - * Time to death: yes
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes: NR

Starting date

1 May 2020

Contact information

Mary Beth Graham, MD, Medical College of Wisconsin, USA

mailto:mbgraham%40mcw.edu?subject=NCT04354831, PRO00037712, A Study Evaluating the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 Plasma in Hospitalized Patients With COVID-19 Infection

Notes

- Recruitment status: not yet recruiting
- Prospective completion date: 1 May 2023

NCT04354831 (Continued)

- Sponsor/funding: Medical College of Wisconsin, USA

NCT04355767

Study name	Convalescent plasma versus placebo in emergency room patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 206 • Setting: patients presenting to ED • Country: USA • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age \geq 18 years old * Patients requiring clinical evaluation in the ED but who do not require hospital admission * Patients who are within 14 days since the onset of COVID-19 symptoms and are confirmed to have the disease via COVID-19 SARS-CoV-2 RT-PCR testing or rapid RNA assay * Patient agrees to storage of specimens for future testing • Exclusion criteria <ul style="list-style-type: none"> * Women who are pregnant or breastfeeding * Received pooled immunoglobulin in the past 30 days * Contraindication to transfusion or history of prior reactions to transfusion blood products
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune globulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: CP, other details not provided * volume: 200-600 mL * number of doses: 1-2 * antibody-titre: $>$ 1:80 * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): within 14 days' onset of disease • For studies including a control group: comparator (type): normal plasma • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: time to disease progression • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR

NCT04355767 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes
 - * Time to disease progression (time frame: 15 days)
 - * Change in symptom severity over time (time frame: 15 days)

Starting date	May 2020
Contact information	Study team; 650-724-7186; jcunning@stanford.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: December 2022 • Sponsor/funding: Stanford University

NCT04355897

Study name	CoVID-19 plasma in treatment of CoVID-19 patients
Methods	<ul style="list-style-type: none"> • Trial design: single-arm intervention study • Sample size: 100 • Setting: hospital • Country: USA • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age 18-80 years * Symptomatic CoVID-19 disease requiring hospitalisation * SARS-CoV-19 PCR positive * Elevated high-sensitivity troponin • Exclusion criteria <ul style="list-style-type: none"> * Multi-organ/system failure * Renal insufficiency (estimated GFR < 30 or renal replacement therapy) * Liver dysfunction (> 3 x ULN serum glutamic oxaloacetic transaminase/serum glutamate pyruvate transaminase) * Chronic immunosuppression therapy * Prior organ transplant * Prior multiple transfusions for myelodysplastic syndrome * Prior treatment with plasma, immunoglobulin transfusion within 30 days * Allergic reaction to blood/ plasma products * Pregnant or breast feeding at the time of study * Inability to provide informed consent

NCT04355897 (Continued)

Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune globulin therapy: CP • Details of CP: <ul style="list-style-type: none"> * type of plasma: CP, details of preparation not specified * volume: 500 mL * number of doses: 1 * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients with elevated high-sensitivity troponin or requiring mechanical ventilation • For studies including a control group: comparator (type): none • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: mortality at day 28 • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes (at day 28) * Time to death: yes • Secondary review outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes * Number of participants with SAEs: yes * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (at day 28) * 30-day and 90-day mortality: NR (until day 28) * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR • Additional outcomes <ul style="list-style-type: none"> * Requirement and duration for mechanical ventilation (at day 28)
Starting date	NR
Contact information	Dean J Kereiakes, MD; 513-585-1777; lindnermd@thechristhospital.com
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: August 2020 • Sponsor/funding: The Christ Hospital

NCT04356482

Study name	Determination of the dose and effectiveness of convalescent plasma in severely and very severely ill patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: interventional, single-arm • Sample size: 90 • Setting: critically ill patients • Country: Mexico • Language: English • Number of centres: 4

NCT04356482 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * All patients with COVID-19 test positive * Severely ill patient <ul style="list-style-type: none"> <input type="checkbox"/> respiratory difficulty <input type="checkbox"/> sat O₂ < 93% without O₂ but improves with the use of supplemental oxygen <input type="checkbox"/> CT scan image: COVID-19-compatible pneumonia <input type="checkbox"/> ≥ 1 of at least: SOFA = 0, D-dimer ≥ 500, age ≥ 65 years, comorbidities such as high blood pressure, diabetes mellitus type I and II, chronic kidney failure, controlled or cured cancer, ≥ 1 degree of obesity * Very severely ill <ul style="list-style-type: none"> <input type="checkbox"/> respiratory difficulty that does not improve with supplemental oxygen, requiring intubation and connecting to ventilatory support of no > 72 h or 3 days <input type="checkbox"/> CT image: COVID-19 compatible pneumonia <input type="checkbox"/> ≥ 1 of at least: SOFA ≥ 1, D-Dimer ≥ 750, age ≥ 65 years, comorbidities such as hypertension, diabetes mellitus type I and II, chronic kidney failure, controlled or cured cancer, ≥ 1 degree of obesity <input type="checkbox"/> survival over 5 days * Pregnant women are accepted • Exclusion criteria <ul style="list-style-type: none"> * Patients with asymptomatic/mild disease for COVID-19 * Children < 16 years old * Patients with atypical pneumonia without COVID-19 diagnostic for PCR-RT
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune globulin therapy: CP therapy • Details of CP: <ul style="list-style-type: none"> * type of plasma: CP, details not provided * volume: different amounts to be given to severe vs very severe ill patients, not specified * number of doses: NR * antibody-titre: NR * pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): none • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: clinical improvement, improvement in tomographic image, test positivity for COVID-19, early and late complications • Primary review outcomes <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR • Secondary review outcomes <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes * Number of participants with SAEs: yes * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (up to 22 days) * 30-day and 90-day mortality: NR * Admission on the ICU: yes * Length of stay on the ICU: yes * Time to discharge from hospital: NR * QoL: NR

NCT04356482 (Continued)

	<ul style="list-style-type: none"> Additional outcomes <ul style="list-style-type: none"> Improvement in tomographic image (time frame: day -1 to day +12) Test positivity for COVID-19 (time frame: day +6 to day +12)
Starting date	May 2020
Contact information	Luis M Villela, MD; +526624756529; luisvillela@yahoo.com Diego Espinoza, MD; +526623862375; dr.espinoza.peralta@gmail.com
Notes	<ul style="list-style-type: none"> Recruitment status: not yet recruiting Prospective completion date: December 2020 Sponsor/funding: Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado

NCT04356534

Study name	Convalescent plasma trial in COVID-19 patients
Methods	<ul style="list-style-type: none"> Trial design: randomised, clinical trial Sample size: 40 Setting: hospitalised patients Country: Bahrain Language: English Number of centres: 1
Participants	<ul style="list-style-type: none"> Inclusion criteria <ul style="list-style-type: none"> COVID-19 diagnosis Hypoxia, (oxygen saturation of $\leq 92\%$ or $PO_2 < 60$ mmHg on arterial blood gas analysis) and patient requiring oxygen therapy) Evidence of infiltrates on chest X-ray or CT scan Able to give informed consent Patients age ≥ 21 with no upper age Exclusion criteria <ul style="list-style-type: none"> Mild disease not requiring oxygen therapy Normal chest X-ray and CT scan Requiring ventilatory support History of allergy to plasma, sodium citrate or methylene blue History of autoimmune disease or selective IGA deficiency
Interventions	<ul style="list-style-type: none"> CP therapy or hyperimmune immunoglobulin therapy: CP Details of CP: <ul style="list-style-type: none"> volume: 400 mL number of doses: 200 mL x 2 (2 consecutive days) antibody-titre: NR pathogen inactivated or not: NR Treatment details, including time of plasma therapy (e.g. early stage of disease): NR For studies including a control group: comparator (type): randomised to local standard of care, which include antivirals and supportive care or plasma therapy using CP with antibody against SARS-CoV-2 plus routine local standard of care Concomitant therapy: NR Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> Primary study outcome: requirement for invasive ventilation

NCT04356534 (Continued)

- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes
 - mortality rate (time frame: mortality rate at 28 days)
 - * Time to death: yes
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes
 - * Time to viral clearance (time frame: 10 days or until discharge)
 - * Radiological improvement (time frame: 10 days or until discharge)
 - * Reduction in white cell count (time frame: 10 days or until discharge)
 - * CRP measurement (time frame: 10 days or until discharge)
 - * LDH measurement (time frame: 10 days or until discharge)
 - * Procalcitonin measurement (time frame: 10 days or until discharge)
 - * D-Dimer measurement (time frame: 10 days or until discharge)
 - * Ferritin measurement (time frame: 10 days or until discharge)
 - * Troponin T measurement (time frame: 10 days or until discharge)
 - * Brain natriuretic peptide measurement (time frame: 10 days or until discharge)

Starting date	19 April 2020
Contact information	Manaf Al Qahtani, Dr. Royal College of Surgeons in Ireland - Bahrain; mailto:mqahtani%40rc-si-mub.com?subject=NCT04356534, BDF/R&REC/2020-423, Convalescent Plasma Trial in COVID -19 Patients
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 30 June 2020 • Sponsor/funding: Royal College of Surgeons in Ireland - Medical University of Bahrain

NCT04358211

Study name	Expanded access to convalescent plasma to treat and prevent pulmonary complications associated with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: single-arm feasibility study, expanded access- compassionate use • Sample size: NR- intermediate-size population • Setting: inpatient • Country: USA • Language: English • Number of centres: NR

NCT04358211 (Continued)

- Participants
- Inclusion criteria
 - * All sexes
 - * ≥ 18 years
 - * COVID-19 confirmed via SARS-CoV-2 RT-PCR testing
 - * Population1
 - Associated severe pulmonary complications-hospitalised and intubated in the ICU with COVID-19 respiratory symptoms
 - Written informed consent and comply with all protocol requirements, or requirement for informed consent is waived due to the inability to communicate with the patient and unable to identify LAR
 - Consents to storage of specimens for future testing, or consent waived
 - The requirements to waive a consent are delineated in 21 CFR 50.23 and will be followed
 - Pregnant and breastfeeding women will not be excluded from the study
 - * Population 2
 - Coronavirus-associated complications in hospitalised patient with COVID-19 respiratory symptoms
 - Hospitalised within 3-7 days from the beginning of illness
 - Patient is willing and able to provide written informed consent and comply with all protocol requirements
 - Patient agrees to storage of specimens for future testing
 - Exclusion criteria
 - * Population 1:
 - Contraindication to transfusion (severe volume overload, history of anaphylaxis to blood products).
 - Severe multi-organ failure with expected life expectancy < 24 h as determined by the treating physician
 - * Population 2:
 - Female participants with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period
 - Receipt of pooled immunoglobulin in past 30 days
 - Contraindication to transfusion or history of prior reactions to transfusion blood products

- Interventions
- Intervention(s): CP
 - Details of CP:
 - * Type of plasma: ABO-compatible SARS-CoV-2 CP
 - * Volume: 200-400 mL
 - * Number of doses: 1-2 units
 - * Antibody-titre: >1:160 (a moving target as assays develop)
 - * Pathogen inactivated: NR
 - Treatment details, including time of plasma therapy (e.g. early stage of disease)
 - * Population 1: intubated, mechanically ventilated patients with confirmed COVID-19 pneumonia by chest X-ray or chest CT
 - * Population 2: hospitalised patients with acute respiratory symptoms between 3 and 7 days after the onset of symptoms, with COVID-19
 - Comparator: N/A
 - Concomitant therapy: NR
 - Treatment cross-overs: yes/ no

- Outcomes
- Primary study outcome(s): NR
 - Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR

NCT04358211 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions):
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes: NR

Starting date	3 April 2020
Contact information	Nakhle Saba, MD nsaba@tulane.edu Tulane Medical Center Available New Orleans, Louisiana, USA, 70112
Notes	<ul style="list-style-type: none"> • Recruitment status: expanded access, available. • Prospective completion date: NR • Sponsor/funding: Nakhle Saba, MD. Tulane

NCT04358783

Study name	Phase II, randomized, double-blind, controlled clinical trial evaluating the efficacy and safety of plasma from patients cured of COVID-19 compared to the best available therapy in subjects with SARS-CoV-2 pneumonia
Methods	<ul style="list-style-type: none"> • Trial design: RCT, double-blind. Phase 2. Parallel assignment. Participants electronically randomised 2:1 (plasma vs BAT) in a double-blind fashion. Quadruple masking (participant, care provider, investigator, outcomes assessor) • Sample size: 20 in one arm, 10 in the other (n = 30) • Setting: inpatient • Country: Mexico • Language: English • Number of centres: 1 <p>Clinical trial comparing convalescent plasma to BAT for the treatment of severely ill and critically ill patient with COVID-19</p> <p>Patients with SARS-CoV-2 PCR-confirmed infection with pulmonary infiltrates and hypoxaemia will be screened and invited to participate</p>

NCT04358783 (Continued)

Participants

- Inclusion criteria
 - * Men or women ≥ 18 years. A woman of childbearing age, must agree to practice abstinence or to use an effective method of contraception during the study period
 - * Vascular access suitable for administration of haemocomponents
 - * SARS-CoV-2-positive RT-PCR
 - * Negative pregnancy test in case of a woman of reproductive age
 - * Signing of evidentiary document of informed consent
 - * Hospital admission for SARS-CoV-2 pneumonia with supplemental oxygen requirements
 - * Participants who access the storage of biological samples for future examination
- Exclusion criteria
 - * Respiratory rate > 30 RPM, $SO_2 < 93\%$, $PaO_2/FiO_2 < 200$ despite intervention with oxygen therapy after 60 min of hospitalisation
 - * New alteration of the state of alert that does not revert after interventions 60 min after admission to hospital
 - * $PAM \leq 65$ mmHg despite initial resuscitation on arrival at the centre
 - * Pregnant or breastfeeding patients
 - * Patients that the investigators consider inappropriate to participate in the clinical trial
 - * Contraindication to transfusion or history of previous severe reaction to blood products
 - * Have received any blood products in the last 120 days

Patients with SARS-CoV-2 PCR-confirmed infection with pulmonary infiltrates and hypoxaemia will be screened and invited to participate

Interventions

- Intervention(s): CP from cured COVID-19 patients and supportive management depending on individual needs.
- Details of CP:
 - * Type of plasma: thawed after storage at -80°C
 - * Volume: 200 mL
 - * Number of doses: 1
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severely ill and critically ill patient with COVID-19
 - * Comparator: BAT. Supportive management depending on individual needs. Including but not be limited to, oxygen therapy by means of a nasal cannula; high-flow nasal cannula; invasive or non-invasive mechanical ventilation; intravenous hydration; antibiotic therapy; thrombus prophylaxis; pain and fever management
 - * Concomitant therapy: supportive management depending on individual needs
 - * Treatment cross-overs: no

Outcomes

- Primary study outcome(s): any cause mortality during the first 14 days of treatment
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: Early all-cause mortality (time frame: 14 days) any cause mortality during the first 14 days of treatment
 - * Time to death: NR

NCT04358783 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions):
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes
 - * Time in days for SARS-CoV-2 RT-PCR-negatives (time frame: 90 days) (48-h sampling interval from day 3 of hospitalisation to 2 consecutive negatives)
 - * The serum anti-SARS-CoV-2 antibody titres (time frame: 90 days). In participants of both arms at day 0, 3, 7, 14 and 90
 - * Detection of serum antibodies (time frame: days 0, 3, 7, 14 and 90). Comparison of anti-SARS-CoV-2 antibody titres.

Starting date	27 April 2020
Contact information	Contact: Eduardo Pérez Alba, MD +52 8117998705 md.eduardo.perez@gmail.com Contact: Laura Marina Nuzzolo Shihadeh, MD +52 8112773423 laura.nuzzolo@gmail.com Hospital Universitario José E. Gonzalez, UANL, Mexico
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 30 May 2021 • Sponsor: Hospital Universitario Dr. Jose E. Gonzalez

NCT04359810

Study name	A phase 2, randomized clinical trial to evaluate the efficacy and safety of human anti-SARS-CoV-2 convalescent plasma in severely ill adults with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: RCT. Double-blind (participant, outcomes assessor). Parallel assignment • Sample size: 70 in one arm, 35 in the other, 2:1 ratio (n = 105) • Setting: e.g. inpatient • Country: USA • Language: English • Number of centres: NR • Intervention model description: a total of 105 eligible participants will be randomised in a 2:1 ratio to receive either CP qualitatively positive for SARS-CoV-2 antibody (anti-SARS-CoV-2 plasma) or non-CP fresh frozen (control plasma)

NCT04359810 (Continued)

Participants

- Inclusion criteria:
 - * All sexes
 - * Willing and able to provide written informed consent prior to performing study procedures or have a LAR available to do so
 - * Age \geq 18 years
 - * Evidence of SARS-CoV-2 infection by PCR test of nasopharyngeal swab sample within 7 days of randomisation
 - * Peripheral capillary oxygen saturation (SpO₂) \leq 94% on room air or requiring supplemental oxygen, non-invasive or invasive mechanical ventilation at screening
 - * Evidence of infiltrates on chest radiography
 - * Women of childbearing age and men, must be willing to practice an effective contraceptive method or remain abstinent during the study period
- Exclusion criteria:
 - * Participation in another clinical trial of anti-viral agent(s) for COVID-19
 - * Receipt of any anti-viral agent(s) with possible activity against SARS-CoV-2 < 24 h prior to study drug administration
 - * Mechanically ventilated (including veno-venous (VV)-ECMO) \geq 5 days
 - * Severe multi-organ failure
 - * History of prior reactions to transfusion blood products meeting definitive case definition criteria, at least severe severity, and probable or definite imputability per National Healthcare Safety Network (NHSN)/Centers for Disease Control and Prevention (CDC) criteria
 - * Known immunoglobulin A (IgA) deficiency
 - * Women who are pregnant

Interventions

- Intervention(s): CP (anti-SARS-CoV-2 plasma)
- Details of CP:
 - * Type of plasma: NR
 - * Volume: 200-250 mL
 - * Number of doses: 1 unit
 - * Antibody-titre: "high"
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease):
- Comparator: non-CP (fresh frozen plasma collected before December 2019)
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome: time to improvement
- Primary review outcomes
 - * All-cause mortality at hospital discharge: time from randomisation to clinical improvement of 1 point on a 7-category ordinal scale or alive discharge from the hospital, whichever comes first. Time frame: up to 28 days
 - * Time to death: NR

NCT04359810 (Continued)

- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: yes
 - Duration of need for supplemental oxygen (time frame: up to 28 days). Compare duration of need for supplemental oxygen and/or mechanical ventilation amongst the anti-SARS-CoV-2 CP and non-CP groups.
 - * 30-day and 90-day mortality: yes
 - In-hospital 28-day mortality rate (time frame: up to 28 days). Compare in-hospital and 28-day mortality amongst the anti-SARS-CoV-2 CP and non-CP groups
 - * Admission on ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: yes
 - Duration of hospitalisation (time frame: up to 28 days). Compare duration of hospitalisation amongst the anti-SARS-CoV-2 CP and non-CP groups
 - * QoL: NR
- Additional outcomes
 - * Rate of SARS-CoV-2 PCR-positivity (time frame: up to 14 days). Compare the rates of SARS-CoV-2 PCR-positivity (RT-PCR) amongst the anti-SARS-CoV-2 CP and non-CP groups
 - * Duration of SARS-CoV-2 PCR-positivity (time frame: up to 14 days). Compare the duration of SARS-CoV-2 PCR-positivity (RT-PCR) amongst the anti-SARS-CoV-2 CP and non-CP groups

Starting date	21 April 2020
Contact information	<p>Contact: Max O'Donnell, MD 212-305-5794 mo2130@cumc.columbia.edu</p> <p>Contact: Andrew Eisenberger, MD 212-305-0983 abe6@cumc.columbia.edu</p> <p>Columbia University Irving Medical Center/NYP Recruiting New York, New York, USA, 10032</p>
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: April 2021 • Sponsor/Funding: Max R. O'Donnell, Columbia University

NCT04360486

Study name	Treatment of COVID-19 with anti-SARS-CoV-2 convalescent plasma (ASCoV2CP)
Methods	<ul style="list-style-type: none"> • Trial design: expanded access open-label, single-arm treatment protocol • Sample size: NR • Setting: Military Treatment Facilities (MTFs) (e.g. hospital ships, field hospitals deployed for the COVID-19 response) • Country: USA • Language: English • Number of centres: initially 1 with capacity to expand to multiple sites (number not specified)

NCT04360486 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Child, adult, older adult * All sexes * Department of Defense (DoD) personnel covered by the Force Health Protection (FHP) program under the Department of Defence Instruction (DoDI) 6200.02 (active duty service members OCONUS and CONUS) and non-DoD personnel who may be treated for COVID-19 at Military Treatment Facilities (MTFs) under the authority of DoDI 6200.03, including Military Health System (MHS) beneficiaries, patients admitted to MTFs, and patients cared for under defence support for civilian authorities (e.g. hospital ships, field hospitals deployed for the COVID-19 response) * Laboratory-confirmed COVID-19 diagnosis * Severe or life-threatening COVID-19 disease, or judged by the subinvestigator (treating physician) to be at high risk for progression to severe or life-threatening disease * Informed consent provided by the patient or LAR, except in situations described in 21 CFR 50.23 * Understands and agrees to comply with planned protocol procedures * Patient agrees to storage of specimens for future testing * Signed an informed consent form • Exclusion criteria <ul style="list-style-type: none"> * Any patient not meeting the inclusion criteria will not be eligible to receive this treatment * Patients will not be excluded because of receipt of another investigational COVID-19 treatment, for example: remdesivir, unless the treating physician subinvestigator (treating physician) feels that the patient would be put at risk by receiving multiple investigational therapies
Interventions	<ul style="list-style-type: none"> • Intervention(s): anti-SARS-CoV-2 convalescent plasma • Details of CP: <ul style="list-style-type: none"> * Type of plasma: FFP, plasma frozen for 24 h (PF-24) or liquid plasma * Volume: NR * Number of doses: NR * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): <ul style="list-style-type: none"> * generally reserved for patients at severe risk or at risk of progression to life-threatening disease. In adults defined as: <ul style="list-style-type: none"> <input type="checkbox"/> Dyspnoea <input type="checkbox"/> Respiratory frequency ≥ 30/min <input type="checkbox"/> Blood oxygen saturation $\leq 93\%$ <input type="checkbox"/> Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 <input type="checkbox"/> Lung infiltrates $> 50\%$ within 24-48 h; i.e. infiltrates increase by $> 50\%$ in < 2 days * Life-threatening COVID-19 is defined as one or more of the following: <ul style="list-style-type: none"> <input type="checkbox"/> Respiratory failure <input type="checkbox"/> Septic shock <input type="checkbox"/> Multiple organ dysfunction or failure • Comparator: N/A • Concomitant therapy: NR • Treatment cross-overs: N/A
Outcomes	<ul style="list-style-type: none"> • Primary study outcome(s): efficacy of this treatment will not be evaluated • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR

NCT04360486 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
- Additional outcomes: NR

Starting date	24 April 2020
Contact information	Andrew P Cap, MS, MD, PhD, FACP andrew.p.cap.mil@mail.mil U.S. Army Medical Research and Development Command
Notes	<ul style="list-style-type: none"> • Recruitment status: expanded access, available • Prospective completion date: NR • Sponsor/Funding: U.S. Army Medical Research and Development Command

NCT04361253

Study name	A prospective, randomized, double-masked, placebo-controlled trial of high-titer COVID-19 convalescent plasma (HT-CCP) for the treatment of hospitalized patients with COVID-19 of moderate severity
Methods	<ul style="list-style-type: none"> • Trial design: phase 3 RCT, double-blind (participant, investigator) parallel assignment • Sample size: 110 in each arm (n = 220) • Setting: e.g. inpatient • Country: USA • Language: English • Number of centres: NR
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age > 1 year * Active COVID-19 infection confirmed by positive SARS-CoV-2 PCR * Meets institutional criteria for admission to hospital for COVID-19 * Admitted to ICU or non-ICU floor within 5 days of enrolment * PaO₂/FiO₂ > 200 mmHg if intubated * Patient or LAR able to provide informed consent • Exclusion criteria: <ul style="list-style-type: none"> * Previous treatment with convalescent plasma for COVID-19 * Current use of investigational antiviral therapy targeting SARS-CoV-2 * History of anaphylactic transfusion reaction * Clinical diagnosis of acute decompensated heart failure * Objection to blood transfusion
Interventions	<ul style="list-style-type: none"> • Intervention(s): e.g. COVID-19 CP (HT-CCP)

NCT04361253 (Continued)

- Details of CP:
 - * Type of plasma: apheresis units
 - * Volume: 2 x 250 mL units (500 mL)
 - * Number of doses: 2 units administered sequentially over no greater than a 24-h period
 - * Antibody-titre: high; NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients but not yet in moderate or severe ARDS
- Comparator: e.g. conventional treatment
 - * 2 units of standard plasma (FFP) or FP24 (each 200-275 mL, approximately 500 mL total) administered sequentially
- Concomitant therapy: NR
- Treatment cross-overs: No

Outcomes

- Primary study outcome(s): modified WHO Ordinal Scale score
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes, using MOS up to 14 days
 - * Time to death: yes, up to 14 days
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: yes, up to 14 days
 - * 30-day and 90-day mortality: NR
 - * Admission on ICU: yes
 - * Length of stay on the ICU: yes up to 14 days
 - * Time to discharge from hospital: yes up to 14 days
 - * QoL: NR
- Additional outcomes
 - * Modified WHO Ordinal Scale score (time frame: day 14). The MOS numerical score is 0-9 where a score of 0 attributes to 'no clinical evidence of infection' and a score of 9 attributes to 'death'. The eligibility requirements for this trial select individuals at level 3 or higher on the modified scale, but the day 14 outcome can be any one of 10 levels.

Starting date 30 April 2020

 Contact information Richard Kaufman, MD 617-732-5232
rmkaufman@bwh.harvard.edu
 Karina Oganezova 6177328624 koganezova@bwh.harvard.edu
 Brigham and Women's Hospital, Boston, Massachusetts, USA, 02115

 Notes

- Recruitment status: recruiting
- Prospective completion date: December 2021
- Sponsor/Funding: Brigham and Women's Hospital, Boston

NCT04362176

Study name A randomized, controlled clinical trial to test the safety and efficacy of convalescent donor plasma to treat COVID-19 in hospitalized adults

NCT04362176 (Continued)

Methods	<ul style="list-style-type: none"> • Trial design: phase 3 RCT, parallel assignment (1:1). Randomization completed in permuted blocks and stratified by site, gender, and age. Triple blinding (participant, care provider, outcomes assessor). Study personnel will not be blinded to the study group assignment • Sample size: 250 in each arm (500) • Setting: inpatient (hospital or ED) • Country: USA • Language: English • Number of centres: NR
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * All sexes * Age \geq 18 years * Currently hospitalised or in an ED with anticipated hospitalisation * Symptoms of acute respiratory infection, defined as \geq 1 of the following: cough, fever ($>$ 37.5 °C/99.5 °F), shortness of breath * Laboratory-confirmed SARS-CoV-2 infection within the past 10 days • Exclusion criteria <ul style="list-style-type: none"> * Prisoner * Unable to randomise within 14 days after onset of acute respiratory infection symptoms * Unable to randomise within 48 h after hospital arrival * Inability to be contacted on Day 29-36 for clinical outcome assessment * Receipt of pooled immunoglobulin in the past 30 days * Contraindications to transfusion or history of prior reactions to transfusion blood products * Previous enrolment in this trial
Interventions	<ul style="list-style-type: none"> • Intervention(s): e.g., SARS-CoV-2 convalescent plasma • Details of CP: <ul style="list-style-type: none"> * Type of plasma: * Volume: 500 mL/h * Number of doses: NR * Antibody-titre: NR * Pathogen inactivated: yes- pathogen reduced • Treatment details, including time of plasma therapy (e.g. early stage of disease): require hospitalisation and given within 12 h of randomisation on study Day 0 • Comparator: 250 mL of lactate Ringers containing multivitamins intravenously on Day 1 as a placebo • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcome(s): <ul style="list-style-type: none"> * COVID Ordinal Outcomes Scale: day 15 (time frame: study day 15) <ol style="list-style-type: none"> a. Death b. Hospitalised on invasive mechanical ventilation or ECMO c. Hospitalised on non-invasive ventilation or high flow nasal cannula d. Hospitalised on supplemental oxygen e. Hospitalised not on supplemental oxygen f. Not hospitalised with limitation in activity (continued symptoms) g. Not hospitalised without limitation in activity (no symptoms)

NCT04362176 (Continued)

- Primary review outcomes
 - * All-cause mortality at hospital discharge: yes
 - All-location, all-cause 14-day mortality (time frame: baseline to study day 14)
 - All-location, all-cause 28-day mortality (time frame: baseline to study day 28)
 - * Time to death: yes
 - Ordinal Outcomes Scale baseline to day 3, days 8, 15 and 29
- Secondary review outcomes
 - * Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - Transfusion reaction (time frame: baseline to day 28). Number of participants with transfusion reaction (fever/rash)
 - TRALI (time frame: baseline to day 28). Number of participants with TRALI
 - TACO (time frame: baseline to day 28). Number of participants with TACO
 - Transfusion-related infection (time frame: baseline to day 28). Number of participants with transfusion related infection
 - * Number of participants with SAEs: yes
 - Acute kidney injury (time frame: baseline to day 28). Number of participants with acute kidney injury
 - Renal replacement therapy (time frame: baseline to day 28). Number of participants requiring renal replacement therapy
 - Documented venous thromboembolic disease (DVT or PE) (time frame: baseline to day 28). Number of participants with documented venous thromboembolic disease (DVT or PE)
 - Documented cardiovascular event (myocardial infarction or ischaemic stroke) (time frame: baseline to day 28). Number of participants with myocardial infarction or ischaemic stroke
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: yes
 - * 30-day and 90-day mortality: yes
 - * Admission on ICU: yes
 - ICU-free days through Day 28 (time frame: baseline to Day 28). Number of days outside of ICU
 - Ventilator-free days through Day 28 (time frame: baseline to Day 28). Number of days without use of a ventilator
 - * Length of stay on the ICU: yes
 - Ordinal Outcomes Scale baseline to day 3, days 8, 15 and 29
 - * Time to discharge from hospital: yes
 - Ordinal Outcomes Scale baseline to day 3, days 8, 15 and 29
 - Hospital-free days through Day 28 (time frame: baseline to Day 28)
 - * QoL: NR
- Additional outcomes:
 - * Composite of death or receipt of ECMO through Day 28 (time frame: baseline to Day 28). Number of participants that died or received ECMO
 - * Oxygen-free days through Day 28 (time frame: baseline to Day 28). Number of days without use of oxygen
 - * Vasopressor-free days through Day 28 (time frame: baseline to Day 28). Number of days without use of vasopressors

Starting date	24 April 2020
Contact information	<p>Amanda J Bistran-Hall (615) 875-8531</p> <p>amanda.j.bistran-hall@vumc.org</p> <p>Principal Investigator: Todd Rice, MD Vanderbilt University Medical Center</p> <p>Vanderbilt University Medical Center</p>

NCT04362176 (Continued)

Nashville, Tennessee, USA, 37203

Notes

- Recruitment status: recruiting
- Prospective completion date: April 2021
- Sponsor/Funding: Vanderbilt University Medical Center

NCT04363034

Study name

Arkansas expanded access COVID-19 convalescent plasma treatment program

Methods

- Trial design: expanded access treatment protocol following standard institutional procedures
- Sample size: up to 100 (intermediate-size population)
- Setting: inpatient
- Country: USA
- Language: English
- Number of centres: NR

Participants

- Inclusion criteria
 - * All sexes
 - * ≥ 18 years
 - * Laboratory-confirmed COVID-19 via SARS-CoV-2 RT-PCR testing
 - * Patients currently hospitalised with severe or life-threatening COVID-19 or patients the treating physician deems to be at high-risk for progressing to severe or life-threatening COVID-19
 - Severe disease, defined as ≥ 1 of the following:
 - dyspnoea
 - respiratory frequency ≥ 30 /min
 - blood oxygen saturation $\leq 93\%$
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 , and/or
 - lung infiltrates $> 50\%$ within 24-48 h
 - Life-threatening disease, defined as ≥ 1 of the following:
 - respiratory failure
 - septic shock, and/or
 - multiple organ dysfunction or failure
 - * Informed consent from patients/LAR
- Exclusion criteria
 - * Female patients with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period
 - * Patients who have received pooled immunoglobulin in past 30 days
 - * Contraindication to transfusions or history of prior reactions to transfusion blood products

Interventions

- Intervention(s): COVID-19 CP
- Details of CP:
 - * Type of plasma: ABO-compatible, low isohemagglutinin titre
 - * Volume: 200-400 mL per unit, not to exceed 550 mL total
 - * Number of doses: 1-2 units (rate of 100 to 250 mL/h) within 4 h
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): participants with severe or life-threatening, laboratory-confirmed COVID-19
- Comparator: N/A
- Concomitant therapy: premedications (e.g. acetaminophen, diphenhydramine, etc.) as necessary
- Treatment cross-overs: N/A

NCT04363034 (Continued)

Outcomes	<ul style="list-style-type: none"> • Primary study outcome(s): NR • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: (give details e.g. 28-day mortality) * Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): * Number of participants with SAEs: no * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: no * 30-day and 90-day mortality: * Admission on ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR • Additional outcomes: NR
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Starting date	27 April 2020
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Contact information	Danielle Evans (501) 526-7906 DEvans@uams.edu David Avery (501) 214-2101 daavery@uams.edu University of Arkansas
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Notes	<ul style="list-style-type: none"> • Recruitment status: expanded access - available • Prospective completion date: NR • Sponsor/Funding: University of Arkansas
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NCT04364737

Study name	Convalescent plasma to limit coronavirus associated complications: a randomized blinded phase 2 study comparing the efficacy and safety of anti-SARS-CoV2 plasma to placebo in COVID-19 hospitalized patients
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Methods	<ul style="list-style-type: none"> • Trial design: phase 2 RCT, double-blind (participant, investigator) 1:1 ratio, parallel assignment • Sample size: 150 in each arm (300) • Setting: inpatient • Country: USA • Language: English • Number of centres: 2
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Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * All sexes * Patients ≥ 18 years of age * Hospitalised for COVID-19 respiratory symptoms * Hospitalised for < 72 h or within day 3-7 days from first signs of illness * Laboratory-confirmed COVID-19 * On supplemental oxygen, non-invasive ventilation or high-flow oxygen * Patients may be on other RCTs of pharmaceuticals for COVID -19 and patients who meet eligibility criteria will not be excluded on this basis
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NCT04364737 (Continued)

- Exclusion criteria
 - * Receipt of pooled immunoglobulin in past 30 days
 - * Contraindication to transfusion or history of prior reactions to transfusion blood products
 - * Invasive mechanical ventilation or ECMO
 - * Volume overload secondary to congestive heart failure or renal failure
 - * Intracranial bleed

Interventions

- Intervention(s): SARS-CoV-2 donor CP
- Details of CP:
 - * Type of plasma: NR (from New York Blood Center)
 - * Volume: ~250-500 mL
 - * Number of doses: 1-2 units
 - * Antibody-titre: with antibodies to SARS-CoV-21 per 13 April 2020 directive by the FDA
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): respiratory symptoms requiring oxygen supplementation within 3-7 days from the onset of illness or within 3 days of hospitalisation
- Comparator: e.g.. lactated Ringer's solution or sterile saline
 - * Equivalent volume to CP
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome(s):
 - * Percentage of participants reporting each severity rating on WHO ordinal scale for clinical improvement (time frame: 14 days post randomisation)
 - No clinical or virological evidence of infection
 - Not hospitalised, no limitations on activities
 - Not hospitalised, limitation on activities
 - Hospitalised, not requiring supplemental oxygen
 - Hospitalised, requiring supplemental oxygen
 - Hospitalised, on non-invasive ventilation or high flow oxygen devices
 - Hospitalised, on invasive mechanical ventilation or ECMO
 - Death
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes
 - see WHO Ordinal Scale up to 14 days post randomisation
 - * Time to death: yes
 - Mortality (time frame: 7, 14, 28 days post randomisation). Rate of mortality
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): no
 - * Number of participants with SAEs: no
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: yes
 - Percentage of subjects reporting each severity rating on WHO ordinal scale for clinical improvement (time frame: 14 days and 28 days post randomisation)
 - * 30-day and 90-day mortality: no
 - * Admission on ICU: yes
 - Rates of ICU admission (time frame: 7, 14, 28 days post randomisation). Percentage of patients requiring ICU admission.
 - * Length of stay on the ICU: no
 - * Time to discharge from hospital: no
 - * QoL: NR

NCT04364737 (Continued)

- Additional outcomes:
 - * Percentage of participants reporting each severity rating on WHO ordinal scale for clinical improvement (time frame: 28 days post-randomisation). See above for criteria in scale
 - * Comparison in anti-SARS-CoV-2 antibody titres (time frame: 0, 1, 7, 14, 28, 90 days post-randomisation). Anti-SARS-CoV-2 titres (IgM, IgG, IgA)
 - * Proportion positive in SARS-CoV-2 RNA (time frame: 0, 7, 14, 28 days post-randomisation). SARS-CoV-2 PCR in nasopharyngeal swabs
 - * Changes from baseline in lymphocyte (time frame: 0, 1, 3, 7, 14 days post-randomisation). Lymphocyte counts
 - * Changes from baseline in neutrophils (time frame: 0, 1, 3, 7, 14 days post-randomisation). Neutrophil counts
 - * Changes from baseline in D-dimer (time frame: 0, 1, 3, 7, 14 days post-randomisation). D-dimer level
 - * Changes from baseline in fibrinogen (time frame: 0, 1, 3, 7, 14 days post-randomisation). Fibrinogen level
 - * Changes from baseline in T lymphocyte subsets (time frame: 0, 7, 28 days post-randomisation). T cell subsets.
 - * Changes from baseline in B lymphocyte subsets (time frame: 0, 1, 3, 7, 14 days post-randomisation). B cell subsets

Starting date	17 April 2020
Contact information	<p>Mila B Ortigoza, MD, PhD Mila.Ortigoza@nyulangone.org</p> <p>Michelle Chang Michelle.Chang3@nyulangone.org</p> <ul style="list-style-type: none"> • Montefiore Medical Center, Bronx, New York, USA, 10467 • NYU Langone Health New York, New York, USA, 10003
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting (NYU Langone Health) <ul style="list-style-type: none"> * Montefiore Medical Center Active- Not recruiting • Prospective completion date: 30 April 2023 • Sponsor/Funding: NYU Langone Health; Albert Einstein Medical Center

NCT04365439

Study name	Convalescent plasma for the treatment of moderate-severe COVID-19: a proof-of-principle study
Methods	<ul style="list-style-type: none"> • Trial design: proof of concept study, single-group assignment, open-label • Sample size: 10 • Setting: e.g. inpatient • Country: Italy • Language: English • Number of centres: NR
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * All sexes * Hospitalised adult patients 18-75 years * Confirmed COVID-19 infection by nasopharyngeal swab * Radiologically confirmed pneumonia * SpO₂ > 92% and < 96% (room air) * ongoing thromboembolic prophylaxis

NCT04365439 (Continued)

- Exclusion criteria
 - * Participation to another COVID-19 trial
 - * severe COVID-19 disease (SpO₂ < 93% in room air)
 - * severe allergic transfusion reactions or anaphylaxis in the patient history
 - * documented IgA deficiency
 - * unstable heart disease with signs of circulatory overload
 - * malignancies or other concomitant diseases with poor short-term prognosis
 - * pregnancy

Interventions

- Intervention(s): CP from patients after COVID-19
- Details of CP:
 - * Type of plasma: NR
 - * Volume: NR
 - * Number of doses: NR
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): patients with moderate to severe COVID-19
- Comparator: N/A
- Concomitant therapy: thromboembolic prophylaxis
- Treatment cross-overs: N/A

Outcomes

- Primary study outcome(s):
 - * Titres of anti-SARS-CoV-2 antibodies in the plasma derived from CP donors (time frame: at plasma donation)
 - * Change in titres of anti-SARS-CoV-2 antibodies in patients' plasma (time frame: change from baseline at day 21)
 - * Change in inflammatory cytokines concentration (e.g. IL-6, HMGB1) (time frame: change from baseline at day 7)
 - * Viral load decay in the recipient after plasma transfusion with semiquantitative assessment of nasopharyngeal swabs (time frame: change from day of diagnosis at day 1)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge:
 - * Time to death: yes
 - within the 7-point ordinal scale (time frame: at day 7). 7-point ordinal scale measure on day 0 (baseline), day 1, 3 and 7 after plasma transfusion

NCT04365439 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - Proportion of participants with AEs, severity of AEs (time frame: at day 21) AE will be assessed by the DAIDS scale on day 1, 3, 7 and 21. Relatedness with plasma transfusion will also be reported.
 - * Number of participants with SAEs: yes
 - Proportion of participants with AEs, severity of AEs (time frame: at day 21) AE will be assessed by the DAIDS scale on day 1, 3, 7 and 21.
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - within the 7-point ordinal scale (time frame: at day 7). 7-point ordinal scale measure on day 0 (baseline), day 1, 3 and 7 after plasma transfusion
 - * 30-day and 90-day mortality: no
 - * Admission on ICU: yes
 - within 7-point ordinal scale
 - * Length of stay on the ICU: yes
 - within 7-point ordinal scale up to day 7
 - * Time to discharge from hospital: yes
 - within 7 point ordinal scale
 - * QoL: NR
- Additional outcomes: NR

Starting date	27 April 2020
Contact information	<p>Contact: Enos Bernasconi, M.D. +41 91 811 60 22 enos.bernasconi@eoc.ch</p> <p>Contact: Beatrice Bernasconi +41 91 811 60 21 beatrice.bernasconi@eoc.ch</p> <p>Ente Ospedaliero Cantonale, Bellinzona</p> <p>Principal Investigator: Stefano Fontana, M.D. Servizio Trasfusionale, Lugano</p>
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 23 June 2020 • Sponsor/Funding: Enos Bernasconi, Ente Ospedaliero Cantonale, Bellinzona

NCT04366245

Study name	Phase I/II multicentre, randomized and controlled clinical trial to evaluate the efficacy of treatment with hyperimmune plasma obtained from convalescent antibodies of COVID-19 infection
Methods	<ul style="list-style-type: none"> • Trial design: phase I/II RCT, open-label, parallel assignment • Sample size: e.g. 36 in each arm (72) • Setting: e.g. inpatient • Country: Spain • Language: English • Number of centres: NR <p>Inclusion criteria:</p>

NCT04366245 (Continued)

- Informed consent prior to performing procedures. Oral consent accepted to prevent paper handling.
- Patients of both sexes, and ≥ 18 years
- SARS-CoV-2 infection determined by PCR in a sample of naso-oro-pharyngeal exudate or other respiratory specimen or determination of specific positive IgM antibodies, in < 72 h before randomisation.
- Patients requiring hospitalisation for pneumonia COVID-19 without need until randomisation of mechanical ventilation (invasive or non-invasive), and at least one of the following:
 - * O₂ saturation $\leq 94\%$ in ambient air, or PaO₂/FiO₂ ≤ 300 mm Hg
 - * Age > 65 years
 - * Presence of: high blood pressure, chronic heart failure, COPD, liver cirrhosis, or other chronic pulmonary and cardiovascular diseases, diabetes, or obesity

Participants

- Inclusion criteria:
 - * All sexes
 - * ≥ 18 years
 - * Informed consent prior to performing procedures. Oral consent accepted to prevent paper handling.
 - * SARS-CoV-2 infection determined by PCR in a sample of naso-oro-pharyngeal exudate or other respiratory specimen or determination of specific positive IgM antibodies, in < 72 h before randomisation.
 - * Patients requiring hospitalisation for pneumonia COVID-19 without need until randomisation of mechanical ventilation (invasive or non-invasive), and at least one of the following:
 - O₂ saturation $\leq 94\%$ in ambient air, or PaO₂/FiO₂ ≤ 300 mm Hg
 - Age > 65 years
 - Presence of: high blood pressure, chronic heart failure, COPD, liver cirrhosis, or other chronic pulmonary and cardiovascular diseases, diabetes, or obesity
- Exclusion criteria:
 - * Requirement before randomisation of mechanical ventilation (invasive or non-invasive)
 - * Any of the following analytical data before randomisation: IL-6 > 80 pg/mL, D-dimer > 10 times ULN, ferritin > 1000 ng/mL
 - * Participation in another clinical trial or experimental treatment for COVID-19
 - * In the opinion of the clinical team, progression to death or mechanical ventilation is highly probable within 24 h, regardless of treatment provision
 - * Incompatibility or allergy to the administration of human plasma
 - * Severe chronic kidney disease grade 4 or requiring dialysis (ie eGFR < 30)
 - * Pregnant, lactating, or fertile women who are not using an effective method of contraception. (Women of childbearing age considered to be all women from 18 years and up to a year after the last menstrual period in the case of menopausal women)

Interventions

- Intervention(s): COVID-19 hyperimmune CP
- Details of CP:
 - * Type of plasma: NR
 - * Volume: NR
 - * Number of doses: NR
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): before mechanical ventilation is required
- Comparator: e.g.. conventional treatment
- Concomitant therapy: hydroxychloroquine + azithromycin or lopinavir/ritonavir + interferon β -1b + hydroxychloroquine
- Treatment cross-overs: no

NCT04366245 (Continued)

Outcomes

- Primary study outcome(s):
 - * Safety: incidence of AEs and SAEs grade 3 and 4, related to the product under investigation or the administration procedure, graduated according to the common toxicity criteria scale (CTCAE). (time frame: 30 days after enrolment).
 - * Efficacy: death from any cause (time frame: day +21 after randomisation)
 - * Efficacy: need for mechanical ventilation (time frame: Day +21 after randomisation)
 - * Efficacy: any of the following analytical data after 72 h of randomisation. (time frame: Day +21 after randomisation). IL-6 > 40 pg/mL, D-dimer > 1500, ferritin > 1000 ng/mL
 - * Efficacy: SOFA scale ≥ 3 after 72 h of randomisation. (time frame: Day +21 after randomisation).
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes
 - Death from any cause (time frame: Day +21 after randomisation)
 - Mortality on days 14 and 28 (time frame: Days 14 and 28)
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - Incidence of AEs and SAEs grade 3 and 4, related to the product under investigation or the administration procedure, graduated according to the common toxicity criteria scale (CTCAE). (time frame: 30 days after enrolment)
 - * Number of participants with SAEs: yes
 - Incidence of AEs and SAEs grade 3 and 4, related to the product under investigation or the administration procedure, graduated according to the common toxicity criteria scale (CTCAE)
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: yes
 - Need for mechanical ventilation (time frame: Day +21 after randomisation)
 - * 30-day and 90-day mortality: no
 - * Admission on ICU: yes
 - Proportion of participants who required mechanical ventilation (time frame: Until day 28)
 - * Length of stay on the ICU: no
 - * Time to discharge from hospital: yes
 - Duration of hospitalisation (days) (time frame: until day 21)
- Additional outcomes
 - * Proportion of participants who develop analytical alterations. (time frame: Day +21 after randomisation.). IL-6 > 40 pg/mL, D-dimer > 1500, ferritin > 1000 ng/mL until the cure test
 - * Cure / clinical improvement (disappearance or improvement of signs and symptoms of COVID-19) in the cure test. (time frame: Day +21 after randomisation)
 - * PCR-negative for SARS-CoV-2 (time frame: on days 7, 14 and 21)
 - * Proportion of participants who required treatment with tocilizumab (time frame: until day 21)
 - * Virology and immunological variables: qualitative PCR for SARS-CoV-2 in naso-oropharyngeal exudate sample (time frame: at baseline and on day 14)
 - * Virology and immunological variables: total antibody quantification (time frame: at baseline and on days 3, 7, 10 (while hospitalisation lasts), and on days 14 and 28 (if able to return to the clinic or are still hospitalised))
 - * Virology and immunological variables: quantification of total antibodies in PC donors recovered from COVID-19 (time frame: before infusion)

 Starting date 23 April 2020

 Contact information Ana Cardesa Gil 697 95 69 41 ext 0034

ana.cardesa@juntadeandalucia.es

 Hospital Universitario Virgen Macarena, Sevilla, Spain, 41009

NCT04366245 (Continued)

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| Notes | <ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: December 2021 • Sponsor/funding: Andalusian Network for Design and Translation of Advanced Therapies |
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NCT04372368

Study name	Convalescent plasma for the treatment of patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: expanded access • Sample size: ≥ 150 • Setting: inpatient • Country: USA • Language: English • Number of centres: 6
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Laboratory-confirmed diagnosis of infection with SARS-CoV-2 • Age ≥ 18 years • Laboratory-confirmed diagnosis of infection with SARS-CoV-2 • Admitted to participating facility for the treatment of COVID-19 complications • Moderate to severe or life-threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease • Informed consent provided by the patient or healthcare proxy • Moderate COVID-19 is defined by ≥ 1 of the following: <ul style="list-style-type: none"> * Hospitalised with COVID-19 * Respiratory rate $> 25/\text{min}$ * Oxygen saturation $< 96\%$ * With or without radiographic evidence of pulmonary involvement • Severe COVID-19 is defined by ≥ 1 of the following: <ul style="list-style-type: none"> * dyspnoea * respiratory frequency $\geq 30/\text{min}$ * blood oxygen saturation $\leq 93\%$ * Radiographic evidence of pulmonary disease • Life-threatening COVID-19 is defined as ≥ 1 of the following: <ul style="list-style-type: none"> * respiratory failure requiring mechanical ventilation or non-rebreather oxygenation in the ICU * Prone oxygenation * multiple organ dysfunction or failure <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Does not meet inclusion criteria • History of transfusion reactions or contraindication to receiving CP • Risk of transfusion exceeds potential benefit based on clinician or blood bank determination
Interventions	<ul style="list-style-type: none"> • Intervention(s): COVID-19 CP

NCT04372368 (Continued)

- Details of CP:
 - * Type of plasma: plasma obtained from volunteers who have recovered from SARS-Cov-2 infection
 - * Volume: 100-200 mL/h
 - * Number of doses: 1-2
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: normal saline solution, 2 infusions be administered with 24-72 h in between
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome: NR
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional study outcomes
 - * NR

Starting date

NR

Contact information

 Contact: John D Beckham, MD303-724-4927 David.beckham@cuanschutz.edu
Notes

Recruitment status: available

Prospective completion date: NR

Sponsor/funding: University of Colorado, Denver, Investigators Principal Investigator: John D Beckham, MD University of Colorado Denver, Anschutz Medical Campus

NCT04372979
Study name

Evaluation of efficacy of COVID-19 convalescent plasma versus standard plasma in the early care of COVID-19 patients hospitalized outside intensive care units

Methods

Trial design: triple-blinded, parallel, clinical RCT

Sample size: 80

Setting: inpatient

Country: France

NCT04372979 (Continued)

Language: translated to English

Number of centres: at least 4

Participants

Inclusion criteria:

- Age 18-80 years
- COVID-19-confirmed case
- Cases showing respiratory symptoms, checking at least 1 of the following criteria:
 - * Cough, dyspnoea, respiratory rate > 24 breaths/min
 - * Oxygen saturation < 95% at rest in ambient air
 - * PaO₂ < 70 mmHg
 - * Scanographic pulmonary compatible with COVID in the absence of any other aetiology
- Risk of deterioration, checking at least 1 of the following comorbidity criteria:
 - * Chronic respiratory pathology
 - * Diabetes
 - * Cancer pathology
 - * Cardiovascular disease
 - * Chronic kidney failure
 - * Congenital or acquired immunodeficiency
 - * Cirrhosis at stage B
 - * Major sickle cell syndrome
 - * BMI > 30 kg/m²

OR 1 of the biological criteria :

- D-dimer 1 µg/mL
- Lymphocytes < 0.8 G/L
- Ferritin > 300 µg/L
- Troponin I > 11 pg/mL

Exclusion criteria:

- Patients admitted in ICU within the first 6 h of hospital care
- Patients after 10 days from the start of symptoms
- Age < 18 years and > 80 years
- Long-term oxygen-dependent patients (at home)
- Decompensated chronic cardiac, respiratory, urological pathology
- Patient refusing administration of blood products
- Allergic reaction to plasma products
- IgA deficiency
- Contraindication to transfusion
- Ig transfusion within 30 days
- Patient currently participating to another clinical trial
- Pregnant women
- Not affiliated to the social security
- Person deprived of liberty by a legal or administrative decision, person under guardianship

Interventions

- Intervention(s): transfusion of SARS-CoV-2 CP
 - * Details of CP: SARS-CoV-2 CP
 - * Type of plasma:
 - * Volume: 200-230 mL
 - * Number of doses: 2 infusions be administered with 24-72 h in between
 - * Antibody-titre: NR
 - * Pathogen inactivated: by amotosalen

NCT04372979 (Continued)

- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: standard plasma
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes	<ul style="list-style-type: none"> • Primary study outcome: survival time without need of a ventilator (time frame: day 30) • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: 30-day mortality without need of a ventilator * Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: yes (length of stay (time frame: day 30) * QoL: NR • Additional study outcomes <ul style="list-style-type: none"> * Morbidity (time frame: Day 15) * Morbidity (time frame: Day 30) * Effect on viral pharyngeal specimen clearance (time frame: at inclusion and Day 7) * Effect on viral blood specimen clearance (time frame: at inclusion and Day 7) * Effect on haemostasis disorders (time frame: at inclusion, Day 1 and every 48 h) * Kinetics of appearance of neutralising antibodies (time frame: at inclusion, Day 7) * Transfusion endotheliopathy effect (time frame: at inclusion, Day 1, Day 7) * Transfusion biological inflammation effect (time frame: at inclusion, Day 1, Day 7) * Transfusion haemovigilance (time frame: 30 days) * Decrease in the consumption of antibiotics (time frame: 30 days)
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Starting date	May 2020
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Contact information	Contact: Christophe MARTINAUD, PU PH +33 141467241 christophe.martinaud@intra.def.gouv.fr Contact: Christophe RENARD +33 140514103 christophe1.renard@intra.def.gouv.fr
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Notes	Recruitment status: not yet recruiting Prospective completion date: October 2020 Sponsor/funding: Direction Centrale du Service de Santé des Armées, University Hospital, Grenoble; Investigators Study Director: Hervé FOEHRENBACH Direction Centrale du Service de Santé des Armées (DCSSA), Study Director: Catherine VERRET Service de Santé des Armées-Direction de la Formation de la Recherche et de l'Innovation, Principal Investigator: Christophe MARTINAUD Centre de Transfusion Sanguine des Armées, Principal Investigator: Jean-Luc BOSSON Statistical and methodological investigator - Laboratoire TIMC UMR 5525 CNRS Equipe Themas
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NCT04373460

Study name	Comparison of the efficacy and safety of human coronavirus immune plasma (HCIP) vs. control (SARS-CoV-2 non-immune) plasma among outpatients with symptomatic COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: phase 2, double-blind, RCT • Sample size: 1344 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • ≥ 18 years of age • Competent and capable to provide informed consent • Positive RNA test for presence of SARS-CoV-2 in fluid collected by oropharyngeal or nasopharyngeal swab • Experiencing any symptoms of COVID-19 including but not limited to fever ($T > 100.5^{\circ} \text{F}$), cough, or other COVID-associated symptoms like anosmia • ≤ 8 days since the first symptoms of COVID-19 • ≤ 8 days since first positive SARS-CoV-2 RNA test • Able and willing to comply with protocol requirements listed in the informed consent <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Hospitalised or expected to be hospitalised within 24 h of enrolment • Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator, would affect participant safety and/or compliance • History of prior reactions to transfusion blood products • Inability to complete therapy with the study product within 24 h after enrolment • Receiving any treatment drug for COVID-19 within 14 days prior to screening evaluation (off-label like hydroxychloroquine, compassionate use or study trial related)
Interventions	<ul style="list-style-type: none"> • Intervention(s): SARS-CoV-2 CP • Details of CP: <ul style="list-style-type: none"> * Type of plasma: plasma obtained from volunteers who have recovered from SARS-Cov-2 infection * Volume: ~200-250 mL * Number of doses: 1 * Antibody-titre: titre ≥ 1:320 or current FDA standard titre * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: standard control plasma • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Cumulative incidence of hospitalisation or death prior to hospitalisation (time frame: Up to day 28) * Cumulative incidence of treatment-related SAEs (time frame: Up to day 28) * Cumulative incidence of treatment-related grade 3 or higher AEs (time frame: Up to day 90) • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: Cumulative incidence of hospitalisation or death prior to hospitalisation (time frame: Up to day 28) * Time to death: NR

NCT04373460 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes (Incidence of adverse plasma transfusion reactions: Cumulative incidence of treatment-related SAEs (time frame: Up to day 28), Cumulative incidence of treatment-related grade 3 or higher AEs (time frame: Up to day 90)
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: yes, (time to ICU admission, invasive mechanical ventilation or death in hospital (time frame: up to day 90)
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional study outcomes
 - * Change in serum SARS-CoV-2 antibody titres (time frame: Days 0, 14, 28 and 90)
 - * Time to SARS-CoV-2 PCR-negativity (time frame: up to day 28)
 - * Change in level of SARS-CoV-2 RNA (time frame: Day 0-Day 28)
 - * Change in oxygen saturation levels (time frame: Day 0-Day 28)
 - * Rate of participant-reported secondary infection of housemates (time frame: up to day 90)
 - * Time to resolution of COVID-19 symptoms (time frame: up to day 90)
 - * Impact of CP on outcome as assessed by change in hospitalisation rate (time frame: Day 0-Day 90)
 - * Impact of donor antibody titres on hospitalisation rate of CP recipients (time frame: Day 0-Day 90)
 - * Impact of donor antibody titres on antibody levels of CP recipients (time frame: Day 0-Day 90)
 - * Impact of donor antibody titres on viral positivity rates of CP recipients (time frame: Day 0-Day 90)

Starting date	19 May 2020
Contact information	David J Sullivan, MD 410-502-2522 dsulliv7@jhmi.edu , David Sullivan, MD 410-502-2522 dsulliv7@jhmi.edu
Notes	<p>Recruitment status: not yet recruiting</p> <p>Prospective completion date: 21 December 2022</p> <p>Sponsor/funding: Johns Hopkins University, State of Maryland, Bloomberg Foundation, Principal Investigator: David J Sullivan, MD The Johns Hopkins University</p>

NCT04374370

Study name	Severe acute respiratory syndrome coronavirus 2 of the genus betacoronavirus (SARSCoV2) convalescent plasma (CP) expanded access protocol (EAP)
Methods	<ul style="list-style-type: none"> • Trial design: intermediate-size population, expanded access • Sample size: NR • Setting: inpatient • Country: USA • Language: English

NCT04374370 (Continued)

	<ul style="list-style-type: none"> • Number of centres: NR
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Ages ≥ 6 years • Willing and able to provide written informed consent, or with a legal representative who can provide informed consent, or enrolled under International Conference on Harmonization (ICH) E6(R2) 4.8.15 emergency use provisions as deemed necessary by the investigator (participants ≥ 18 years of age); or willing and able to provide assent as required per Institutional Review Board (IRB) prior to performing study procedures • Must have laboratory-confirmed COVID-19-positive test • Must have severe or immediately life-threatening COVID-19 <p>Severe disease is defined as:</p> <ul style="list-style-type: none"> • dyspnoea • respiratory frequency ≥ 30/min • blood oxygen saturation $\leq 93\%$ • partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or • lung infiltrates $> 50\%$ within 24-48 h <p>Life-threatening disease is defined as:</p> <ul style="list-style-type: none"> • respiratory failure • septic shock, and/or • multiple organ dysfunction or failure <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Known contraindication to transfusion or history of prior reactions to transfusion of blood products
Interventions	<ul style="list-style-type: none"> • Intervention(s): SARS-CoV2 CP • Details of CP: <ul style="list-style-type: none"> * Type of plasma: SARS-CoV2 CP * Volume: NR * Number of doses: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: NR • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: NR • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR

NCT04374370 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional study outcomes
 - * NR

Starting date	NR
Contact information	Contact: Chris Ensor, Pharm D 413.519.7056 Chris.Ensor@AdventHealth.com
Notes	<p>Recruitment status: available</p> <p>Prospective completion date: NR</p> <p>Sponsor/funding: AdventHealth Orlando, Available: Orlando, Florida, United States, 32803, Principal Investigator: Eduardo Oliveira, MD AdventHealth</p>

NCT04374487

Study name	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma to limit COVID-19 associated complications
Methods	<ul style="list-style-type: none"> • Trial design: phase II, open-label, RCT • Sample size: 100 (50 each group) • Setting: inpatient • Country: India • Language: English • Number of centres: 1
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Patients admitted with RT-PCR-confirmed COVID-19 illness. • Age > 18 years • Written informed consent • Has any of the 2 <ul style="list-style-type: none"> * PaO₂/ FiO₂ < 300 * Respiratory Rate > 24/min and SaO₂ < 93% on room air <p>Or in case of severe or immediately life-threatening COVID-19, for example:</p>

NCT04374487 (Continued)

- Severe disease is defined as:
 - * dyspnoea
 - * respiratory frequency $\geq 30/\text{min}$
 - * blood oxygen saturation $\leq 93\%$
 - * partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
 - * lung infiltrates $> 50\%$ within 24 -48 h
- Life-threatening disease is defined as:
 - * respiratory failure
 - * septic shock
 - * multiple organ dysfunction or failure

Exclusion criteria:

- Pregnant women
- Breastfeeding women
- Known hypersensitivity to blood products
- Receipt of pooled immunoglobulin in last 30 days
- Participating in any other clinical trial
- Clinical status precluding infusion of blood products

Interventions

- Intervention(s): CP
- Details of CP:
 - * Type of plasma: ABO-compatible plasma transfusion
 - * Volume: 200 mL
 - * Number of doses: NR
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: standard care treatment according to institutional protocols
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome:
 - * The primary outcome is a composite measure of the avoidance of
 - 1. Progression to severe ARDS (P/F ratio 100) and
 - 2. All-cause mortality at 28 days (time frame: depends on the total treatment time of the participants within 1-year period of the trial)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: all-cause mortality at 28 days (time frame: depends on the total treatment time of the participants within 1-year period of the trial)
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection: yes (duration of respiratory support required a. duration of invasive mechanical ventilation b. duration of non-invasive (time frame: 1 year)
 - * 30-day and 90-day mortality: yes (28-day mortality)
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR

NCT04374487 (Continued)

- Additional study outcomes
 - * Progression to severe ARDS (P/F ratio 100)
 - * Time to symptom resolution - fever, shortness of breath, fatigue (time frame: 1 year)
 - * Change in SOFA pre- and post-transfusion (time frame: 1 year)
 - * Radiological improvement (time frame: 1 year)
 - * AEs associated with transfusion (time frame: 1 year)
 - * To measure the change in RNA levels (Ct values) of SARS-CoV-2 from RT-PCR (time frame: days 0, 1, 3, and 7 after transfusion) (time frame: 1 year)
 - * Levels of bio-markers pre- and post-transfusion (time frame: 1 year)
 - * Need of vasopressor use (time frame: 1 year)

Starting date	9 May 2020
Contact information	Sangeeta Pathak, MBBS, Diploma 9873081647 sangeeta.pathak@maxhealthcare.com Sandeep Budhiraja, MRCP, FACP 9810262954 sbudhiraja@maxhealthcare.com
Notes	Recruitment status: not yet recruiting Prospective completion date: 9 May 2021 Sponsor/funding: Max Healthcare Insititute Limited, Investigators Principal Investigator: Sangeeta Pathak, MBBS, Diploma Max Super Speciality Hospital, Saket (DDF)

NCT04374526

Study name	Early transfusion of COVID-19 convalescent plasma in elderly COVID-19 patients to prevent disease progression
Methods	<ul style="list-style-type: none"> • Trial design: randomized phase 2/3 • Sample size: 182 • Setting: inpatient • Country: Italy • Language: translated to English • Number of centres: 3
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Age \geq 65 • pneumonia at CT scan • PaO₂/FiO₂ \geq 300 mmHg • Presence of \geq 1 comorbidities (consider the list provided in Appendix A) • Signed informed consent <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Age < 65 • PaO₂/FiO₂ < 300 mmHg • pending cardiopulmonary arrest • refusal to blood product transfusions • Severe IgA deficiency • any life-threatening comorbidity or any other medical condition which, in the opinion of the investigator, makes the patient unsuitable for inclusion
Interventions	<ul style="list-style-type: none"> • Intervention(s): COVID-19 CP

NCT04374526 (Continued)

- Details of CP:
 - * Type of plasma: ABO-matched pathogen-inactivated CCP
 - * Volume: 200 mL/day
 - * Number of doses: 3 (days 1, 2, and 3)
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: standard therapy
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome: rate of COVID-19 progression (time frame: days 1-14)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional study outcomes: N
 - * NR

Starting date

27 May 2020

Contact information

 Raffaele Landolfi, Prof. 06 30154435 ext +39 raffaele.landolfi@unicatt.it

 Luciana Teofili, Prof. 06 30154180 ext +39 luciana.teofili@unicatt.it

Notes

Recruitment status: recruiting

Prospective completion date: 30 June 2021

Sponsor/funding: Fondazione Policlinico Universitario Agostino Gemelli IRCCS

NCT04374565

Study name

Efficacy and safety of high-titer anti-SARS-CoV-2 (COVID19) convalescent plasma for hospitalized patients with infection due to COVID-19 to decrease complications: a phase II trial

Methods

- Trial design: single-arm phase II trial
- Sample size: 29
- Setting: inpatient
- Country: USA
- Language: English

NCT04374565 (Continued)

Participants	<ul style="list-style-type: none"> • Number of centres: 2 <hr/> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patients must be ≥ 18 years • Patients hospitalised with COVID-19 respiratory symptoms within 72 h of admission to a "floor" bed (non-ICU bed) and confirmation via SARS-CoV-2 RT-PCR testing • Patient and/or surrogate is willing and able to provide written informed consent and comply with all protocol requirements. • Patients with haematologic malignancies or solid tumours are eligible. • Patients with autoimmune disorders are eligible. • Patients with immunodeficiency and organ or stem cell transplant recipients are eligible. • Patients who have received or are receiving hydroxychloroquine or chloroquine are eligible (but will be taken off the drug). • Prior use of IVIG is allowed but the investigator should consider the potential for a hypercoagulable state. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Patients requiring mechanical ventilation or > 6 L/min nasal cannula oxygen • Patients on other anti-COVID-19 trials being treated with tocilizumab (anti-IL-6 receptor), siltuximab (anti-IL-2), remdesivir, or other pharmacological trials that may be initiated hereafter. • A pre-existing condition or use of a medication that, in the opinion of the site investigator, may place the individual at a substantially increased risk of thrombosis (e.g. cryoglobulinemia, severe refractory hypertriglyceridaemia, or clinically significant monoclonal gammopathy) • Contraindication to transfusion or history of prior reactions to transfusion blood products. • Medical conditions for which receipt of 500-600 mL of IV fluid may be dangerous to the subject (e.g. decompensated congestive heart failure)
Interventions	<ul style="list-style-type: none"> • Intervention(s): high-titre anti-SARS-CoV-2 (COVID 19) CP • Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: ~200 mL * Number of doses: 2 given preferably in 1 day, but allowable to be given over 2 days if clinical circumstances delay infusions in 1 day * Antibody-titre: high-titre * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: historical control group via retrospective chart review • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Transfer to ICU (time frame: Days 0-60) * 28 day mortality (time frame: Days 0-60) • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: 28-day mortality (time frame: Days 0-60) * Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes (cumulative incidence of AEs (AE), grades 3 and 4 AE), Incidence of adverse plasma transfusion reactions: yes (grade 3 or 4 AEs; time frame: days 0-60) * Number of participants with SAEs: yes (Cumulative incidence of SAEs (time frame: Days 0 - 60) * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (ventilator-free days (time frame: Days))

NCT04374565 (Continued)

- * 30-day and 90-day mortality: yes (60-day mortality)
- * Admission on the ICU: yes, (ICU-free days (time frame: Days 0-28), transfer to ICU (time frame: Days 0 - 60),
- * Need for ECMO (time frame: Days 0-60)
- * Length of stay on the ICU: yes (ICU LOS (time frame: days 0-60))
- * Time to discharge from hospital: yes (hospital length of stay (LOS) (time frame: Days 0-60))
- * QoL: NR
- Additional study outcomes
 - * Rates and duration of SARS-CoV-2 (time frame: Days 0, 7, 14, and 21)
 - * Sequential organ failure assessment score (time frame: days 0, 1, 4, 7, 14, 21, 28)
 - * Serum of plasma antibody titre to SARS-CoV-2 (time frame: Days 0, 7, 14, and 28)
 - * Cellular and humoral immune response (time frame: Days 0, 7, 14, 28)
 - * Supplemental oxygen-free days (time frame: Days 0-28)
 - * Ventilator-free days (time frame: Days 0 - 28)
 - * Need for vasopressors (time frame: Days 0 - 60)
 - * Need for renal replacement therapy (time frame: Days 0 - 60)

Starting date	5 May 2020
Contact information	Kristen M Petros De Guex, MA 434) 924-5059 KMP6F@hscmail.mcc.virginia.edu William B Harrington, MPH 434-409-5060 wh7fd@hscmail.mcc.virginia.edu
Notes	Recruitment status: recruiting Prospective completion date: 5 April 2021 Sponsor/funding:

NCT04375098

Study name	Efficacy and safety of early anti-SARS-COV-2 convalescent plasma in patients admitted for COVID-19 infection: a randomized phase II trial
Methods	<ul style="list-style-type: none"> • Trial design: randomized, open-label, phase II trial • Sample size: 30 • Setting: inpatient • Country: Chile • Language: translated to English • Number of centres: 1
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patient > 18 years • CALL score ≥ 9 (progression risk score) • PCR-confirmed COVID-19 infection with ≤ 7 days of symptoms • Any symptoms of COVID-19 infection • Admission due to COVID-19 infection • Signed informed consent • ECOG before COVID-19 infection 0-2 <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • PaFi < 200 or mechanical ventilation indication

NCT04375098 (Continued)

- Clinically relevant co-infection at admission
- Pregnancy or lactation
- IgA deficiency or IgA nephropathy
- Immunoglobulin or plasma administration in the last 60 days
- Contraindication to transfusion or previous allergy to blood-derived products
- Do-not-resuscitate status
- Patients receiving other investigational drug for COVID-19 in a clinical trial
- Any condition, that in opinion of the investigator may increase the risk associated with study participation or interfere with the interpretation of study results

Interventions

- Intervention(s): CP
- Details of CP:
 - * Type of plasma: early COVID-19 CP
 - * Volume: 200 mL
 - * Number of doses: 2, day 1 and 2 at admission after confirmation of eligibility
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: COVID-19 CP 200 mL day 1 and 2 only if worsening of respiratory function or persistence of COVID symptoms for > 7 days after enrolment
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome:
 - * Percentage mechanical ventilation, hospitalisation > 14 days or death during hospitalisation (time frame: 1-year follow-up)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: 30-day mortality (percentage)
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection: yes (median duration of mechanical ventilation (time frame: 1-year follow-up))
 - * 30-day and 90-day mortality: yes (30-day mortality, (time frame: 1-year follow-up), hospital mortality rate (percentage) (time frame: 1-year follow-up))
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: yes (percentage mechanical ventilation, hospitalisation > 14 days or death during hospitalisation (time frame: 1-year follow-up), median length of ICU stay (time frame: 1-year follow-up))
 - * Time to discharge from hospital: yes (median length of admission (time frame: 1-year follow-up))
- Additional study outcomes
 - * Median duration of fever (time frame: 1 year)
 - * Readmission rate (percentage) (time frame: 1-year follow-up)
 - * Median length of viral clearance (time frame: 1-year follow-up)

Starting date

4 May 2020

Contact information

 Contact: Maria Elvira Balcells, MD +562 23543508 ebalcells@uc.cl
Notes

Recruitment status: recruiting

NCT04375098 (Continued)

Prospective completion date: December 2020

Sponsor/funding: Pontificia Universidad Catolica de Chile, Fundacion Arturo Lopez Perez, Principal Investigator: Maria Elvira Balcells, MD ebalcells@uc.cl

NCT04376034

Study name	Convalescent plasma collection from individuals that recovered from COVID19 and treatment of critically ill individuals with donor convalescent plasma
Methods	<ul style="list-style-type: none"> • Trial design: prospective, non-randomized, sequential-assigned, clinical trial • Sample size: 240 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Individuals of any age > 30 days of life, sex, or pregnancy status suffering from confirmed COVID-19 and in rapid progression, severe or critical condition meeting the FDA IND guidelines. * Must have laboratory-confirmed COVID-19 * Must have severe or immediately life-threatening COVID-19 * Must provide informed consent/assent • Exclusion criteria: <ul style="list-style-type: none"> * Individuals with COVID-19 who are not in clinical concern for rapid progression, severe or critical condition * Individuals who are in critical condition that are not confirmed to have COVID-19 * Individuals with known selective IgA deficiency, that has not been found to be absent of anti-IgA antibodies • Donor eligibility criteria: <ul style="list-style-type: none"> * Prior diagnosis of COVID-19 documented by a laboratory test <ul style="list-style-type: none"> <input type="checkbox"/> Abbott RealTime SARS-CoV-2 real-time RT-PCR test on the Abbott m2000 System (inpatient WVU testing) <input type="checkbox"/> Other testing methods and vendors using FDA-approved detection methods of SARS-CoV-2 under the Emergency Use Authorization (EUA) * Complete resolution of symptoms at least 28 days prior to donation * Complete resolution of symptoms for at least 14 days with negative repeat COVID-19 testing approved by the FDA EUA * Female donors age 18+ that have never been pregnant or negative for HLA antibodies * Male donors age 18+ * Negative results for COVID-19 either from ≥ 1 nasopharyngeal swab specimens or by a molecular diagnostic test from blood. A partial list of available tests can be accessed at www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations. * Defined SARS-CoV-2 neutralising antibody titres, if testing can be conducted (e.g. of at least 1:1602, 1:360 up to 1:640 is preferred. In shortage case 1:80 is acceptable) * ≥ 50 kg of weight • Donor exclusion criteria: <ul style="list-style-type: none"> * Individuals that do not meet the requirement from the American Red Cross for plasma donation or equivalent * Individuals' plasma that has not passed safety screening after procurement by the American Red Cross for plasma donation or equivalent
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP

NCT04376034 (Continued)

- Details of CP for moderate severity: 1 unit
 - * Type of plasma: plasma obtained from volunteers who have recovered from SARS-Cov-2 infection
 - * Volume: 200-250 mL (adult recipient), 10 mL/kg up to 1 unit of plasma (pediatric recipient)
 - * Number of doses: 2 infusions be administered with 24-72 h in between
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
 - * Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Details of CP for severe or critical severity: 2 units
 - * Type of plasma: plasma obtained from volunteers who have recovered from SARS-Cov-2 infection
 - * Volume: 200-250 mL (adult recipient), 10 mL/kg up to 1 unit of plasma (pediatric recipient)
 - * Number of doses: 2 infusions be administered with 24-72 h in between
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
 - * Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator for mild severity: standard of care
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome:
 - * Plasma donor (time frame: measured in days for 365 days), time it takes to identify eligible donors who are willing to donate
 - * Plasma donor (time frame: measured in days for 365 days), time it takes the plasma collection center to contact willing donors who are allowed to donate plasma
 - * Plasma recipient (time frame: measured every 24 h up to 30 days), time from consent to infusion
 - * Plasma recipient (time frame: measured in days with 30 day from discharge follow-up), survival
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes, 30-day mortality
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: yes (30-day mortality)
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional study outcomes
 - * Plasma recipient (time frame: Day 1, 2, 3, 4, 7, and 30 day) morbidity reduction
 - * Plasma donor (time frame: measured every 24 h up to 1 year) time until plasma is donated

Starting date 16 April 2020

 Contact information Brian Peppers, DO, PhD 304-594-2483 brian.peppers@hsc.wvu.edu
 Lisa Giblin Sutton, Pharm D 304-293-0928 giblinl@wvumedicine.org

Notes Recruitment status: not yet recruiting

NCT04376034 (Continued)

Prospective completion date: 30 March 2021

Sponsor/funding: West Virginia University

NCT04376788

Study name	Exchange transfusion versus plasma from convalescent patients with methylene blue in patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: randomized, parallel-assigned, open-label, phase 2 • Sample size: 15 (5 each group) • Setting: inpatient • Country: Egypt • Language: translated to English • Number of centres: 1
Participants	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Adult patients are ≥ 18 years 2. Inpatients diagnosed as severe COVID-19 disease according to WHO criteria 3. CT chest with extensive lung disease (ground-glass and consolidative pulmonary opacities) 4. O₂ saturation $< 93\%$ resting 5. Respiratory rate ≥ 30/min <p>Exclusion criteria:</p> <ol style="list-style-type: none"> 1. Patients with pregnancy and lactation 2. Renal failure and heart failure 3. Contraindication for plasma or blood transfusion
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP • Details of CP (group I): <ul style="list-style-type: none"> * Type of plasma: will receive exchange transfusion by venesection of 500 cc blood with good replacement of one unit packed washed RBCs daily for 3 days according to daily clinical and investigational follow-up * Volume: 500 cc blood * Number of doses: * Antibody-titre: NR * Pathogen inactivated: NR * Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Details of CP (group II): <ul style="list-style-type: none"> * Type of plasma: will receive IV methylene blue 1 mg/kg IV over 30 min with 200 cc plasma from convalescent matching single patient by plasma extractor machine for 3 days according to daily clinical and investigational follow-up. * Volume: IV methylene blue 1 mg/kg IV over 30 min with 200 cc plasma * Number of doses: * Antibody-titre: NR * Pathogen inactivated: NR * Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Details of CP (group III): <ul style="list-style-type: none"> * Type of plasma: will receive exchange transfusion by venesection of 500 cc blood with good replacement of 1 unit packed washed RBCs and IV methylene blue 1 mg/kg IV over 30 min with 200 CC plasma from convalescent matching single patient by plasma extractor machine for 3 days according to daily clinical and investigational follow-up

NCT04376788 (Continued)

- * Volume: venesection of 500 cc blood
- * Number of doses: 1
- * Antibody-titre: NR
- * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome:
 - * improvement of condition (time frame: 3-5 days) (improvement of general condition of the participants as the ventilator parameters and serum level of ferritin, D dimer, complete blood count, oxygen level in blood and patient o2 saturation)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional study outcomes
 - * improvement of condition (time frame: 3-5 days) (improvement of general condition of the participants as the ventilator parameters and serum level of ferritin, D dimer, complete blood count, oxygen level in blood and patient o2 saturation)
 - * change in organs function with PFS and OS (time frame: 1 month) change in the liver, kidney function and change in ferritin level with normal D Dimer

Starting date 5 May 2020

Contact information Mohamed M Moussa +201001553744 drmohamed_metwali1@med.asu.edu.eg
 Essam A Hassan, MD +201001839394 essam.abdelwahed@yahoo.com

Notes Recruitment status: not yet recruiting
 Prospective completion date: 1 June 2020
 Sponsor/funding: Ain Shams University Investigators: Principal Investigator: Mohamed M Moussa, Ain Shams University

NCT04377568

Study name CONCOR-KIDS: a randomized, multicentered, open-label phase 2 clinical trial of the safety and efficacy of human coronavirus-immune convalescent plasma for the treatment of COVID-19 disease in hospitalized children

Methods • Trial design: open-label, phase 2, RCT

NCT04377568 (Continued)

- Sample size: 100
- Setting: inpatient children
- Country: Canada
- Language: English
- Number of centres: 12

Participants

Inclusion criteria:

- Age 0 to < 19 years old
- hospitalised with symptoms compatible with COVID-19 illness
- Laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen prior to randomisation
- ABO-compatible CP available

Exclusion criteria:

- Onset of symptoms began > 12 days before screening
- History of adverse reactions to blood products or other contraindication to transfusion
- Refusal of plasma for religious or other reasons
- Acute heart failure with fluid overload
- Any condition or diagnosis, that could in the opinion of the Site Principal Investigator interfere with the participant's ability to comply with study instructions, or put the participant at risk
- Anticipated discharge within 24 h

Interventions

- Intervention(s): CP
- Details of CP:
 - * Type of plasma: NR
 - * Volume: proportional to their weight (10 mL/kg), up to a maximum of 500 mL
 - * Number of doses: 1
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: standard of care
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome:
 - * Clinical recovery at day 30
- Secondary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: yes
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: yes
 - * QoL: yes

NCT04377568 (Continued)

- Additional outcomes
 - * Clinical recovery (time frame: at day 30) defined in the last 24 h as normal respiratory and heart rate (or return to baseline, absence of fever, absence of low blood pressure, oxygen saturation > 94% or room air (or return to baseline), no need for intravenous fluids (or return to baseline)
 - * Combined mortality/intubation at day 30
 - * Time to intubation
 - * Mean number of ventilator-free days in 30 days
 - * Mean number of ventilator days in 30 days
 - * The number of oxygen-free days in the first 30 days or the incidence and duration of new oxygen use during the trial, defined as oxygen use that was not present at time of randomisation but occurs subsequently
 - * The proportion of participants needing ECMO in 30 days
 - * The proportion of participants needing renal replacement therapy
 - * The proportion of participants developing myocarditis
 - * Proportion of participants with negative virology (time frame: at day 3, 5, 10 and 15)
 - * Modulation of biomarkers (time frame: up to 365 days)
 - * Resolution of fever (time frame: h)
 - * Levels of IgG, IgA antibodies and neutralising antibody titres (time frame: at 30 days)
 - * Efficacy of C19-CP on respiratory measures using pediatric-validated dyspnoea (breathlessness) scales
 - * Evaluate the efficacy of C19-CP on rehospitalisation after discharge

Starting date	1 May 2020
Contact information	Contact: Julia Upton 416 813 7654 ext 208634 julia.upton@sickkids.ca Contact: Christoph Licht christoph.licht@sickkids.ca
Notes	Recruitment status: not yet recruiting Prospective completion date: 1 May 2022 Sponsor/funding: The Hospital for Sick Children, C17 Council (regulatory sponsor)

NCT04377672

Study name	Human convalescent plasma for high risk children exposed or infected with SARS-CoV-2 (COVID-19)
Methods	<ul style="list-style-type: none"> • Trial design: single-centre, single-arm, open-label interventional trial • Sample size: 30 participants • Setting: inpatient • Country: USA • Language: English • Number of centres: 1
Participants	Inclusion criteria: <ul style="list-style-type: none"> • Between 1 month and 18 years of age at the time of consent • Determined to be at high-risk for severe SARS-CoV-2 disease based on the American Academy of Pediatrics definition of immunocompromised children and reported high-risk paediatric subpopulations. These include the following groups: immunocompromised, haemodynamically significant cardiac disease {e.g. congenital heart disease}, lung disease with chronic respiratory failure, infant, i.e. child \leq 1 year old

NCT04377672 (Continued)

- Confirmed SARS-CoV-2 infection or high-risk exposure as defined:
 - * Confirmed infection: child who tested positive for COVID-19 and is no more than 96 h after onset of symptoms (and within 120 h at the time of receipt of plasma)
 - * High-risk exposure: susceptible child who was not previously infected or otherwise immune to SARS-CoV-2 and exposed within 96 h prior to enrolment (and within 120 h at the time of receipt of plasma). Both criteria below should be met: a household member or daycare center (same room) exposure to a person with confirmed SARS-CoV-2 or with clinically compatible disease in regions with widespread ongoing transmission) and a negative for SARS-CoV-2 (nasopharyngeal swab)
- Participant is judged by the investigator to have the initiative and means to be compliant with the protocol
- Participants or their legal representatives must have the ability to read, understand, and provide written informed consent for the initiation of any study related procedures.

Exclusion criteria:

- History of severe reactions (e.g. anaphylaxis) to transfusion of blood products. Participants with minor reactions such as fever, itching, chills, etc. that resolve spontaneously or respond to pre-medications, and that do not represent more significant allergic reactions will not be excluded
- Inability to complete therapy with the study product within the stipulated time frame outlined above
- Female participants of child-bearing age with a positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period.
- Participant/caregiver deemed by the study team to be non-compliant with the study protocol

Interventions

- Interventions: CP
- Details of CP:
 - * Type of plasma: CP
 - * Volume: 200-250 mL
 - * Number of doses: 1-2. Total volume will be based on weight 5 mL/kg with a maximum volume of 500 mL
 - * Antibody titre: $\geq 1:320$
 - * Pathogen inactivated: NR
- Treatment details: NR
- Comparator: NA
- Concomitant therapy: NR
- Treatment cross-overs: NA

Outcomes

- Primary study outcome: safety of treatment with high-titre anti-SARS-CoV-2 plasma as assessed by AEs (time frame: 28 days). Proportion of participants with grade 3 and 4 AEs during the study period
- Primary review outcomes reported:
 - * All-cause mortality at hospital discharge: 28-day mortality
 - * Time to death: NR

NCT04377672 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection: yes
 - * 30-day and 90-day mortality: yes (28-day mortality)
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes: NR

Starting date	28 May 2020
Contact information	Contact: Oren Gordon, MD 4106141211 ogordon3@jhmi.edu Contact: Mary Katherine Brosnan 410-955-8264 mbrosna1@jhmi.edu
Notes	Estimated primary completion date 28 May 2021 Institution - John Hopkins University

NCT04380935

Study name	Effectiveness and safety of convalescent plasma therapy on COVID-19 patients with acute respiratory distress syndrome
Methods	<ul style="list-style-type: none"> • Trial design: multicentre, open-label RCT • Sample size: 60 • Setting: inpatients • Country: Indonesia • Language English • Number of centres: 3
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patients aged ≥ 18 years • COVID-19 confirmed by RT-PCR • Having severe pneumonia • PAO₂ / FIO₂ < 300 • Using mechanical ventilation <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Contraindication to blood transfusions (fluid overload, history of anaphylaxis of blood products) • Multiple and severe organ failure, haemodynamically unstable • Other uncontrolled infections • DIC, which requires a replacement factor/FFP • Haemodialysis patients or CRRT (continuous renal replacement therapy) • Active intracranial bleeding • Significant myocardial ischaemia

NCT04380935 (Continued)

	<ul style="list-style-type: none"> Receiving tocilizumab treatment
Interventions	<ul style="list-style-type: none"> Intervention(s): standard of care and CP Details of CP: <ul style="list-style-type: none"> Type of plasma: NR Volume: NR Number of doses: NR Antibody-titre: NR Pathogen inactivated: NR Treatment details, including time of plasma therapy (e.g. early stage of disease): NR Comparator: standard therapy Concomitant therapy: NR Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> Primary study outcome: all cause mortality at 28-day Primary review outcomes reported <ul style="list-style-type: none"> All-cause mortality at hospital discharge: 28-day mortality Time to death: NR Secondary review outcomes reported <ul style="list-style-type: none"> Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): allergic reactions, haemolytic transfusion reaction, TRALI, TACO Number of participants with SAEs: NR Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection: only duration of mechanical ventilation 30-day and 90-day mortality: yes (28-day mortality) Admission on the ICU: yes Length of stay on the ICU: yes Time to discharge from hospital: NR QoL: NR Additional outcomes: NR
Starting date	11 May 2020 Estimated completion date 31 August 2020
Contact information	Contact: Robert Sinto, MD +628158835432 rsinto@yahoo.com
Notes	Recruitment status: recruiting Prospective completion date: 31 August 2020 Sponsor/funding: Indonesia University/NR

NCT04381858

Study name	Convalescent plasma vs human immunoglobulin to treat COVID-19 pneumonia
Methods	<ul style="list-style-type: none"> Trial design: single-centre, double-blind, RCT Sample size: 500 Setting: inpatient Country: Mexico Language English

NCT04381858 (Continued)

	<ul style="list-style-type: none"> Number of centres: 1
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Patients who are admitted to hospital centres with a positive RT-qPCR SARS-CoV-2 test or a CT scan compatible with a diagnosis of COVID-19 pneumonia, in addition to 1 of the following 2 criteria: <ol style="list-style-type: none"> Severe respiratory failure (respiratory rate > 25 to < 35 x min, oxygen saturation ≤ 90% with reservoir mask (FiO₂ = 100%)) Requiring invasive mechanical ventilation <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Patients with a viral infection other than COVID-19
Interventions	<ul style="list-style-type: none"> Intervention(s): CP or human immunoglobulin Details of CP: <ul style="list-style-type: none"> Type of plasma: CP Volume: 400 mL Number of doses: 2 Antibody-titre: when assay available > 1:640 Pathogen inactivated: NR Treatment details, including time of plasma therapy (e.g. early stage of disease): NR Comparator: human immunoglobulin 0.3 g/kg/day for 5 doses Concomitant therapy: NR Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> Primary study outcome: mean hospitalisation time Primary review outcomes reported <ul style="list-style-type: none"> All-cause mortality at hospital discharge: yes Time to death: yes Secondary review outcomes reported <ul style="list-style-type: none"> Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR Number of participants with SAEs: NR Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: oxygenation index, rate of ARDS, mean time with invasive mechanical ventilation 30-day and 90-day mortality: yes Admission on the ICU: NR Length of stay on the ICU: NR Time to discharge from hospital: yes (hospitalisation time) QoL: NR Additional outcomes <ul style="list-style-type: none"> Time to viral PCR negativisation
Starting date	6 May 2020
	Completion 30 September 2020
Contact information	Jose Manuel Arreola, MD, PhD 4494632049 dr.jmag@gmail.com
Notes	<p>Recruitment status: recruiting</p> <p>Prospective completion date: 30 September 2020</p>

NCT04381858 (Continued)

Sponsor/funding: Centenario Hospital Miguel Hidalgo

NCT04381936

Study name	Randomised evaluation of COVID-19 therapy (RECOVERY)
Methods	<ul style="list-style-type: none"> • Trial design: multicentre, randomised adaptive trial • Sample size: 12,000 • Setting: inpatient • Country: UK • Language: English • Number of centres: multiple (currently 176 active sites)
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Hospitalised * SARS-CoV-2 infection (clinically suspected or laboratory-confirmed) * No medical history that might, in the opinion of the attending clinician, put the patient at significant risk if he/she were to participate in the trial • Exclusion criteria: <ul style="list-style-type: none"> * If the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms (see Protocol Appendix 2; section 8.2 and Appendix 3; section 8.3 for children) or that the patient should definitely be receiving one of the active drug treatment arms then that arm will not be available for randomisation for that patient. For patients who lack capacity, an advanced directive or behaviour that clearly indicates that they would not wish to participate in the trial would be considered sufficient reason to exclude them from the trial. * Exclusion for CP randomisation: known moderate or severe allergy to blood components, Not willing to receive a blood product
Interventions	<ul style="list-style-type: none"> • Intervention(s): randomised factorial assignment <ul style="list-style-type: none"> * Main randomisation (part A): eligible patients will be randomly allocated between the available 5 treatment arms. No additional treatment vs lopinavir-ritonavir vs low-dose corticosteroids vs hydroxychloroquine vs azithromycin * Main randomisation (part B): simultaneously, eligible patients will be randomly allocated between CP or no additional treatment * Participants with progressive COVID-19 (as evidenced by hypoxia and an inflammatory state) may undergo an optional second randomisation: no additional treatment vs tocilizumab • Details of CP: <ul style="list-style-type: none"> * Type of plasma: ABO-identical if possible * Volume: 275 mLs +/- 75 mL * Number of doses: 1-2 * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients • Comparator: standard therapy and/or lopinavir-ritonavir, low-dose corticosteroids, hydroxychloroquine, azithromycin, tocilizumab • Concomitant therapy: standard therapy and/or lopinavir-ritonavir, low-dose corticosteroids, hydroxychloroquine, azithromycin, tocilizumab • Treatment cross-overs: participants with progressive COVID-19 (as evidenced by hypoxia and an inflammatory state) may undergo an optional second randomisation: no additional treatment vs tocilizumab. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated.
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: all-cause mortality (time frame: within 28 days after randomisation)

NCT04381936 (Continued)

- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: yes
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes (additional safety data will be collected in a subset of participants randomised to part B. These will be tabulated separately by allocation (CP vs no additional treatment): (i) sudden worsening in respiratory status; (ii) severe allergic reaction; (iii) temperature > 39 °C or ≥ 2 °C rise since randomisation; (iv) sudden hypotension, clinical haemolysis and thrombotic event)
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (within 28 days and up to 6 months after the main randomisation)
 - * 30-day and 90-day mortality: yes (up to 6 months after main randomisation)
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional outcomes:
 - * Need for renal replacement
 - * Development of new major cardiac arrhythmias

Starting date	19 March 2020
Contact information	Richard Haynes +44 (0)1865 743743 recoverytrial@ndph.ox.ac.uk
Notes	Recruitment status: recruiting Prospective completion date: June 2021 Sponsor/funding: University of Oxford

NCT04383535

Study name	Convalescent plasma and placebo for the treatment of COVID-19 severe pneumonia
Methods	<ul style="list-style-type: none"> • Trial design: multicentre randomized, double-blind, placebo-controlled clinical trial • Sample size: 333 • Setting: inpatient • Country: Argentina • Language: English • Number of centres: NR
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Confirmed diagnosis of COVID-19 through qualitative qRT-PCR (GeneDX Co, Ltd or similar) • Imaging-diagnosed pneumonia (X-ray or CT scan) • MSOFA score (Modified SOFA) of ≥ 2 (modified organic failure assessment) • Informed consent <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Pregnant women

NCT04383535 (Continued)

	<ul style="list-style-type: none"> • Women at reproductive age not willing to avoid unprotected sexual intercourse up to Day 30 after study initiation • Women in the breastfeeding period • Patients receiving experimental treatments under development within 30 days prior to study initiation • Patients with a previous history of allergic reactions to blood or blood-components transfusion • Diagnosis or clinical suspicion of an alternative microbiological cause for pneumonia besides COVID-19 • Use of systemic corticosteroids within 15 days prior to entering the study
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP and placebo • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP from pool of 10 donor plasma * Volume: 10-15 mL/kg * Number of doses: NR * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: saline 10-15 mL/kg • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: clinical status during follow-up at 30th day: Ordinal outcome with 6 mutually exclusive categories to describe the participant's clinical status during follow-up. The 6 categories are: (1) death; (2) in intensive care; (3) hospitalised but requiring supplemental oxygen; (4) hospitalised and not requiring supplemental oxygen; (5) discharged but unable to resume normal activities; or (6) discharged with full resumption of normal activities. • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes * Time to death: yes • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes * Number of participants with SAEs: yes * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: yes (30 day) * Admission on the ICU: yes * Length of stay on the ICU: yes (ICU hospitalisation) * Time to discharge from hospital: yes (hospitalisation time) * QoL: NR • Additional study outcomes <ul style="list-style-type: none"> * Plasma concentration of neutralising antibodies (day 2/7) * Results of other laboratory tests
Starting date	15 May 2020
Contact information	Contact: Waldo H Belloso, PhD +541149590200 waldo.belloso@hiba.org.ar Contact: Ventura Simonovich, MD +541149590200 ventura.simonovich@hiba.org.ar
Notes	Recruitment status: recruiting Prospective completion date: August 2020

NCT04383535 (Continued)

Sponsor/funding: Hospital Italiano de Buenos Aires/NR

NCT04383548

Study name	Clinical study for efficacy of anti-corona VS2 immunoglobulins prepared from COVID19 convalescent plasma prepared by VIPS mini-pool IVIG medical devices in prevention of SARS-CoV-2 infection in high risk groups as well as treatment of early cases of COVID19 patients
Methods	<ul style="list-style-type: none"> • Trial design: interventional, single-arm, open-label, clinical trial • Sample size: 100 • Setting: inpatients • Country: Egypt • Language: English • Number of centres: NR
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Passive immunisation group (Group A) <ul style="list-style-type: none"> * 20 high-risk exposed people (HCPs) who are nasopharyngeal swab SARS-CoV-2 PCR-negative and seronegative for SARS-CoV-2 IgM/IgG antibodies to receive prophylactic anti-SARS-CoV-2 hyper immunoglobulin. Selected population can be both male and female with age range 21-50 years * 20 high-risk people (HCPs) who are nasopharyngeal swab SARS-CoV-2 PCR negative and seronegative for SARS-CoV-2 IgM/IgG antibodies as control group. Selected population can be both male and female with age range 21-50 years • Patient group (group B) <ul style="list-style-type: none"> * 30 patients with COVID-19 disease and nasopharyngeal swab or sputum SARS-CoV-2-positive PCR to receive anti-SARS-CoV-2 in addition to applied clinical management protocol. Selected test group can be male or female with age > 20 years * 30 patients with COVID-19 disease and nasopharyngeal swab or sputum SARS-CoV-2 PCR-positive managed according to applied clinical management protocols of COVID-19 disease as control group. Selected test group can be male or female with age > 30 years <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Passive immunisation group (Group A) <ul style="list-style-type: none"> * Age < 21 or > 50 years * Nasopharyngeal swab SARS-CoV-2-positive PCR * Presence of anti-SARS-CoV-2 IgM, IgG * Presence of comorbidities such as hypertension, diabetes, chronic renal disease, previous thrombotic events or states of allergy such as urticaria or bronchial asthma as well as previous AEs due to infusion of IVIG • Patient group (group B) <ul style="list-style-type: none"> a. Age < 20 years b. SARS-CoV-2 PCR-negative c. COVID-19 patients who may suffer from co-morbidities such as hypertension, diabetes, chronic renal disease, thrombotic tendency or history of AEs to IVIG as well as old age will be excluded to reduce the possibility of development of SAEs related to infusion of IVIG unless it will be for compassionate use in advanced stages of COVID-19 patients and after obtaining informed consent
Interventions	<ul style="list-style-type: none"> • Intervention(s): hyper immunoglobulin

NCT04383548 (Continued)

- Details of CP:
 - * Type of plasma: hyperimmune globulin - prepared from CP using VIPS Mini-Pool IVIG medical device
 - * Volume: NR
 - * Number of doses: NR
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: NA
- Concomitant therapy: NR
- Treatment cross-overs: NA

Outcomes

- Primary study outcome: efficacy of COVID19 hyper immunoglobulins for patients
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional study outcomes: NR

Starting date

1 June 2020

Contact information

 Contact: Alshaimaa M Selim, specialist 01003580480 shaimaamokhtargood@yahoo.com

 Contact: Maha A Mohamed, Professor 01000004572 atwa_maha@yahoo.com

Notes

Recruitment status: not yet recruiting

Prospective completion date: 1 January 2021

Sponsor/funding: Assiut University

NCT04384497

Study name

Convalescent plasma for treatment of COVID-19: an exploratory dose identifying study

Methods

- Trial design: single-arm, open, non-randomised clinical trial
- Sample size: 50
- Setting: inpatient
- Country: Sweden
- Language: English
- Number of centres: 1

Participants

Inclusion criteria:

NCT04384497 (Continued)

- Age \geq 18
- Admitted to a study hospital
- Active COVID-19 defined as symptoms + SARS CoV-2 identified from upper or lower airway samples
- Negative pregnancy test taken before inclusion and use of an acceptable effective method of contraception until treatment discontinuation if the participant is a woman of childbearing potential
- Written informed consent after meeting with a study physician and ability and willingness to complete follow-up

Exclusion criteria:

- No matching plasma donor (exact matching in both the ABO system is required)
- Unavailability of plasma
- Significant growth of alternative lower airway pathogen such as *Streptococcus pneumoniae* or *Haemophilus influenzae* in sputum
- Estimated GFR $<$ 60 (kidney failure \geq stage III)
- Pregnancy (urinary-hCG)
- Breast feeding
- History of severe allergic reactions to foods or other substances that the donor may have been exposed to (for example severe peanut allergy)
- Inability to give informed consent

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: 200 mL
 - * Number of doses: up to 7
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: NA
- Concomitant therapy: NR
- Treatment cross-overs: NA

Outcomes

- Primary study outcome: number and proportion of participants with progression to ventilation or sustained requirement of supplementary oxygen therapy
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional study outcomes
 - * antibody response, inflammatory parameters, clearance of viraemia, fever and symptoms

Starting date

7 May 2020

NCT04384588 (Continued)

- Details of CP:
 - * Type of plasma: NR
 - * Volume: NR
 - * Number of doses: NR
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: NA
- Concomitant therapy: NR
- Treatment cross-overs: NA

Outcomes

- Primary study outcome: in hospital mortality
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: days on ventilatory support
 - * 30-day and 90-day mortality: yes
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional study outcomes
 - * viral load, laboratory studies

Starting date

7 April 2020

Contact information

 Contact: Christian Caglevic, MD56981369487 christian.caglevic@falp.org
Notes

Recruitment status: recruiting

Prospective completion date: 6 April 20201

Sponsor/funding: Fundacion Arturo Lopez PerezConfederación de la Producción y del Comercio (CPC)Bolsa de Santiago

NCT04385043
Study name

Phase 2b/3 trial to evaluate the safety and efficacy of plasma transfusion from convalescent patients with SARS-CoV-2 infection on severity and mortality of COVID-19 in hospitalized patients

Methods

- Trial design: randomised, parallel, open-label clinical trial
- Sample size: 200 in each arm (400)
- Setting: inpatient
- Country: Italy
- Language: translated to English
- Number of centres: 5

NCT04385043 (Continued)

Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> inclusion criteria for donors: null-gravid, with a negative history of transfusion of blood components; possibility to sign the informed consent inclusion criteria for COVID-19 infected patients: serious COVID-19 infection, possibility to sign the informed consent (also through the legal tutor) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> exclusion criteria for donors: presence of pregnancy, recent history of transfusion of blood components, < 18 years exclusion criteria for COVID-19-infected patients: non-serious COVID-19 infection, impossibility to sign the informed consent (also through the legal tutor)
Interventions	<ul style="list-style-type: none"> Intervention(s): plasma-hyperimmune add on to the standard therapy Details of CP: <ul style="list-style-type: none"> Type of plasma: NR Volume: NR Number of doses: NR Antibody-titre: NR Pathogen inactivated: NR Treatment details, including time of plasma therapy (e.g. early stage of disease): NR Comparator: standard therapy Concomitant therapy: NR Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> Primary review outcomes reported <ul style="list-style-type: none"> All-cause mortality at hospital discharge: 30-day mortality Time to death: NR Secondary review outcomes reported <ul style="list-style-type: none"> Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR Number of participants with SAEs: NR Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection: NR 30-day and 90-day mortality: yes (30-day mortality) Admission on the ICU: NR Length of stay on the ICU: NR Time to discharge from hospital: NR QoL: NR Additional study outcomes <ul style="list-style-type: none"> lymphocytes (time frame: 7 and 14 days) PCR levels vs control (time frame: 7 and 14 days) PCR levels vs before treatment (time frame: 7 and 14 days) AB levels and clinical improvement (time frame: 30 days) Inflammatory cytokines vs controls (time frame: 7 and 14 days) Inflammatory cytokines vs before treatment (time frame: 7 and 14 days)
Starting date	1 May 2020
Contact information	Luca Gallelli, University of Catanzaro
Notes	Recruitment status: recruiting

NCT04385043 (Continued)

Prospective completion date: 15 October 2020 (primary), 15 May 2021 (study)

Sponsor/funding: University of Catanzaro; Azienda Ospedaliera Policlinico "Mater Domini", Azienda Sanitaria Provinciale Di Catanzaro, Annunziata Hospital, Cosenza, Italy, Azienda Ospedaliera Bianchi-Melacrino-Morelli

NCT04385186

Study name	Inactivated convalescent plasma as a therapeutic alternative in hospitalized patients COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: multicentre, single-blind, clinical RCT • Sample size: 100 in each arm (60) • Setting: inpatient • Country: Colombia • Language: translated to English • Number of centres: 10
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • >18 years • Confirmed laboratory diagnosis for qRT-PCR to SARS-CoV-2 • Meet any of the following medical criteria (defined by WHO): be currently hospitalised with: pneumonia, severe pneumonia, ARDS (moderate or severe), sepsis or septic shock • The patient, or his representative, must sign an informed consent <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Participate in another clinical trial for COVID-19 • History of acute allergic transfusion reactions due to transfusion of blood or other components, especially plasma components (FFP, cryoprecipitate and platelets), • History of allergic reaction due to IgA deficiency • Allergic reaction to sodium citrate or riboflavin (vitamin B2) <p>History of immunosuppression</p>
Interventions	<ul style="list-style-type: none"> • Intervention(s): inactivated CP SARS-Cov-2 + support treatment under medical decision (day 0) • Details of CP: <ul style="list-style-type: none"> * Type of plasma: ABO-Rh compatible inactivated CP SARS-Cov-2 * Volume: 200 mL * Number of doses: 2, day 0 and day1 * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): transfusion day 0 and day 1 • Comparator: support treatment, Day 0: start of support treatment selected by medical staff according to each institutional protocol • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: mortality reduction in COVID-19 patients treated with inactivated CP + support treatment • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: 28-day mortality (mortality reduction in COVID-19 patients treated with inactivated CP + support treatment (time frame: over a period of 28 days) * Time to death: NR

NCT04385186 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes (incidence of AEs (time frame: up to 28 days)
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: yes (ICU-free days through Day 28 (time frame: until hospital discharge or a maximum of 28 days whichever comes first)
 - * Time to discharge from hospital: yes (hospital-free days through Day 60 (time frame: until hospital discharge or a maximum of 60 days whichever comes first)
 - * QoL: NR
- Additional study outcomes
 - * Clinical evolution (time frame: over a period of 28 days)
 - * Clinical evolution by 7-parameter ordinal scale (time frame: 3, 7, 14 and 28 days)
 - * Multi-organ failure progression (time frame: 3, 7, 14 and 28 days)
 - * Change in haemoglobin concentration (time frame: 3, 7, 14 and 28 days)
 - * Change in blood cell count (time frame: 3, 7, 14 and 28 days)
 - * Change in serum creatinine level (time frame: 3, 7, 14 and 28 days)
 - * Change in AST level (time frame: 3, 7, 14 and 28 days)
 - * Change in ALT level (time frame: 3, 7, 14 and 28 days)
 - * Change in bilirubin level (time frame: 3, 7, 14 and 28 days)
 - * Change in lactate dehydrogenase level (time frame: 3, 7, 14 and 28 days)
 - * Change in creatine kinase level (time frame: 3, 7, 14 and 28 days)
 - * Change in creatine kinase MB level (time frame: 3, 7, 14 and 28 days)
 - * Change in CRP concentration (time frame: 3, 7, 14 and 28 days)
 - * Change in D Dimer concentration (time frame: 3, 7, 14 and 28 days)
 - * Change in procalcitonin concentration (time frame: 3, 7, 14 and 28 days)
 - * Change in IL6 level (time frame: 3, 7, 14 and 28 days)
 - * Radiography imaging (time frame: Over a period of 60 days)
 - * Tomography imaging (time frame: Over a period of 60 days)
 - * Assessment of oxygenation (time frame: 3, 7, 14 and 28 days)
 - * Viral load (time frame: 0, 3, 7 days and until hospital discharge or a maximum of 60 days whichever comes first)

Starting date	20 June 2020
Contact information	Andrés F Zuluaga, MD, MSc, MeH 3014020291 andres.zuluaga@udea.edu.co Ana L Muñoz, MSc, PhD ana.munoz@hemolifeamerica.org
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 30 December 2020 estimated study completion date; 30 November 2020 (final data collection date for primary outcome measure) • Sponsor/funding: National Blood Center Foundation, Hemolife, Principal Investigator: Andrés F Zuluaga, MD, MSc, MeH, Universidad de Antioquia

NCT04385199

Study name	The use of convalescent plasma for patients hospitalized with COVID-19 disease
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NCT04385199 (Continued)

Methods	<ul style="list-style-type: none"> • Trial design: open, parallel, RCT • Sample size: 30 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * age > 18 with ≥ 1 of the following: <ul style="list-style-type: none"> <input type="checkbox"/> dyspnoea respiratory rate ≥ 30 breaths/min <input type="checkbox"/> Oxygen saturation ≤ 93% PaO₂/FiO₂ <input type="checkbox"/> < 300 bilateral airspace opacities on chest radiograph at 24-48 h • Exclusion criteria <ul style="list-style-type: none"> * Acute myocardial infarction in past 30 days * Acute stroke in past 30 days * VV ECMO VA ECMO
Interventions	<ul style="list-style-type: none"> • Intervention(s): conventional treatment and CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: ABO-compatible CP * Volume: 200 mL * Number of doses: 1 * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients • Comparator: conventional treatment • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: improvement in respiratory disease (time frame: days 1, 3, 5, 7, 14, 28 post-transfusion) <ul style="list-style-type: none"> * For intubated participants improvement in PaO₂/FiO₂ * For non-intubated participants time to intubation post-transfusion • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes * Number of participants with SAEs: yes * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: NR * Admission on the ICU: yes * Length of stay on the ICU: yes * Time to discharge from hospital: yes * QoL: NR • Additional study outcomes: radiographic improvement (Time frame: 3, 28 days post transfusion)
Starting date	4 May 2020

NCT04385199 (Continued)

Contact information	Geneva Tatem, MD313-587-6775, gatem1@hfhs.org
Notes	<ul style="list-style-type: none"> Recruitment status: recruiting Prospective completion date: 1 August 2020 Sponsor/funding: Henry Ford Health System

NCT04388410

Study name	Phase 2b/3 trial to evaluate the safety and efficacy of plasma transfusion from convalescent patients with SARS-CoV-2 infection on severity and mortality of COVID-19 in hospitalized patients.
Methods	<ul style="list-style-type: none"> Trial design: RCT, double-blinded, multicentre, placebo-controlled Sample size: 250 Setting: inpatient Country: Mexico Language: English Number of centres: at least 6
Participants	<ul style="list-style-type: none"> Inclusion criteria <ul style="list-style-type: none"> * Adults \geq 18 years * Confirmed SARS-CoV2 infection * Hospitalised for COVID-19 * Severe disease or risk for severe disease * Informed consent from patient or responsible person Exclusion criteria <ul style="list-style-type: none"> * History of allergic reactions to blood products * SOFA scale > 12 points * Absolute contraindication for administration of plasma * Participation in other blinded clinical trial * Projected life expectancy < 3 months * Any condition perceived by the investigator as not appropriate for participation of the patient in the trial
Interventions	<ul style="list-style-type: none"> Intervention(s): normal saline and CP therapy Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: 200 mL * Number of doses: 2 separated by 24-72 h * Antibody-titre: NR * Pathogen inactivated: NR Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients Comparator: normal saline Concomitant therapy: NR Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> Primary study outcome: <ul style="list-style-type: none"> * Severity and death (time frame: 28 days) * AEs that require study treatment interruption (time frame: 28 days) Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: mortality (time frame: 28 days) * Time to death: yes (time frame: 28 days)

NCT04388410 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes by ordinal 8-point severity outcome scale (time frame: Days 1, 3, 5, 7, 12, 14, 21, 28)
 - * 30-day and 90-day mortality: yes (28-day mortality)
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: yes (ICU hospitalisation)
 - * Time to discharge from hospital: yes (hospitalisation time)
 - * QoL: NR
- Additional study outcomes
 - * Antibodies against SARS-CoV-2 (time frame: Days 0, 3, 7, 14, 21, 28)
 - * Time on mechanical ventilation (time frame: 28 days)
 - * Number of days with fever (time frame: 28 days)

Starting date	1 June 2020
Contact information	Not provided
Notes	<ul style="list-style-type: none"> • Recruitment status: Not yet recruiting • Prospective completion date: December 31, 2020 • Sponsor/funding: Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran

NCT04388527

Study name	An open-label, single arm, phase 1, safety and exploratory efficacy study of convalescent plasma for severely ill mechanically ventilated participants with COVID-19 caused by SARS-CoV-2
Methods	<ul style="list-style-type: none"> • Trial design: single-arm intervention • Sample size: 50 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Adult \geq 18 years of age * Laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other authorised or approved assay in any specimen collected within 72 h prior to enrolment. Note - an exception must be requested to the Sponsor if \geq 72 h since positive test * Hospitalised, on invasive mechanical ventilation or ECMO, consistent with a clinical status assessment 8-point ordinal scale severity score of 7 * Documentation of pneumonia with radiographic evidence of infiltrates by imaging (e.g. chest X-ray or CT scan) * Patient or proxy is willing and able to provide written informed consent and comply with all protocol requirements.

NCT04388527 (Continued)

- Exclusion criteria
 - * Contraindication to transfusion (e.g. severe volume overload, history of severe allergic reaction to blood products), as judged by the investigator
 - * Clinical suspicion that the aetiology of acute illness (acute decompensation) is primarily due to a condition other than COVID-19
 - * Receipt of other investigational therapy as a part of another clinical trial. a. Note: investigational therapies used as part of clinical care, (e.g., remdesivir, hydroxychloroquine) are permissible.

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: ABO-compatible donors
 - * Volume: NR
 - * Number of doses: 2
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): critically ill patients
- Comparator: not applicable
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome:
 - * Cumulative incidence of SAEs at Day 29
 - * Survival and time to clinical improvement as measured by removal from mechanical ventilation (up to 60 days)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: 14, 28-day mortality
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes, using 8-point ordinal scale, of CP administration as compared to placebo recipients in DMID Protocol Number: 20-0006. (time frame: from enrolment, daily while hospitalised until discharge or death and on Days 15, 22, and 29) and using the National Early Warning Score (NEWS) of CP administration as compared to placebo recipients in DMID Protocol Number: 20-0006. (time frame: from enrolment, daily while hospitalised until discharge or death and on Days 15 and 29.)
 - * 30-day and 90-day mortality: yes (until day 28)
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: yes (until day 29)
 - * QoL: NR

NCT04388527 (Continued)

- Additional study outcomes
 - * Incidence of new oxygenation use up to Day 29 of CP administration as compared to placebo recipients in DMID Protocol Number: 20-0006 (time frame: from enrolment to Day 29)
 - * Duration of new oxygen use up to Day 29 of CP administration as compared to placebo recipients in DMID Protocol Number: 20-0006 (time frame: from enrolment to Day 29)
 - * Oxygen-free days of CP administration as compared to placebo recipients in DMID Protocol Number: 20-0006 (time frame: from enrolment to Day 29)
 - * Non-invasive ventilation/high flow oxygen days up to Day 29 of CP administration as compared to placebo recipients in DMID Protocol Number: 20-0006 (time frame: from enrolment to Day 29)
 - * Incidence of non-invasive ventilation/high flow oxygen up to Day 29 of CP administration as compared to placebo recipients in DMID Protocol Number: 20-0006 (time frame: from enrolment to Day 29.)
 - * Duration of non-invasive ventilation/high flow oxygen up to Day 29 of CP administration as compared to placebo recipients in DMID Protocol Number: 20-0006 (time frame: from enrolment to Day 29)
 - * Ventilator/ECMO-free days to Day 29 of CP administration as compared to placebo recipients in DMID Protocol Number: 20-0006 (time frame: from enrolment to Day 29)
 - * Incidence of new mechanical ventilation or ECMO use of CP administration as compared to placebo recipients in DMID Protocol Number: 20-0006 (time frame: from enrolment to Day 29)
 - * Duration of new mechanical ventilation or ECMO use of CP administration as compared to placebo recipients in DMID Protocol Number: 20-0006 (time frame: from enrolment to Day 29)
 - * Changes in WBC with differential through day 29 of CP administration as compared to matched participants from the control arm of DMID Protocol No. 20-0006 (time frame: through Day 29.)
 - * Changes in haemoglobin measurement through Day 29 of CP administration as compared to matched participants from the control arm of DMID Protocol No. 20-0006 (time frame: through Day 29)
 - * Changes in platelets measurement through Day 29 of CP administration as compared to matched participants from the control arm of DMID Protocol No. 20-0006 (time frame: through Day 29)
 - * Changes in creatinine measurement through Day 29 of CP administration as compared to matched participants from the control arm of DMID Protocol No. 20-0006 (time frame: through Day 29)
 - * Changes in glucose measurement through Day 29 of CP administration as compared to matched participants from the control arm of DMID Protocol No. 20-0006 (time frame: through Day 29)
 - * Changes in bilirubin measurement through Day 29 of CP administration as compared to matched participants from the control arm of DMID Protocol No. 20-0006 (time frame: through Day 29)
 - * Changes in ALT measurement laboratory AEs through Day 29 of CP administration as compared to matched participants from the control arm of DMID Protocol No. 20-0006 (time frame: through Day 29)
 - * Changes in AST measurement through Day 29 of CP administration as compared to matched participants from the control arm of DMID Protocol No. 20-0006 (time frame: through Day 29)
 - * Changes in PT measurement laboratory AEs through Day 29 of CP administration as compared to matched participants from the control arm of DMID Protocol No. 20-0006 (time frame: through Day 29)

Starting date	30 April 2020
Contact information	<ul style="list-style-type: none"> • Katharine J. Bar, MD (215) 349-8092 BarK@pennmedicine.upenn.edu • Julie Starr 215-349-8527 jstarr@pennmedicine.upenn.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 30 September 2020 • Sponsor/funding: University of Pennsylvania

NCT04389710

Study name	Convalescent plasma for the treatment of patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: single-arm intervention • Sample size: 100 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age ≥ 18 years * Laboratory-confirmed diagnosis of SARS-CoV-2 * Admitted to an acute care facility for the treatment of COVID-19 complications * Informed consent provided by patient or LAR * Severe or life-threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease * Severe disease defined as any of the following <ul style="list-style-type: none"> <input type="checkbox"/> Dyspnoea <input type="checkbox"/> Respiratory rate > 30/min <input type="checkbox"/> Oxygen saturation < 94% <input type="checkbox"/> Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 <input type="checkbox"/> Lung infiltrates > 50% within 24-48 h * Life-threatening disease defined as any of the following <ul style="list-style-type: none"> <input type="checkbox"/> Respiratory failure <input type="checkbox"/> Septic shock <input type="checkbox"/> Multiple organ dysfunction or failure <input type="checkbox"/> Informed consent provided by patient or healthcare proxy • Exclusion criteria <ul style="list-style-type: none"> * Receipt of pooled immunoglobulin in past 30 days * Contraindication to transfusion or history of prior reactions to transfusion blood products
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: ABO-compatible * Volume: 200-600 mL * Number of doses: 1-2 * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): inpatient with severe or life-threatening disease • Comparator: nil • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: number of participants who receive COVID-19 CP transfusions in acute care facilities infected with SARS-CoV-2 (time frame: 1 year) • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes * Time to death: yes

NCT04389710 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection
 - * 30-day and 90-day mortality: yes
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional study outcomes
 - * Changes in complete blood count
 - * Abnormal changes in basic metabolic panel (BMP) measures
 - * Changes in CRP, d-dimer, fibrinogen, prothrombin time (PT), partial thromboplastin time (PTT) in participants after receiving CP (time frame: 0 and 7 days)

Starting date	15 April 2020
Contact information	<ul style="list-style-type: none"> • Michael Baram, MD215-955-5161 Michael.Baram@jefferson.edu • Anna Marie Chang, MD215-605-5897 AnnaMarie.Chang@jefferson.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 14 April 2021 • Sponsor/funding: Thomas Jefferson University

NCT04389944

Study name	Amotosalen-ultraviolet a pathogen-inactivated convalescent plasma in addition to best supportive care and antiviral therapy on clinical deterioration in adults presenting with moderate to severe coronavirus disease 2019 infectious disease (COVID-19)
Methods	<ul style="list-style-type: none"> • Trial design: single-arm intervention • Sample size: 15 • Setting: inpatient • Country: Switzerland • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * SARS-CoV-2 infection confirmed by PCR in respiratory secretions (nasopharyngeal swab, broncho-alveolar lavage, sputum) * hospitalised * pulmonary infiltrates compatible with COVID-19 on CT-scan * availability of blood group-compatible CP * signed informed consent • Exclusion criteria <ul style="list-style-type: none"> * nil
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy

NCT04389944 (Continued)

- Details of CP:
 - * Type of plasma: male donors who have been tested positive for SARS-CoV2 at University Hospital Basel, Switzerland or in the near surroundings > 10 days before enrolment, 18-60 years of age, asymptomatic (thus successfully overcome COVID-19) > 14 days back, 2 consecutive naso-pharyngeal swabs tested negative for quantitative PCR-test for SARS-CoV-2 prior to plasma donation to demonstrate infection Resolution, or more than 28 days asymptomatic after SARS-CoV2 infection, Body weight of at least 50 kg, donor eligibility criteria according to the Swiss Red Cross Blood Transfusion Service as for regular blood donation, not treated with Actemra® (Tocilizumab) in the course of COVID-19
 - * Volume: 200 mL
 - * Number of doses: 2 (at enrolment, and at 12-24 h post)
 - * Antibody-titre: NR
 - * Pathogen inactivated: yes (INTERCEPT Blood System)
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients (moderate to severe)
- Comparator: conventional treatment
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome:
 - * SAEs (up to 24 h)
 - * Virologic clearance in nasopharyngeal swab of CP-treated participants (up to 28 days)
 - * ICU admission (up to 28 days)
 - * In-hospital death (up to 28 days)
 - * Virologic clearance in plasma of CP-treated participants (up to 28 days)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: 28-day mortality
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: yes (28-day mortality)
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: yes (up to 28 days)
 - * QoL: NR
- Additional study outcomes: humoral immune response (up to 28 days)

Starting date 31 March 2020

 Contact information

- Nina Khanna, Prof. Dr. med +41 61 328 73 25 nina.khanna@usb.ch
- Andreas Buser, Prof. Dr. med.+41 61 328 60 92 andreas.buser@usb.ch

 Notes

- Recruitment status: recruiting
- Prospective completion date: 30 June 2020
- Sponsor/funding: University Hospital, Basel, Switzerland

NCT04390178

Study name	Convalescent plasma as treatment for acute coronavirus disease (COVID-19)
Methods	<ul style="list-style-type: none"> • Trial design: single-arm intervention • Sample size: 10 • Setting: inpatient • Country: Sweden • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age 18 and < 81 years * Active COVID-19 defined as symptoms + SARS CoV-2 identified from upper or lower airway samples * Fever ≥ 38.5 C, admitted to a study hospital, hypoxaemia defined as having a peripheral oxygen saturation below 93% (measured by pulse oximetry) and a breathing rate of > 20 breaths/min without supplemental oxygen treatment * A negative pregnancy test taken before inclusion and use of an acceptable effective method of contraception until treatment discontinuation if the participant is a woman of childbearing potential * Written informed consent after meeting with a study physician and ability and willingness to complete follow-up • Exclusion criteria <ul style="list-style-type: none"> * No matching plasma donor (exact matching in both the ABO system and the Rh system is required) * Unavailability of plasma * Significant growth of alternative lower airway pathogen such as <i>Streptococcus pneumoniae</i> or <i>Haemophilus influenzae</i> in sputum * Disease duration > 8 days * Estimated GFR <60 (kidney failure \geq stage III) * Pregnancy (urinary-hCG), breast feeding, * History of severe allergic reactions * Inability to give informed consent * Significantly compromised immunity <ul style="list-style-type: none"> <input type="checkbox"/> Compromised immunity includes but is not limited to treatment with major immunosuppressive agents including high-dose corticosteroids, anti-tumor necrosis factor (TNF) agents, calcineurin inhibitors, m TOR inhibitors, lymphocyte depleting biological agents, chemotherapeutic anti neoplastic agents. Also patients with advanced HIV/AIDS, severe immunodeficiency such as hypoglobulinaemia, decompensated liver cirrhosis and bone marrow transplant the last year will be excluded
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: 1, 5, 10, 50, 134 mL and 180-200 mL * Number of doses: 1 * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients with < 8 days disease duration • Comparator: none • Concomitant therapy: NR • Treatment cross-overs: not applicable
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Decrease in progression to requiring non-invasive or invasive ventilation (within 28 days)

NCT04390178 (Continued)

- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional study outcomes:
 - * Clearance of viraemia (evaluated daily until discharge, at day 28, and last measurement taken at 6 months of follow-up after inclusion), CRP, white blood cell count (WBC), haemoglobin (Hb), Pro-calcitonin, and Creatine Kinase (until discharged from the hospital, up to 2 months), antibody response to SARS-CoV-2 (evaluated daily until discharge, at day 28, and last measurement taken at 6 months of follow-up after inclusion)

Starting date	10 April 2020
Contact information	Principal Investigator: Johan Ursing, MD, PhD, Danderyd Hospital
Notes	<ul style="list-style-type: none"> • Recruitment status: active, not recruiting • Prospective completion date: 20 December 2020 • Sponsor/funding: Joakim Dillner, Danderyd Hospital, Karolinska Institutet, Karolinska University Hospital

NCT04390503

Study name	A phase 2 randomized, double-blinded trial to evaluate the efficacy and safety of human anti-SARS-CoV-2 plasma in close contacts of COVID-19 cases
Methods	<ul style="list-style-type: none"> • Trial design: double-blinded RCT • Sample size: 200 • Setting: close contacts of COVID-19 cases • Country: USA • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <p>Group B: SARS-CoV-2 PCR-positive but asymptomatic or mild symptoms at screening</p> <ul style="list-style-type: none"> • Participants must be ≥ 18 years • Close contact* of a person with COVID-19 within the last 7 days. It is anticipated that most contacts will be household contacts with extensive interaction. All must meet the CDC criteria for close contacts. • Evidence of infection by nasopharyngeal swab PCR that is positive for SARS-CoV-2

NCT04390503 (Continued)

- No symptoms or no more than 5 days of mild symptoms+ may include:
 - * Mild rhinorrhoea
 - * Mild sore throat or throat irritation
 - * Mild nonproductive cough
 - * Mild fatigue (able to perform Activities of Daily Living (ADLs))
- High risk for severe COVID-19 based on a risk score of ≥ 2 Calculated Risk Score of ≥ 2 points, with risk factors based on Center for Disease Control and Prevention (CDC) description
 - * Age 65-74: 1 point
 - * Age ≥ 75 : 2 points
 - * Known cardiovascular disease (including hypertension): 1 point
 - * Diabetes mellitus: 1 point
 - * Pulmonary disease (COPD, moderate to severe asthma, current smoking or other): 1 point
 - * Morbid obesity: 1 point
 - * Immunocompromised state: 1 point
 - * Received a bone marrow or solid organ transplant at any time, received chemotherapy for a malignancy within the past 6 months, has an acquired or congenital immunodeficiency, currently receiving immunosuppressive or immune modulating medications, HIV with non-suppressed viral load and/or cluster of differentiation 4 (CD4+) T cell count < 200 cells/mL
- Mild symptoms are rated by participant as mild and not interfering with normal daily activities

Group C: SARS-CoV-2 PCR-negative (uninfected) at time of screening but asymptomatic or mildly symptomatic at screening

- Participants must be ≥ 18 years
- Close contact* of a person with COVID-19 within the last 7 days. It is anticipated that most contacts will be household contacts with extensive interaction. All must meet the CDC criteria for close contacts.
- Nasopharyngeal swab negative for SARS-Cov-2 at screening
- No symptoms or no more than 5 days of mild symptoms at the time of screening. Mild symptoms+ may include:
 - * Mild rhinorrhoea
 - * Mild sore throat or throat irritation
 - * Mild nonproductive cough
 - * Mild fatigue (able to perform ADLs)
- High risk for severe COVID-19 based on a risk score of ≥ 2 , as above.

*Close contact is defined by CDC as being within approximately 6 feet (2 meters) of a COVID-19 case for a prolonged period of time (without PPE); close contact can occur while caring for, living with, visiting, or sharing a healthcare waiting area or room with a COVID-19 case

+Mild symptoms are rated by participant as mild and not interfering with normal daily activities

- Exclusion criteria

Group B: SARS-CoV-2 PCR-positive but asymptomatic or mild symptoms at screening

- Receipt of any blood product in past 120 days
- Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator, would affect participant safety and/or compliance
- Confirmed or self-reported presumed COVID-19 at least 1 week before index case first became ill with COVID-19
- Symptoms consistent with COVID-19 infection that are more than mild (as defined above) at time of screening. Participants who report fever ($T_{max} > 100.4$ F) are not eligible for enrolment
- Symptoms that have worsened in the period between screening and enrolment such that the participant is deemed to be medically unstable on the day of planned enrolment
- History of allergic reaction to transfusion blood products

NCT04390503 (Continued)

- Inability to complete infusion of the product within 48 h after randomisation
- Pregnancy (or planning for pregnancy in next 3 months) or breastfeeding
- Resident of a long-term or skilled nursing facility
- Known prior diagnosis of immunoglobulin A (IgA) deficiency
- Oxygen saturation that is < 95% at the screening visit
- Participation in another clinical trial of anti-viral agent(s) for COVID-19

Group C: SARS-CoV-2 PCR-negative (uninfected) at time of screening

- Receipt any blood product in past 120 days
- Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principle investigator, would affect participant safety and/or compliance
- Confirmed or self-reported presumed COVID-19 at least 1 week before index case first became ill with COVID-19
- Symptoms consistent with severe COVID-19 infection that are more than mild (as defined above) at time of screening. Participants who report fever (Tmax > 100.4 F) are not eligible for enrolment
- Symptoms that have worsened in the period between screening and enrolment such that the participant is deemed to be medically unstable on the day of planned enrolment
- Laboratory evidence of SARS-CoV-2 infection (i.e. RT-PCR) at time of screening
- History of allergic reaction to blood products
- Inability to complete infusion of the product within 48 h after randomisation
- Pregnancy (or planning for pregnancy in next 3 months) or breastfeeding
- Resident of a long-term or skilled nursing facility
- Known history of immunoglobulin A (IgA) deficiency
- Oxygen saturation that is < 95% at the screening visit
- Participation in another clinical trial of anti-viral agent(s) for COVID-19

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: NR
 - * Volume: 200-250 mL
 - * Number of doses: 1
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): close contacts of COVID-19 cases without symptoms or with mild symptoms
- Comparator: 250 mL of albumin (human) 5% infusion
- Concomitant therapy: NR
- Treatment cross-overs: not applicable

Outcomes

- Primary study outcome:
 - * Efficacy of treatment, determined by rating disease severity on day 28, or last rating evaluated, using a 7-category severity scale
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR

NCT04390503 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional study outcomes:
 - * Rate of measurable anti-SARS-CoV-2 titres (up to 90 days), rate of SARS-CoV-2 PCR positivity (up to 28 days), duration of SARS-CoV-2 PCR positivity (up to 28 days), levels of SARS-CoV-2 RNA (up to 28 days)

Starting date	May 2020
Contact information	<ul style="list-style-type: none"> • Jessica Justman, MD 212-342-0537 jj2158@cumc.columbia.edu • Jennifer Zech, MSc 212-304-5506 jz2973@cumc.columbia.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: April 2021 • Sponsor/funding: Columbia University

NCT04391101

Study name	Efficacy of convalescent plasma for the treatment of severe SARS-CoV-2 infection: a randomized, open label clinical trial
Methods	<ul style="list-style-type: none"> • Trial design: open-label, RCT • Sample size: 231 • Setting: ICU • Country: Colombia • Language: English • Number of centres: 8
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * > 18 years of age * SARS-CoV-2 infection confirmed by PCR in any sample * Hospitalised in the ICU due to shock or respiratory failure, with < 24 h after entering the ICU • Exclusion criteria <ul style="list-style-type: none"> * Serious volume overload or other condition that contraindicates plasma transfusion * History of anaphylaxis or serious adverse reaction to plasma * Previous diagnosis of immunoglobulin A deficiency

NCT04391101 (Continued)

- Donor eligibility criteria
 - * > 18 years of age
 - * men or nulliparous women with no history of recent abortions or transfusions SARS-CoV-2 infection by PCR in any sample or serological test with a maximum of 60 days from resolution of symptoms
 - * If donation is done within 14-28 days after resolution of symptoms, the patient must have a negative PCR test for SARS-CoV-2. If donation is done after 28 days of resolving symptoms, no negative control test will be required.
- Donor exclusion criteria
 - * Severe SARS-CoV-2 infections with an ICU requirement or those with asymptomatic infections will not be accepted as donors.
 - * Nor will a person who has received CP as part of the COVID-19 treatment

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: NR
 - * Volume: 400-500 mL total
 - * Number of doses: 2
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): ICU patients within 24 h of entering ICU
- Comparator: standard management
- Concomitant therapy: NR
- Treatment cross-overs: not applicable

Outcomes

- Primary study outcome:
 - * In-hospital mortality from any cause (up to 28 days)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: 28-day mortality
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: yes (28-day and 60-day mortality)
 - * Admission on the ICU: no (only ICU patients included)
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: yes (up to 60 days)
 - * QoL: NR
- Additional study outcomes: none

Starting date

June 2020

Contact information

- Oliver G Perilla Suarez, Hematologist +573136395608 gerardoperilla@gmail.com
- Fabian A Jaimes Barragan, Epidemiologist +5742192420 fabian.jaimes@udea.edu.co

Notes

- Recruitment status: not yet recruiting
- Prospective completion date: December 2021

NCT04391101 (Continued)

- Sponsor/funding: Hospital San Vicente Fundación, Clínica León XIII, Grupo de Inmunodeficiencias primarias Universidad de Antioquia, Clínica Universitaria Bolivariana, Hospital Pablo Tobón Uribe, Clínica Rosario El Tesoro, Clínica Las Américas, Clínica Cardiovid

NCT04392232

Study name	A phase 2 study of COVID 19 convalescent plasma in high risk patients with COVID 19 infection
Methods	<ul style="list-style-type: none"> • Trial design: single-arm intervention • Sample size: 100 • Setting: inpatient • Country: USA • Language: English • Number of centres: 2
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Participants will be ≥ 16 years * COVID-19 infection demonstrated via SARS-CoV-2 PCR testing * Admitted to the hospital for treatment of COVID-19. * Patients must have severe/high risk disease as defined by the presence of any one of the following: <ul style="list-style-type: none"> <input type="checkbox"/> Respiratory frequency ≥ 25/min Oxygen saturation $\leq 93\%$ on room air Partial pressure of arterial oxygen to fraction of inspired oxygen ration < 300, or pulse oximetric saturation to fraction of inspired oxygen ratio < 315 <input type="checkbox"/> Lung infiltrates $> 50\%$ within 24-48 h of admission on Chest X-Ray or, Ferritin > 1000 or absolute lymphocyte count < 600 or D-Dimer > 1.00 * ABO blood type available * Pregnant women will be permitted to participate in this study. • Exclusion criteria <ul style="list-style-type: none"> * Previous history of life-threatening or severe adverse reactions to transfusion blood products
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: FDA-registered blood establishment (Hoxworth) that follows donor eligibility criteria and donor qualifications as outlined in section III.C.I of the Investigational COVID-19 CP Guidance for Industry * Volume: NR * Number of doses: NR * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: not applicable • Concomitant therapy: NR • Treatment cross-overs: not applicable
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Survival rate (at 28 days) • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: 28-day mortality * Time to death: NR

NCT04392232 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: yes (28-day mortality)
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional study outcomes: none

Starting date	5 May 2020
Contact information	<ul style="list-style-type: none"> • William Judd, MBA, MHA (C.) 513 865 5020 William_Judd@TriHealth.com
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 31 December 2020 • Sponsor/funding: TriHealth Inc

NCT04392414

Study name	Randomized, open label, prospective study of the safety and efficacy of hyperimmune convalescent plasma in moderate and severe COVID-19 disease
Methods	<ul style="list-style-type: none"> • Trial design: open-label RCT • Sample size: 60 • Setting: inpatient • Country: Russia • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Men or women aged 18-75 years * The presence of COVID-19 infection, confirmed by PCR testing * The presence of the COVID-19 pneumonia pattern on the chest HRCT with a damage to more than 25% of the lung parenchyma * Morning fever ≥ 38.0 °C over the last 3 days * CRP blood level ≥ 50 mg/mL or ferritin blood level ≥ 600 $\mu\text{g} / \text{mL}$ * A signed informed consent • Exclusion criteria <ul style="list-style-type: none"> * Respiratory index ≤ 200 * Contraindications for the transfusion of donor immune plasma or history of prior reactions to blood transfusions * Mechanical ventilation * The presence of chronic lung diseases with chronic respiratory failure * The need for home continuous oxygen therapy before the onset of current disease * Serum creatinine level higher than $150 \mu\text{mol/L}$ • Pregnancy or breastfeeding

NCT04392414 (Continued)

Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: 300 mL per dose * Number of doses: 2, with the 2nd dose administered within 24 h of the 1st dose * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients (moderate to severe) • Comparator: standard plasma • Concomitant therapy: NR • Treatment cross-overs: not applicable
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * The number and proportion of participants with the normal body temperature (≤ 37.2 C) at day 1, 2, 3, 4, 5, 6, 7 after the start of therapy • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: 30-day mortality * Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: yes (30-day mortality) * Admission on the ICU: NR * Length of stay on the ICU: yes * Time to discharge from hospital: yes (up to 30 days) * QoL: NR • Additional study outcomes: changes of the plasma levels of IL2, IL6, IL10, TNF alpha and INF gamma on days 3 and 7, changes of the plasma levels of CRP on days 1, 2, 3, 4, 5, 6, 7
Starting date	1 May 2020
Contact information	<ul style="list-style-type: none"> • Mikhail A Konoplyannikov, PhD +79154027268 mkonopl@mail.ru • Alexander V Averyanov, MD, PhD, dr.averyanov@gmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: September 15, 2020 • Sponsor/funding: Federal Research Clinical Center of Federal Medical & Biological Agency, Russia

NCT04393727

Study name	Transfusion of convalescent plasma for the early treatment of pneumonia due to SARSCoV2: a multicenter open label randomized control trial
Methods	<ul style="list-style-type: none"> • Trial design: open-label RCT • Sample size: 126 • Setting: inpatient • Country: Italy

NCT04393727 (Continued)

	<ul style="list-style-type: none"> • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Any gender * Age > 18 years on day of signing informed consent * Informed written consent for participation in the study * Virological diagnosis of SARS-CoV-2 infection (real-time PCR) * Hospitalised due to clinical instrumental diagnosis of pneumonia * PaO₂/FiO₂ ratio 200-350 • Exclusion criteria <ul style="list-style-type: none"> * mechanical ventilation (both invasive and non-invasive) * PaO₂/FiO₂ < 200 * known hypersensitivity to immunoglobulin or blood components
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: 200 mL * Number of doses: 1 * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients with pneumonia not requiring mechanical ventilation • Comparator: standard therapy • Concomitant therapy: NR • Treatment cross-overs: not applicable
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Need of invasive mechanical ventilation defined as PaO₂/FiO₂ < 150 (at 30 days) • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: 30-day mortality * Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes * Number of participants with SAEs: yes * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: yes (30-day mortality) * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: yes (up to 28 days) * QoL: NR • Additional study outcomes: time to virologic cure, defined as 2 consecutive nasopharynx swabs (up to 30 days)
Starting date	1 May 2020
Contact information	<ul style="list-style-type: none"> • Marco Falcone 050996735 marco.falcone@unipi.it
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 30 October 2020

NCT04393727 (Continued)

- Sponsor/funding: Azienda Ospedaliero, Universitaria Pisana

NCT04395170

Study name	A multicenter randomized clinical trial to evaluate the efficacy and safety of the use of convalescent plasma (PC) compared to anti-COVID-19 human immunoglobulin and standard treatment in hospitalized patients
Methods	<ul style="list-style-type: none"> • Trial design: open-label RCT • Sample size: 75 • Setting: inpatient • Country: Colombia • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Obtaining the informed written consent before carrying out the study procedures, by the patients * Adult patients ≥ 18 years at the time of recruitment for the study * Patients with laboratory-confirmed SARS-CoV-2 infection as determined by PCR on nasal/oropharyngeal swabs or any other relevant specimen < 72 h before randomisation * Patients requiring hospitalisation for COVID-19 without mechanical ventilation (invasive or non-invasive, including an oxygen mask with reserve bag) and at least one of the following: <ul style="list-style-type: none"> <input type="checkbox"/> Radiographic evidence of pulmonary infiltrates by images (chest radiography, computed tomography, etc.) <input type="checkbox"/> Clinical evaluation (evidence of rales/crackles on examination) and oxygen saturation $\leq 94\%$ in ambient air requiring supplemental oxygen * Patient with no more than 72 h (3 days) of hospitalisation prior to the administration of CP treatment (except the days after initial hospital admission for other reasons and prior to COVID-19 infection). * Patients who do not have more than 10 days between the onset of symptoms (fever or cough) and the day of administration of treatment or the demonstration of the absence of anti-SARS-CoV-2 antibodies (patients with more than 10 days of symptoms they can only be included if a negative antibody result has been confirmed). • Exclusion criteria <ul style="list-style-type: none"> * Patient in a state of pregnancy * Require mechanical ventilation (invasive or non-invasive, including oxygen mask with reserve bag) on examination * Participation in any other clinical trial of an experimental treatment for COVID-19 * At the discretion of the clinical team, progression to death is imminent and inevitable within the next 24 h, regardless of the provision of treatments * Any incompatibility or allergy to the administration of plasma of human origin * Severe chronic kidney disease in stage 4 or requiring dialysis (that is, GFR < 30) * Any condition that in the investigator's opinion limits participation in the study.
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy and hyperimmune immunoglobulin therapy • Details of intervention <p>CP:</p> <ul style="list-style-type: none"> • Type of plasma: NR • Volume: 200-250 mL • Number of doses: 2, at days 1 and 3 of treatment • Antibody-titre: NR

NCT04395170 (Continued)

- Pathogen inactivated: yes

hyperimmune immunoglobulin:

- Anti-COVID-19 human immunoglobulin produced by Lifefactors Zona Franca S.A.S, IV at a dose of immunoglobulin 10% IgG solution (10% mL vial) for:
 - * participant \geq 50 Kg, a dose of 50 mL, administered on days 1 and 3 of treatment
 - * participant < 50 Kg, the dose will be 1 mL/Kg, administered on days 1 and 3 of treatment
 - * The supply of anti-COVID-19 human immunoglobulin produced by Lifefactors Zona Franca S.A.S included once it has been authorised by INVIMA and/or the regulatory requirements in force for the production of drugs are met.
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients not requiring mechanical ventilation
- Comparator: standard therapy for COVID-19 according to the recommended pharmacological recommendations of the Colombian Association of Infectious Diseases - ACIN. This therapy is subject to changes that are defined by the Colombian Health Regulatory Authorities. To date, these therapies may include remdesivir, chloroquine, hydroxychloroquine, azithromycin
- Concomitant therapy: non-specific supportive treatment for COVID-19 such as oxygen, IV liquid or corticosteroids
- Treatment cross-overs: not applicable

Outcomes

- Primary study outcome:
 - * Admission to ICU and/or mechanical ventilation within 1 year
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: mortality (up to 1 year)
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: yes (28-day mortality)
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional study outcomes: neutralising antibody (IgG) titres against COVID-19 (up to 1 year)

Starting date

June 2020

Contact information

- Santiago Jaramillo +573128092776 sjaramillo@lifefactors.co

Notes

- Recruitment status: not yet recruiting
- Prospective completion date: June 2021
- Sponsor/funding: Lifefactors Zona Franca, SAS

NCT04397523

Study name

Efficacy and safety of COVID-19 convalescent plasma

Methods

- Trial design: single-arm intervention
- Sample size: 20

NCT04397523 (Continued)

- Setting: inpatient
- Country: North Macedonia
- Language: English
- Number of centres: 1

Participants

- Inclusion criteria
 - * Age: >18 years
 - * Admitted to an acute care facility for the treatment of COVID-19 complications
 - * Patients with severe or immediately life-threatening COVID-19, or
 - * Patients who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease.
 - * Informed consent provided by the patient or healthcare proxy
- Exclusion criteria
 - * Age: < 18 years
 - * Contraindication to transfusion (severe volume overload, history of anaphylaxis to blood products)
 - * Patients who received in the past 30 days immunoglobulin therapy
 - * Women who are pregnant or breastfeeding
- Donor eligibility criteria
 - * Age: > 18 and < 60 years
 - * Body weight: > 60 kg
 - * Confirmed previous SARS CoV-2 infection
 - * 2 negative SARS CoV-2 test results
 - * 21 days without symptoms from the second SARS CoV2-negative test
 - * Written informed consent to participate in this clinical trial, to donate plasma and to store the specimen for future testing
 - * Concentration of COVID-19 IgG antibodies > 5 AU/mL (because measurement of neutralising antibody titres is not available now, storing of retention sample from the CP donation is performed for determining antibody titres at a later date)
 - * Male donors, or female donors who have not been pregnant, or female donors who have been pregnant tested negative for HLA antibodies
 - * Individuals who meet all regular voluntary donor eligibility requirements
- Donor exclusion criteria
 - * Age: < 18 or > 60 years
 - * Female participants who are pregnant
 - * HIV1,2 hepatitis B,C or syphilis infection
 - * Donors ineligible for regular voluntary blood donation

Interventions

- Intervention(s): CP therapy
 - Details of CP:
 - * Type of plasma: NR
 - * Volume: NR
 - * Number of doses: NR
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
 - Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients (severe or at high risk of progressing to severe disease)
 - Comparator: not applicable
 - Concomitant therapy: NR
 - Treatment cross-overs: not applicable
-

NCT04397523 (Continued)

- Outcomes
- Primary study outcome:
 - * Duration of oxygenation and ventilation support (up to 28 days or until hospital discharge, whichever comes first)
 - * Hospital length of stay (LOS) (up to 28 days or until hospital discharge, whichever comes first)
 - * ICU admission (up to 28 days or until hospital discharge, whichever comes first)
 - * Ventilator-free days (up to 28 days or until hospital discharge, whichever comes first)
 - * Incidence of SAEs (up to 28 days or until hospital discharge, whichever comes first)
 - Primary review outcomes reported
 - * All-cause mortality at hospital discharge: 28-day mortality or until hospital discharge, whichever comes first
 - * Time to death: NR
 - Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: yes (28-day mortality)
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: yes (up to 28 days)
 - * QoL: NR
 - Additional study outcomes: none

Starting date 30 April 2020

Contact information Rada Grubovic Rastvorceva, MD MSci PhD +38923226923 ext 126 drgrubovic@gmail.com

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- Notes
- Recruitment status: recruiting
 - Prospective completion date: April 29, 2021
 - Sponsor/funding: Institute for Transfusion Medicine of RNM, University Clinic for Infectious Diseases, North Macedonia
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NCT04397757

Study name COVID-19 convalescent plasma for the treatment of hospitalized patients with pneumonia caused by SARS-CoV-2

-
- Methods
- Trial design: open-label RCT
 - Sample size: 80
 - Setting: inpatient
 - Country: USA
 - Language: English
 - Number of centres: 1

-
- Participants
- Inclusion criteria
 - * Adult \geq 18 years of age
 - * Laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other authorised or approved assay in any specimen collected within 72 h prior to enrolment

Note - An exception must be requested to the Sponsor if \geq 72 h since positive test

NCT04397757 (Continued)

- * Hospitalised in participating facility
- * Documentation of pneumonia with radiographic evidence of infiltrates by imaging (e.g., chest X-ray or CT scan)
- * Abnormal respiratory status that is judged worse than baseline by the investigator and as documented at any point within 24 h prior to randomisation, consistent with ordinal scale levels 5, 6 or 7, specifically defined as:
 - Room air saturation of oxygen (SaO₂) < 93%, OR
 - Requiring supplemental oxygen, OR
 - Tachypnea with respiratory rate ≥ 30
- * Patient or proxy is willing and able to provide written informed consent and comply with all protocol requirements
- Exclusion criteria
 - * Contraindication to transfusion (e.g. severe volume overload, history of severe allergic reaction to blood products), as judged by the investigator
 - * Clinical suspicion that the aetiology of acute illness (acute decompensation) is primarily due to a condition other than COVID-19
 - * Receipt of other investigational therapy as a part of another clinical trial. Note: investigational therapies used as part of clinical care, (e.g., remdesivir, hydroxychloroquine) are permissible.

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: NR
 - * Volume: NR
 - * Number of doses: 2
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients (severe)
- Comparator: standard care
- Concomitant therapy: NR
- Treatment cross-overs: not applicable

Outcomes

- Primary study outcome:
 - * Participants with SAEs (at day 29)
 - * Comparison of clinical severity score between patients on the experimental versus control arms (at day 29)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: 29-day mortality
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - * Number of participants with SAEs: yes
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: yes (28-day mortality)
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: yes (up to 29 days)
 - * QoL: NR
- Additional study outcomes: time to recovery (defined as clinical severity score 1-3), clinical status assessment using the National Early Warning Score (NEWS) of CP administration, WBC, hemoglobin, platelet counts, creatinine, glucose, bilirubin, ALT, AST, PT

NCT04397757 (Continued)

Starting date	13 March 2020
Contact information	<ul style="list-style-type: none"> Katharine J. Bar, MD (215) 349-8092 BarK@pennmedicine.upenn.edu Julie Starr 215-349-8527 jstarr@penmedicine.upenn.edu
Notes	<ul style="list-style-type: none"> Recruitment status: recruiting Prospective completion date: 13 November 2020 Sponsor/funding: University of Pennsylvania

NCT04403477

Study name	Convalescent plasma transfusion therapy in severe COVID-19 patients - a tolerability, efficacy and dose-response phase II RCT
Methods	<ul style="list-style-type: none"> Trial design: RCT Sample size: 60 in 3 arms of 20 each Setting: inpatient Country: Bangladesh Language: English Number of centres: 3
Participants	<ul style="list-style-type: none"> Inclusion criteria <ul style="list-style-type: none"> * Respiratory rate > 30 breaths/min; PLUS * Severe respiratory distress; or SpO₂ ≤ 88% on room air or PaO₂/FiO₂ ≤ 300 mm of Hg, PLUS * Radiological evidence of bilateral lung infiltrate, AND OR * Systolic BP < 90 mm of Hg or diastolic BP < 60 mm of Hg. AND OR * Criteria 1 to 4 AND or patient in ventilator support Exclusion criteria <ul style="list-style-type: none"> * Patients < 18 years * Pregnant women and breast-feeding mothers * Previous history of allergic reaction to plasma * Those who will not give consent Donor eligibility criteria <ul style="list-style-type: none"> * Between day 22 and day 35 of recovery * 2 consecutive negative RT-PCR samples * Antibody titre > 1:320 Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> Intervention(s): CP therapy Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: 200 mL (Arm-B); 400 mL (Arm-C) * Number of doses: 1 * Antibody-titre: determined by endpoint dilution * Pathogen inactivated: NR Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients with RT-PCR-confirmed diagnosis Comparator: standard care (Arm-A) Concomitant therapy: enoxaparin, antibiotic, fluid, immune modulator (steroid) and or antiviral (favipiravir or ramdesivir or lopinavir + ritonavir) Treatment cross-overs: no

NCT04403477 (Continued)

Outcomes

- Primary study outcome:
 - * Proportion of in-hospital mortality
 - * Time to death
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: yes
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: yes
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes, to 14 days
 - * 30-day and 90-day mortality: yes to 7 days
 - * Admission on the ICU: yes to 14 days
 - * Length of stay on the ICU: yes to 14 days
 - * Time to discharge from hospital: yes to 14 days
 - * QoL: NR
- Additional outcomes
 - * Fever (time frame: 7 days); temperature in degree Fahrenheit at Day 0, 1, 3, 7
 - * Respiratory distress (time frame: 7 days); respiratory rate per minute at Day 0, 1, 3, 7
 - * Saturation of oxygen (time frame: 7 days); saturation of oxygen in % at Day 0, 1, 3, 7
 - * Blood pressure (time frame: 7 days); blood pressure in mm of Hg at Day 0, 1, 3, 7
 - * CRP (time frame: Day 0, 3 and 7); CRP level in mg/L
 - * Ferritin (time frame: Day 0, 3 and 7); serum ferritin level in ng/mL
 - * Serum glutamic-pyruvic transaminase (SGPT) (time frame: Day 0, 3 and 7); serum SGPT level in I/U
 - * Serum glutamic-oxaloacetic transaminase (SGOT) (time frame: Day 0, 3 and 7); serum SGOT level in I/U

Starting date	20 May 2020
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Contact information	Mohammad S Rahman, M Phil, FCPS +88 01971840757 srkhasru@gmail.com Fazle R Chowdhury, FCPS; PhD +88 01916578699 mastershakil@hotmail.com
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Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 20 July 2020 • Sponsor/funding: Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; Dhaka Medical College
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NCT04404634

Study name	Convalescent plasma to limit coronavirus associated complications: a randomized blinded phase 2 study comparing the efficacy and safety of anti-SARS-CoV-2 plasma to placebo in COVID-19 hospitalized patients
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Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 300 • Setting: inpatient • Country: USA • Language: English
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NCT04404634 (Continued)

	<ul style="list-style-type: none"> • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Patients ≥ 18 years of age * Hospitalised with COVID-19 with respiratory symptoms, cough, chest pain, shortness of breath, fever, or oxygen saturation ≤ 94%, or abnormal imaging * Hospitalised for < 72 h OR within day 3 to 7 days from first signs of illness * Laboratory-confirmed COVID-19 * On supplemental oxygen, non-invasive ventilation or high-flow oxygen * Participants may be on other RCTs of pharmaceuticals for COVID-19 and patients who meet eligibility criteria will not be excluded on this basis. • Exclusion criteria <ul style="list-style-type: none"> * Receipt of pooled immunoglobulin in past 30 days * Contraindication to transfusion or history of prior reactions to transfusion blood products * Invasive mechanical ventilation or ECMO * Volume overload secondary to congestive heart failure or renal failure * Intracranial bleed • Donor eligibility criteria NR • Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: SARS-CoV-2 CP * Volume: 250-500 mL * Number of doses: 1-2 * Antibody-titre: NR * Pathogen inactivated NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): • Comparator: Lactated Ringer's Solution or Sterile Saline Solution (placebo) • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Clinical status at 14 days (time frame: 14 days post-randomisation); this outcome will be assessed by the WHO 10-point ordinal scale for clinical improvement: uninfected 0 uninfected; no viral RNA detected ambulatory 1 asymptomatic; viral RNA detected 2 symptomatic; independent 3 symptomatic; assistance needed hospitalised: mild disease 4 hospitalised; no oxygen therapy 5 hospitalised; oxygen by mask or nasal prongs hospitalised: severe disease 6 hospitalised; oxygen by NIV or high flow 7 intubation & mechanical ventilation 8 mechanical ventilation 9 mechanical ventilation and vasopressors, dialysis or extracorporeal membrane oxygenation (ECMO) death 10 dead • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes to 28 days * Time to death: NR

NCT04404634 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: yes to 28 days
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes
 - * Clinical Status at 28 days (time frame: 28 days post-randomisation). This outcome will be assessed by the WHO 10-point ordinal scale for clinical improvement
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes to 28 days
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: yes to 28 days
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes
 - * Clinical Status at 28 days (time frame: 28 days post-randomisation) This outcome will be assessed by the World Health Organization (WHO) 10-point ordinal scale for clinical improvement:
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes to 28 days
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: yes to 28 days
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes
 - * Clinical Status at 28 days (time frame: 28 days post-randomisation). This outcome will be assessed by the WHO 10-point ordinal scale for clinical improvement

Starting date

May 2020

NCT04404634 (Continued)

 Contact information Mahalia Desruisseaux, MD203-737-4057 mahalia.desruisseaux@yale.edu

 Alessandro Santin, MD203-737-4450 alessandro.santin@yale.edu

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| Notes | <ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: January 2023 • Sponsor/funding: Yale University |
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NCT04405310

Study name	Convalescent plasma of COVID-19 to treat SARS-COV-2 a randomized double blind 2 center trial
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| Methods | <ul style="list-style-type: none"> • Trial design: RCT • Sample size: 80 • Setting: inpatient • Country: Mexico • Language: English • Number of centres: 2 |
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|--------------|---|
| Participants | <ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Adults 18-70 years of age * Serious or critically ill patients confirmed for SARS-CoV-2 disease (RT-PCR) * Meet the criteria for disease with SARS-CoV-2 disease, phase II (moderate) and phase III (severe) * Suspected cytokine release syndrome with Hscore 169 points * Presence of severe acute hypoxaemia with SpO2 < 90% in ambient air and/or PaO2 / FiO2 < 300 mmHg * Meet criteria (plain chest CT or plain chest radiograph) for SARS-CoV-2 disease * Supplemental oxygen requirement either through the facial store plus reservoir bag, high-flow nasal tips or advanced airway management and invasive mechanical ventilation support • Exclusion criteria <ul style="list-style-type: none"> * Patient has no interest in participating in the trial * Bilateral pulmonary infiltrate related to heart failure or other cause of water overload * Virus-positive respiratory viral panel other than COVID-19 * History of allergy to plasma, sodium citrate, or methylene blue * Patients with a history of autoimmune diseases or selective IgA insufficiency * Those patients who are participating in other protocols • Donor eligibility criteria <ul style="list-style-type: none"> * Between 10 and 14 days after SARS-CoV-2 illness • Donor exclusion criteria NR |
|--------------|---|

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| Interventions | <ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: NR * Number of doses: 1-3 depending on response to treatment * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): patients with pneumonia due to SARS-COV-2 • Comparator: placebo 20% albumin in Hartman solution • Concomitant therapy: azithromycin, hydroxychloroquine |
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NCT04405310 (Continued)

	<ul style="list-style-type: none"> Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> Primary study outcome: all-cause mortality within 15 days Primary review outcomes reported <ul style="list-style-type: none"> All-cause mortality at hospital discharge: yes, to 15 days Time to death: NR Secondary review outcomes reported <ul style="list-style-type: none"> Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR Number of participants with SAEs: NR Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes, to 15 days 30-day and 90-day mortality: NR Admission on the ICU: yes, to 15 days Length of stay on the ICU: yes, to 15 days Time to discharge from hospital: NR QoL: NR Additional outcomes <ul style="list-style-type: none"> Viral Load by RT-PCR (time frame: 15 days) changes in viral load Inflammatory biomarkers (time frame: 15 days) changes in pro-inflammatory and anti-inflammatory biomarkers (IL-6, PCR, ferritin, D Dimer, IL-8 IL-10 SOFA (time frame: 15 days) changes in SOFA scale
Starting date	20 May 2020
Contact information	<p>Angela Perez-Calatayud, MD +525542389377 gmemiinv@gmail.com</p> <p>Yanet Ventura, MD +52554848965 yanereb@gmail.com</p>
Notes	<p>Recruitment status: recruiting</p> <p>Prospective completion date: 20 June 2020</p> <p>Sponsor/funding:</p> <p>Grupo Mexicano para el Estudio de la Medicina Intensiva</p> <p>Hospital General Naval de Alta Especialidad - Escuela Medico Naval</p> <p>National Institute of Pediatrics, Mexico</p> <p>Instituto Nacional de Enfermedades Respiratorias</p>

NCT04407208

Study name	Convalescent plasma therapy in patients with COVID-19
Methods	<ul style="list-style-type: none"> Trial design: single-arm intervention Sample size: 10 Setting: inpatient Country: Indonesia Language: English Number of centres: 1

NCT04407208 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Confirmed COVID-19 case with RT-PCR * Stage IIb of COVID-19 or higher * Consent was given by the patient or legal guardian • Exclusion criteria <ul style="list-style-type: none"> * Pregnant * History of anaphylactic reaction in previous blood product transfusion • Donor eligibility criteria <ul style="list-style-type: none"> * Willingly give informed consent • Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: 2 x 100 mL on 3 separate days * Number of doses: 6 * Antibody-titre: NR * Pathogen inactivated NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): severe (non-critical) COVID-19 patients in stage IIb of disease. CP therapy given on 1st, 3rd and 6th day of study • Comparator: not applicable • Concomitant therapy: NR • Treatment cross-overs: not applicable
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Plaque reduction neutralisation test (PN (time frame: day 7 after first transfusion) PNRT50 * D-dimer (time frame: day 1, 4, 7, 14 after first transfusion) * CRP (time frame: day 1, 4, 7, 14 after first transfusion) * International normalised ratio (INR) (time frame: day 1, 4, 7, 14 after first transfusion) * Oxygenation index (time frame: day 1, 4, 7, 14 after first transfusion) * Chest X-ray (time frame: day 1, 4, 7, 28 after first transfusion) • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: yes * Number of participants with SAEs: yes * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR • Additional outcomes: <ul style="list-style-type: none"> * Plaque reduction neutralisation test (time frame: day 7 after first transfusion) PNRT50 * D-dimer (time frame: day 1, 4, 7, 14 after first transfusion) * CRP (time frame: day 1, 4, 7, 14 after first transfusion) * International normalised ratio (INR) (time frame: day 1,4,7,14 after first transfusion) * Oxygenation Index (time frame: day 1, 4, 7, 14 after first transfusion) * Chest X-ray (time frame: day 1, 4, 7, 28 after first transfusion)

NCT04407208 (Continued)

Starting date	1 May 2020
Contact information	Marliana Sri Rejeki, Sp.FK +6281323756199 marlianasr@gmail.com Familia Bela, Sp. PA +6285228878818
Notes	<p>Recruitment status: recruiting</p> <p>Prospective completion date: 1 August 2020</p> <p>Sponsor/funding: Biofarma</p> <p>Rumah Sakit Pusat Angkatan Darat Gatot Soebroto</p> <p>Eijkman Institute for Molecular Biology</p>

NCT04408040

Study name	Use of convalescent plasma collected from donors recovered from COVID-19 virus disease for transfusion, as an empirical and preemptive treatment during viral pandemic outbreak
Methods	<ul style="list-style-type: none"> • Trial design: non-randomised • Sample size: 700 • Setting: inpatient and healthcare providers • Country: USA • Language: English • Number of centres:
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Documented COVID-19 infection by nasal pharyngeal sampling * COVID-19 disease falling into 1 of the following groups: <ul style="list-style-type: none"> <input type="checkbox"/> Critical disease: respiratory failure requiring mechanical ventilation, pressor support, or multiple organ dysfunction/failure <input type="checkbox"/> Severe disease: tachypnoea ≥ 30 per min, O₂ sats $\leq 93\%$ at rest, PaO₂/FiO₂ index ≤ 300 mmHg <input type="checkbox"/> High risk: upper respiratory symptoms but no radiographic evidence of disease, immunocompromised, insulin-dependent diabetes, poorly controlled HIV disease, moderate to severe asthma history, severe COPD, morbid obesity (BMI ≥ 40, age ≥ 65 years) <input type="checkbox"/> Healthcare providers: healthcare providers at risk to exposure to COVID-19 infection or those with mild to non-severe disease • Exclusion criteria <ul style="list-style-type: none"> * History of IgA deficiency * History of anaphylactic reaction to blood product transfusion including hypersensitivity to immunoglobulin therapy • Donor eligibility criteria NR • Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP collected from donors recovered from COVID-19 virus * Volume: 200-425 mL * Number of doses: NR * Antibody-titre: NR * Pathogen inactivated NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR

NCT04408040 (Continued)

- Comparator: not applicable
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome:
 - * Arms 1 & 2: number of critical and severe COVID-19-infected patients who are transfused with CP result in lower death rates than the reported fatality rate (time frame: 30 days after initial treatment)
 - * Arms 1 & 2: number of critical and severe COVID-19-infected patients who survive the infection (time frame: 30 days after initial treatment)
 - * Arm 3: number of high-risk COVID-19-infected patients who are transfused with CP result in lower incidence of progression to severe or critical disease than the reported case rate (time frame: 30 days after initial treatment)
 - * Arm 4: number of healthcare providers who are at risk to exposure to COVID-19 who are transfused with CP result in lower incidence of developing COVID-19 infection than the reported case rate (time frame: 30 days after initial treatment)
 - * To estimate infection-related mortality rates; overall survival; progression incidence rates; rate of infection among healthy people exposed to COVID-19
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: yes
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: yes
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes: NR

Starting date

June 2020

Contact information

Stacey Brown 404-780-7965 stacey.brown@northside.com

Notes

- Recruitment status: not yet recruiting
- Prospective completion date: June 2022
- Sponsor/funding: Northside Hospital Inc.

NCT04408209

Study name

Convalescent plasma for the treatment of patients with severe COVID-19 infection - a multicenter phase II trial

Methods

- Trial design: interventional; historic control
- Sample size: 60
- Setting: inpatient
- Country: Greece
- Language: English

NCT04408209 (Continued)

Participants	<ul style="list-style-type: none"> • Number of centres: 6 <hr/> <ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age > 18 years * Confirmed SARS-CoV2 infection by PCR of the nasal/pharyngeal swab, sputum, BAL * Onset of the disease symptoms no more than 12 days before the inclusion of the patients in the trial * Severe COVID-19 infection as determined with one of the following: <ul style="list-style-type: none"> <input type="checkbox"/> Respiratory rate 30/min <input type="checkbox"/> Oxygen haemoglobin saturation SAT 93 <input type="checkbox"/> CRP > 1.5 (ULN < 0.5) <input type="checkbox"/> Ferritin value > 100 <input type="checkbox"/> Ratio of PaO₂:FiO₂ < 300 mmHg <input type="checkbox"/> Pulmonary infiltrates in chest X-ray or chest CT scan > 50% during 24-48 h * Life-threatening infection as determined by one of the following: <ul style="list-style-type: none"> <input type="checkbox"/> Respiratory failure <input type="checkbox"/> Septic shock <input type="checkbox"/> Multiple organ failure * Signature of informed consent by the patient or legal representative. Patients fulfilling criteria 1, 2, 3, 6 and one of criteria 4 or 5 will be eligible for the study. • Exclusion criteria <ul style="list-style-type: none"> * Critical illness due to progressive COVID-19 with expected survival time < 48 h * Intubated patients > 72 h * Chronic heart failure NYHA 3 and/or pre-existing left ventricular ejection fraction 30% * Cardiovascular failure requiring 0.5 µg/Kg/min nor-adrenaline or equivalent or > 2 types of vasopressor medication * Liver cirrhosis Child C * Liver failure with bilirubin > 5 x ULN and increase of ALT/AST (at least 1 > 10 x ULN) * Previous history of allergic reaction to blood or blood products transfusion * Known IgA deficiency * Pregnancy * Breast feeding women * Pulmonary oedema • Donor eligibility criteria <ul style="list-style-type: none"> * All donors will be tested for: <ul style="list-style-type: none"> <input type="checkbox"/> the titre of IgG anti-SARS-CoV-2 antibodies (Pasteur Institute) <input type="checkbox"/> the titre of neutralising anti-SARS-CoV-2 antibodies (Pasteur Institute) • Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP will be collected by plasmapheresis from patients fully recovered from COVID-19 infection * Volume: NR * Number of doses: 3 * Antibody-titre: NR * Pathogen inactivated NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): early treatment of patients with severe COVID-19 • Comparator: historical matched control • Concomitant therapy: NR • Treatment cross-overs: not applicable

NCT04408209 (Continued)

Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * The primary endpoint of this trial is the survival on day 21. The primary endpoint, as a dichotomous composite of survival (yes/no) and no longer fulfilling criteria of severe COVID-19, will be analysed according their classification. * Survival (time frame: Day 21) * Survival (time frame: Day 35) * Survival (time frame: Day 60) • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes * Time to death: yes • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: yes * Number of participants with SAEs: yes * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: yes * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR • Additional outcomes <ul style="list-style-type: none"> * Clinical improvement, i.e. percentage of participants not fulfilling the criteria for severe disease (time frame: Day 21) * The secondary endpoint of this trial is that no longer fulfilling criteria of severe COVID-19 within 21 days after inclusion. This will be assessed on the basis of respiratory rate and ventilation support.
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Starting date	23 April 2020
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Contact information	Aikaterini Niarchou +30 6949124743 aniarchou@med.uoa.gr Ioanna Charitaki +30 6976156403 j.charitaki@gmail.com
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Notes	<p>Recruitment status: recruiting</p> <p>Prospective completion date: 30 June 2020</p> <p>Sponsor/funding: National and Kapodistrian University of Athens Hellenic Society of Hematology</p>
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NCT04411602

Study name	Feasibility study of anti-SARS-CoV-2 plasma transfusions in COVID-19 patients with SRD
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Methods	<ul style="list-style-type: none"> • Trial design: interventional; single-arm • Sample size: 90 • Setting: inpatient • Country: USA • Language: English • Number of centres: 3
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NCT04411602 (Continued)

Participants

- Inclusion criteria
 - * Age > 18 years
 - * Laboratory-confirmed COVID-19
 - * Severe or immediately life-threatening COVID-19
 - * Dyspnoea
 - * Respiratory frequency > 30/min
 - * Blood oxygen saturation < 93%
 - * Life-threatening disease is defined as the following:
 - respiratory failure
 - septic shock, and/or
 - multiple organ dysfunction or failure
- Exclusion criteria
 - * Contraindication to transfusion (severe volume overload, history of anaphylaxis to blood products)
 - * Other documented uncontrolled infection
 - * Severe DIC needing factor replacement, FFP, cryoprecipitate
 - * On dialysis
 - * Active intracranial bleeding
 - * Clinically significant myocardial ischaemia
- Donor eligibility criteria NR
- Donor exclusion criteria NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: plasma from COVID-19+ clinically resolved individuals (≥ 14 days post-resolution); obtained from the American Red Cross or local plasma supply (medicDal center or city/region-wide shared blood bank) from patients identified as having recovered from COVID-19
 - * Volume: NR
 - * Number of doses: dosing of single or double plasma units (weight based < and > 90 kg) will be administered on days 0, 2, 4, 6, and 8 (based on plasma availability), or until futility (if either occurs before day 8) is determined by the ICU
 - * Antibody-titre: NR
 - * Pathogen inactivated NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: not applicable
- Concomitant therapy: NR
- Treatment cross-overs: not applicable

Outcomes

- Primary study outcome:
 - * Transfusion of patients in the ICU with CP for COVID-19-induced respiratory failure
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: NR

NCT04411602 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
- Additional outcomes
 - * Ventilator-free days
 - * Length of stay from the time of admission to the hospital and subsequent admission to the ICU

Starting date	7 April 2020
Contact information	Yulia Abidov, RN248-849-5328 yulia.abidov@ascension.org Shukri David, MD(248) 552-9858 shukri.david@ascension.org
Notes	Recruitment status: recruiting Prospective completion date: 31 December 2020 Sponsor/funding: Ascension South East Michigan

NCT04412486

Study name	An open label trial of transfusion of COVID-19 convalescent plasma (CCP) to patients with moderate to severe COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: single-arm interventional • Sample size: 100 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age \geq 18 * Clinician judged serious or life threatening COVID-19 (or at significant risk to develop serious COVID) manifested by at least 1 of the following: <ul style="list-style-type: none"> <input type="checkbox"/> Laboratory-confirmed diagnosis of SARS-CoV-2 infection <input type="checkbox"/> Hypoxia (PaO₂/FIO₂ < 300, pulse oximetry < 93% at rest <input type="checkbox"/> Evidence of pulmonary infiltration <input type="checkbox"/> Respiratory failure <input type="checkbox"/> Sepsis <input type="checkbox"/> Multiple organ dysfunction or failure (assessed by SOFA score) * Informed consent provided by the patient or LAR

NCT04412486 (Continued)

- Exclusion criteria
 - * > 21 days from confirmed COVID-19 diagnosis
 - * Receipt of pooled immunoglobulin transfusion in previous 28 days
 - * History of prior reaction to transfused blood products
 - * Currently enrolled in other drug trials that preclude investigational treatment with CoV-2 CP transfusion
- Donor eligibility criteria NR
- Donor exclusion criteria NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: plasma from donors who have recovered from COVID-19 with high antibody levels to the CoV-2 virus
 - * Volume:
 - * Number of doses:
 - * Antibody-titre:
 - * Pathogen inactivated
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: not applicable
- Concomitant therapy: NR
- Treatment cross-overs: not applicable

Outcomes

- Primary study outcome:
 - * Change in PaO₂/FiO₂ after CCP transfusion (time frame: 3 Days)
 - * Change in pulse oximetry status after CCP transfusion (time frame: 3 Days)
 - * Change in aO₂ after CCP transfusion (time frame: 3 Days)
 - * Change in respiratory rate after CCP transfusion (time frame: 3 Days)
 - * Change in intubation status after CCP transfusion (time frame: 3 Days)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: yes
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - * 30-day and 90-day mortality: yes
 - * Admission on the ICU: yes
 - * Length of stay on the ICU: yes
 - * Time to discharge from hospital: yes
 - * QoL: NR
- Additional outcomes
 - * Change in SOFA (time frame: Days 1, 3, 7, and 28)
 - * Change in 8-point ordinal clinical deterioration scale (time frame: Days 1, 3, 7, and 28);
 - * Change in 8-point ordinal clinical deterioration scale pre-transfusion to Days 1, 3, 7, and 28 post-transfusion. The 8-point ordinal scale measured by: 8-death, 7-ventilation in addition to ECMO, CRRT and/or vasopressor; 6-intubation and mechanical ventilation; 5-non-invasive mechanical ventilation or high flow oxygen 4- supplemental oxygen by mask or nasal cannula; 3-hospitalisation without supplemental oxygen; 2- limitation of activities and 1- no limitation of activities, discharge from hospital
 - * Length of ICU/hospital stay (time frame: Days 1, 3, 7, and 28)
 - * Development of plasma transfusion reactions (time frame: Days 1, 3, 7, and 28)

NCT04412486 (Continued)

- * Development of immune complex disorders (time frame: Days 1, 3, 7, and 28)
- * Change in anti CoV-2 IgM and IgG levels (time frame: Days 1, 3, 7, and 28)

Starting date	1 June 2020
Contact information	Gailen D Marshall, Jr., MD, PhD 601-815-5527 gmarshall@umc.edu
Notes	<p>Recruitment status: recruiting</p> <p>Prospective completion date: 31 May 2022</p> <p>Sponsor/funding:</p> <p>Gailen D. Marshall Jr., MD PhD</p> <p>University of Mississippi Medical Center</p>

NCT04415086

Study name	Treatment of patients with COVID-19 with convalescent plasma transfusion: a multicenter, open-labeled, randomized and controlled study
Methods	<ul style="list-style-type: none"> • Trial design: randomised • Sample size: 120 • Setting: hospitalised patients • Country: Brazil • Language: English • Number of centres: 1 • Trial registration number: NCT04415086 • Date of registration: 4 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Age \geq 18 years * Laboratory-proven COVID-19 infection by RT-PCR in any clinical sample * Time since symptom onset < 10 days at the time of screening * Presence of COVID-19 pneumonia, with a typical, indeterminate or atypical compatible image in a chest tomography exam (see definition below) * Presence of one of the following criteria: <ul style="list-style-type: none"> <input type="checkbox"/> Need for > 3L of O₂ in the catheter/mask or > 25% in the Venturi mask to maintain O₂ saturation > 92% <input type="checkbox"/> presence of respiratory distress syndrome with PaO₂ / FiO₂ < 300 mmHg If intubated, within 48 h of orotracheal intubation <input type="checkbox"/> Absence of a history of serious adverse reactions to transfusion, for example, anaphylaxis <input type="checkbox"/> Participation approval by the research clinician • Exclusion criteria: <ul style="list-style-type: none"> * Already enrolled in another clinical trial evaluating antiviral or immunobiological therapy for the treatment of COVID-19 * IgA deficiency * Presence of a clinical condition that does not allow infusion of 400 mL of volume at clinical discretion * Pregnancy or breastfeeding * Receipt of immunoglobulin in the last 30 days * Presence of significant risk of death within the next 48 h at clinical discretion • Donor eligibility criteria: NR

NCT04415086 (Continued)

Interventions	<ul style="list-style-type: none"> • Donor exclusion criteria: NR <hr/> <ul style="list-style-type: none"> • Intervention(s): CP therapy (3 arms, randomised 1:1:1 into 3 treatment groups: A- standard (control); B- standard and CP in a volume of 200 mL (150-300 mL); C- standard and CP in a volume of 400 mL (300-600 mL) • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: 200 mL or 400 mL * Number of doses: NR * Antibody test and antibody-titre: NR * Pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody: NR * Severity of disease: NR * Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients • Comparator: nil • Concomitant therapy: standard of care • Duration of follow-up: 28 days • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Time elapsed until clinical improvement or hospital discharge • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: reported * Time to death: reported • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported * Number of participants with SAEs: reported * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported * WHO ordinal scale: reported * 30-day and 90-day mortality: reported * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: reported * QoL: NR * Virological response: <ul style="list-style-type: none"> <input type="checkbox"/> SARS-CoV-2 in nasopharyngeal swab (time frame: Days 0, 1, 3, 7, 14 and 28 after transfusion and control groups) <input type="checkbox"/> IgG, IgM and IgA titres for SARS-CoV-2 (time frame: Days 0, 1, 3, 5, 7, 14 and 28 after transfusion and control groups) <input type="checkbox"/> Neutralising antibodies (time frame: 0,1,7 14 and 28 days after transfusion and control groups) • Additional outcomes: nil
Starting date	1 June 2020
Contact information	<ul style="list-style-type: none"> • Zelinda B Nakagawa, MsC55-11-2661-7214 zelinda.bartolomei@gmail.com

NCT04415086 (Continued)

- Natália B Cerqueira55-112661-2277natalia.b.cerqueira@gmail.com

Notes

- Recruitment status: recruiting
- Prospective completion date: 22 May 2022
- Sponsor/funding: University of Sao Paulo General Hospital

NCT04418518

Study name CONCOR-1: a randomized open-label trial of convalescent plasma for hospitalized adults with acute COVID-19 respiratory illness

Methods

- Trial design: randomised
- Sample size: 1200
- Setting: hospitalised patients
- Country: USA
- Language: English
- Number of centres: 3
- Trial registration number: NCT04418518
- Date of registration: 5 June 2020

Participants

- Inclusion criteria:
 - * ≥ 18 years old
 - * Admitted to hospital with confirmed COVID-19 respiratory illness
 - * Receiving supplemental oxygen
 - * 500 mL of ABO compatible convalescent plasma is available
- Exclusion criteria:
 - * Onset of symptoms > 12 days prior to randomisation
 - * Intubated or plan for intubation in place
 - * Plasma is contraindicated (e.g. history of anaphylaxis from transfusion)
 - * Decision in place for no active treatment
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: 500 mL
 - * Number of doses: 1 (or 2 x 250 ml)
 - * Antibody test and antibody-titre: NR
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator: nil
- Concomitant therapy: standard of care
- Duration of follow-up: 90 days

NCT04418518 (Continued)

	<ul style="list-style-type: none"> Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> Primary study outcome: <ul style="list-style-type: none"> * Intubation or death in hospital Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: reported * Time to death: reported Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported * Number of participants with SAEs: reported * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported * WHO ordinal scale: NR * 30-day and 90-day mortality: reported * Admission on the ICU: reported * Length of stay on the ICU: reported * Time to discharge from hospital: reported * QoL: NR * Virological response: NR Additional outcomes: need for intubation, time of intubation, need for renal replacement therapy, development of myocarditis
Starting date	24 June 2020
Contact information	Celine Arar212-746-4177cea4002@med.cornell.edu
Notes	<ul style="list-style-type: none"> Recruitment status: recruiting Prospective completion date: December 2021 Sponsor/funding: Weill Medical College of Cornell University

NCT04418531

Study name	A pilot study to explore the efficacy and safety of rescue therapy with antibodies from convalescent patients obtained with double-filtration plasmapheresis (DFPP) and infused in patients with coronavirus disease 2019 (COVID-19) and need of oxygen support without mechanical ventilation
Methods	<ul style="list-style-type: none"> Trial design: single-arm interventional Sample size: 10 Setting: hospitalised patients with respiratory failure requiring oxygen without mechanical ventilation Country: Italy Language: English Number of centres: 6 Trial registration number: NCT04418531 Date of registration: 9 June 2020

NCT04418531 (Continued)

Participants

- Inclusion criteria:
 - * > 18 years of age
 - * COVID-19 pneumonia diagnosed by standard criteria (viral detection in naso-pharyngeal or BAL by RT-PCR for SARS-COV-2, typical chest X Ray or CT scan, ventilatory dysfunction not directly explained by heart failure or fluid overload)
 - * Respiratory failure (i.e. room air PaO₂ < 60 mmHg) needing oxygen support with Venturi mask (FiO₂ between 28% and 60%), non-rebreathing mask or high flow-nasal cannula (HFNC);
 - * Patient written informed consent
- Exclusion criteria:
 - * Need of CPAP ventilator support, non-invasive ventilation (NIV) or intubation for invasive mechanical ventilation
 - * Involvement in any clinical trial
- Donor eligibility criteria:
 - * Adult (> 18 and < 65 years) men and women
 - * Convalescent donor who recovered from COVID-19 at least 14 days earlier according to the clinical and laboratory criteria defined by the Consiglio Superiore di Sanità on February 20, 2019 ("The recovered patient is the one who resolves the symptoms of COVID-19 infection and who is negative in two consecutive tests for the search for SARS-Cov-2, performed 24 hours apart") with the exceptions mentioned in the attached derogation (that is "no upper age limit to donation provided there are no clinical contraindications to the procedure and independent of documented evidence of two negative tests for SARS-Cov 2 naso-pharyngeal contamination")
 - * Male or female donor; if female only if nulliparous; in both cases with a negative history of blood component transfusions
 - * Careful clinical evaluation of the patient-donor with particular reference to the criteria established by current legislation to protect the health of the donor who donates by apheresis
 - * Presence of adequate levels of neutralising anti-SARS-COV-2 antibodies
 - * Biological qualification test negative defined by current indications (performed at SIMT of HPG23)
 - * Test negative for: HAV RNA, HEV RNA, PVB19 DNA (performed at HPG23)
 - * Informed written consent
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: NR
 - * Number of doses: NR
 - * Antibody test and antibody-titre: adequate levels of neutralizing anti-SARS-COV-2 antibodies (technique not specified)
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: both, exclude females with previous pregnancy
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: 14 days
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients with respiratory failure requiring oxygen without mechanical ventilation
- Comparator: nil
- Concomitant therapy: NR
- Duration of follow-up: 3 months
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * Time to weaning off oxygen support

NCT04418531 (Continued)

- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response:
 - Viral titre (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
 - Anti COVID 19 IgG antibodies (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
- Additional outcomes:
 - * Chest X-ray/CT scan findings
 - * Anti-COVID 19 IgM antibodies (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
 - * C5a concentration (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
 - * C3a concentration (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
 - * Serum C5b-9 concentration marker of complement activation (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
 - * Serum IL-6 levels (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
 - * Serum IL-1b levels (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
 - * Serum IFN γ levels (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
 - * Serum MCP-1 levels (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
 - * Serum TNF α levels (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
 - * Serum IL-10 levels (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
 - * Serum IL-2 levels (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)
 - * Serum IL-7 levels (time frame: changes from before Ig administration, 1 day after Ig administration and every week through study completion, an average of 3 months)

Starting date	June 2020
Contact information	Piero Luigi Ruggenenti, MD0039035267 ext 3814 pruggenenti@asst-pg23.it
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: September 2020

NCT04418531 (Continued)

- Sponsor/funding: Piero Luigi Ruggenti

NCT04420988

Study name	Investigational COVID-19 convalescent plasma infusion for severely or life-threateningly ill COVID-19 patients
Methods	<ul style="list-style-type: none"> • Trial design: expanded access scheme • Sample size: NR • Setting: hospitalised patients, with severely or life-threateningly ill COVID-19 • Country: USA • Language: English • Number of centres: 2 • Trial registration number: NCT04420988 • Date of registration: June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Laboratory-confirmed COVID-19 * Severe or life-threatening COVID-19 * Severe disease is defined as one or more of the following <ul style="list-style-type: none"> <input type="checkbox"/> dyspnea <input type="checkbox"/> respiratory frequency $\geq 30/\text{min}$ <input type="checkbox"/> blood oxygen saturation $\leq 93\%$ <input type="checkbox"/> PaO₂:FiO₂ ratio < 300 <input type="checkbox"/> lung infiltrates $> 50\%$ within 24-48 h * Life-threatening disease is defined as one or more of the following <ul style="list-style-type: none"> <input type="checkbox"/> respiratory failure <input type="checkbox"/> septic shock <input type="checkbox"/> multiple organ dysfunction or failure • Exclusion criteria: <ul style="list-style-type: none"> * Contraindication to transfusion (severe volume overload, history of anaphylaxis to blood products) * Severe multi-organ failure and haemodynamic instability requiring high doses of pressor agents * Other documented uncontrolled infection * Severe DIC needing factor replacement, FFP, cryoprecipitate * Acute renal failure requiring dialysis * Active intracranial bleeding * Clinically significant myocardial ischaemia • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: NR * Number of doses: NR * Antibody test and antibody-titre: NR * Pathogen inactivated or not: NR * RT-PCR tested: NR

NCT04420988 (Continued)

- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severe/critically ill patients
- Comparator: nil
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * NR
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: nil

Starting date

NR

Contact information

- Marc Klapholz, MD, MBA973-972-4595 klapholz@njms.rutgers.edu
- Khyati Mehta, MPH973-972-6794 mehtakp@njms.rutgers.edu

Notes

- Recruitment status: recruiting (expanded access scheme available)
- Prospective completion date: NR
- Sponsor/funding: Rutgers, The State University of New Jersey

NCT04421404

Study name

A randomized controlled adaptive study comparing COVID-19 convalescent plasma (CCP) to non-immune plasma to limit coronavirus-associated complications in hospitalized patients

Methods

- Trial design: RCT
- Sample size:
- Setting: hospitalised patients
- Country: USA
- Language: English

NCT04421404 (Continued)

- Number of centres: 3
- Trial registration number: NCT04421404
- Date of registration: 9 June 2020

Participants

- Inclusion criteria:
 - * Patients \geq 18 years of age
 - * Hospitalised with COVID-19
 - * Enrolled within 72 h of hospitalisation OR within day 14 from first signs of illness
 - * Pulmonary infiltrates on chest imaging
 - * Oxygenation of $<$ 95% on room air
 - * Laboratory-confirmed COVID-19
- Exclusion criteria:
 - * Contraindication to transfusion due to inability to tolerate additional fluid, such as due to de-compensated congestive heart failure
 - * Baseline requirement for oxygen supplementation prior to COVID-19 infection or use of positive pressure therapy for sleep-disordered breathing
 - * Currently experiencing severe hypoxaemic failure, as defined in study endpoints
 - * Prior receipt of plasma products, IVIG, or hyperimmune globulin within past 3 months
 - * Not currently enrolled another interventional clinical trial of COVID-19 treatment
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: NR
 - * Number of doses: NR
 - * Antibody test and antibody-titre: NR
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): enrolled within 72 h of hospitalisation OR within day 14 from first signs of illness
- Comparator: standard plasma
- Concomitant therapy: standard of care
- Duration of follow-up: 29 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * Mechanical ventilation or death endpoint
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported

NCT04421404 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: reported
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: nil

Starting date	9 June 2020
Contact information	<ul style="list-style-type: none"> • Rebecca Park, MS628-206-5801 rebecca.park@ucsf.edu • Victor Arechiga, BA618-206-5145 victor.arechiga@ucsf.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: April 30, 2021 • Sponsor/funding: Priscilla Hsue, MD

NCT04425837

Study name	Effectiveness and safety of convalescent plasma in patients with high-risk COVID-19: a randomized, controlled study CRI-CP (Coronavirus Investigation - Convalescent Plasma)
Methods	<ul style="list-style-type: none"> • Trial design: randomised • Sample size: 236 • Setting: critically ill or high risk of progression • Country: Colombia • Language: English • Number of centres: 1 • Trial registration number: NCT04425837 • Date of registration: 11 June 2020

NCT04425837 (Continued)

Participants

- Inclusion criteria:
 - * Patients diagnosed with COVID-19 infection by RT-PCR technique
 - * Patients ≥ 18 years of age
 - * Patients in standard care according to the national guide
 - * Onset of symptoms ≤ 14 days
 - * Signature of informed consent report
 - * Patients at high risk of progression, defined by all of the following:
 - score > 9 on the CALL scale
 - Pao₂/Fio₂ ≤ 200 (parameters adjusted to the height of Bogotá, Colombia)
 - X-ray or CT compatible with pneumonia
 - Hospitalised patients
 - * Critically ill patients, defined by any of the following:
 - mechanical ventilation requirement
 - patients in IICU or Intermediate Care Unit
 - ventilatory failure, septic shock, dysfunction or multi-organ failure
- Exclusion criteria:
 - * Negative RT-PCR result from secretion 48 h prior to study recruitment
 - * History of allergic reaction to blood or plasma in patients with a known history of IgA deficiency
 - * Patients participating in other clinical trial
 - * History of allergy to blood products
 - * History of confirmed infection and that required antibiotic or antifungal treatment 30 days prior to recruitment
 - * Pregnant women
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: 400 mL
 - * Number of doses: 2
 - * Antibody test and antibody-titre: titre $\geq 1:160$
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): critically ill/high risk of progression
- Comparator: standard of care
- Concomitant therapy: standard of care
- Duration of follow-up: 30 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * Mortality
 - * Safety: presence of adverse events
 - * ICU admission
 - * Mechanical ventilation

NCT04425837 (Continued)

- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: reported
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response:
- Additional outcomes: laboratory parameters (CRP, ferritin, procalcitonin, lymphocyte count, LDH), SOFA score, Increase in PaO₂/Fio₂, lung infiltration

Starting date	July 2020
Contact information	<ul style="list-style-type: none"> • Guillermo E Quintero, Hematologist5716030303 ext 1221quiquequintero@yahoo.com.mx • José A De la Hoz, Epidemiologist5716030303 ext 1127jose.delahoz@fsfb.org.co
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: February 2021 • Sponsor/funding: Fundación Santa Fe de Bogota

NCT04425915

Study name	Efficacy of convalescent plasma therapy in patients with COVID-19: a randomized control trial
Methods	<ul style="list-style-type: none"> • Trial design: randomised parallel-assignment • Sample size: 400 • Setting: severe disease • Country: India • Language: English • Number of centres: 3 • Trial registration number: NCT04425915 • Date of registration: 11 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Patients with severe COVID-19 will be considered for randomisation and will be transfused CP within 3 days of symptom onset (severe COVID-19). Severe COVID -19 defined by WHO Interim Guidance and the Guideline of Diagnosis and Treatment of COVID-19 of National Health Commission of China (version 5.0) along with confirmation by real-time RT-PCR assay with severe disease i.e. meeting any 2 of the following criteria: <ul style="list-style-type: none"> <input type="checkbox"/> Patients on ventilator (in last 24 h) <input type="checkbox"/> Respiratory distress, respiratory rate \geq 30 breaths/min <input type="checkbox"/> Oxygen saturation level < 90% in resting state <input type="checkbox"/> PaO₂/Fio₂ \leq 300 mmHg <input type="checkbox"/> Lung infiltrates > 50% within 24-48 h

NCT04425915 (Continued)

- Exclusion criteria:
 - * Patient/family members who do not give consent to participate in the study
 - * Patients with age < 18 years
 - * Patients presenting with multi-organ failure
 - * Pregnancy
 - * Individuals with HIV and viral hepatitis and cancer
 - * Extremely moribund patients with an expected life expectancy of < 24 h
 - * Hemodynamic instability requiring vasopressors
 - * Previous history of allergy to plasma
 - * Cirrhosis
 - * Severe renal impairment with GFR < 30 mL/min or recipients of RRT, peritoneal dialysis
 - * Patients with uncontrolled diabetes mellitus, hypertension, arrhythmias and unstable angina
- Donor eligibility criteria:
 - * Virologically documented (PCR-positive by nasopharyngeal swab) who is recovered and free of symptoms for 14 days
 - * Has tested negative for SARS-CoV-2 on 2 consecutive tests 24 h apart.
 - * Fulfill all criteria of donor eligibility for donor plasmapheresis under the Drugs & Cosmetics Act 1940 and Rules 1945, amended 11 March 2020
 - * Women who have been pregnant may be tested for anti-HLA antibodies and eligible if negative for the same
- Donor exclusion criteria:
 - * Do not fulfil all criteria of donor eligibility for donor plasmapheresis under the Drugs & Cosmetics Act 1940 and Rules 1945, amended 11 March 2020
 - * Females who have been pregnant and have not been tested for HLA antibodies or are HLA antibody positive if tested and previously transfused donors (to prevent TRALI)
 - * Donors who have taken steroids during treatment for COVID-19

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: 250 mL
 - * Number of doses: 2
 - * Antibody test and antibody-titre: NR
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: yes
- Details of donors:
 - * Gender: both, exclude women with previous pregnancy without previous testing for HLA antibodies or HLA antibody-positive
 - * HLA and HNA antibody: HLA tested in females with previous pregnancy
 - * Severity of disease: NR
 - * Timing from recovery from disease: 14 days asymptomatic since last negative test
- Treatment details, including time of plasma therapy (e.g. early stage of disease): within 3 days of severe disease
- Comparator: standard of care
- Concomitant therapy: standard of care
- Duration of follow-up: 28 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * Efficacy of CP in severe COVID-19 patients in time to clinical improvement
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported

NCT04425915 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: reported
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: presence of antibodies against SARS-CoV-2 in serum after plasma administration (Days 3, 7, 14, 21, 28)
- Additional outcomes: changes in acute phase reactants, cytokines, correlation of the titres in COVID-19 CP donors with duration of illness, the severity of symptoms, duration of hospital stay, drugs used in therapy, duration between recovery, and donation

Starting date	9 June 2020
Contact information	<ul style="list-style-type: none"> • Dr Meenu Bajpai, MD01146300000 meenubajpai@hotmail.com • Dr Ankit Bhardwaj, Masters-CT01146300000 bhardwaj.ankit3@gmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 30 May 2021 • Sponsor/funding: Institute of Liver and Biliary Sciences, India

NCT04428021

Study name	Effectiveness of adding standard plasma or COVID-19 convalescent plasma to standard treatment, versus standard treatment alone, in patients with recent onset of COVID-19 respiratory failure. A randomized, three-arms, phase 2 trial
Methods	<ul style="list-style-type: none"> • Trial design: randomised • Sample size: 180 • Setting: hospitalised patients within 5 days of respiratory failure • Country: Italy • Language: English • Number of centres: 1 • Trial registration number: NCT04428021 • Date of registration: 11 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Confirmed SARS-Cov-2 diagnosis by RT-PCR on nasopharyngeal swab or on BAL * Respiratory failure onset or progression within 5 days * Signed informed consent • Exclusion criteria: <ul style="list-style-type: none"> * Pregnancy * Previous severe reactions to plasma transfusion * Unavailability of blood group-compatible COVID-19 CP • Donor eligibility criteria: NR

NCT04428021 (Continued)

	<ul style="list-style-type: none"> • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy <ul style="list-style-type: none"> * Enrolled patients will be stratified according to severity of respiratory failure and randomised in 3 arms: 1) Standard Therapy Protocol (STP), 2) Standard Therapy Protocol + 170-350 mL standard plasma (SP) on day 1-3-5 after randomisation, 3) Standard Therapy Protocol + 170-350 mL COVID-19 CP on day 1-3-5 after randomisation. • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: 170-300 mL * Number of doses: 3 * Antibody test and antibody-titre: NR * Pathogen inactivated or not: yes (virus inactivated with riboflavin and ultraviolet light illumination technology) * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody: NR * Severity of disease: NR * Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): within 5 days of respiratory failure • Comparator: standard of care, standard plasma • Concomitant therapy: standard of care • Duration of follow-up: 12 months • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * 30-day survival • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: reported * Time to death: reported • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported * WHO ordinal scale: reported * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR * Virological response: proportion of participants showing seroconversion to IgG anti-SARS-Cov-2, proportion of participants showing viral clearance by RT-PCR on plasma and respiratory tract samples • Additional outcomes: SOFA score, variation from standard therapy protocol, Incidence of complications, 6-month survival, ventilator-free survival
Starting date	15 June 2020

NCT04428021 (Continued)

Contact information Paola Maria Manzini, Principal Investigator, Azienda Ospedaliera Città della Salute e della Scienza di Torino

Notes

- Recruitment status: recruiting
- Prospective completion date: 15 December 2021
- Sponsor/funding: Azienda Ospedaliera Città della Salute e della Scienza di Torino

NCT04429854

Study name A randomized, open-label, adaptive, proof-of-concept clinical trial of donated antibodies working against with COVID-19: DAWN-PLASMA

Methods

- Trial design: randomised
- Sample size: 483 (483 patients with 2:1 randomisation. 322 participants receiving CP - 161 participants receiving standard of care)
- Setting: without non-invasive/invasive ventilation
- Country: Belgium
- Language: English
- Number of centres: 14
- Trial registration number: NCT04429854
- Date of registration: 12 June 2020

Participants

- Inclusion criteria:
 - * Participant (≥ 18 years old) or LAR provides informed consent prior to initiation of any study procedures
 - * Participant (or LAR) understands and agrees to comply with planned study procedures
 - * Male or non-pregnant female adult ≥ 18 years of age at time of enrolment
 - * Patient should be hospitalised
 - * Has a confirmed diagnosis of SARS-CoV-2 infection, defined as either:
 - laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen as diagnosed within 60 h prior to randomisation or
 - the combination of upper or lower respiratory infection symptoms (fever, cough, dyspnea, desaturation) and typical findings on chest CT scan and absence of other plausible diagnoses
 - * Illness of any duration, and at least 1 of the following:
 - radiographic infiltrates by imaging (chest X-ray, CT scan, etc.), or
 - clinical assessment (evidence of rales/crackles on exam) AND SpO₂ $\leq 94\%$ on room air, or
 - requiring supplemental oxygen
 - * ABO D typing of the participant should be done at least once and the result should be known
- Exclusion criteria:
 - * Receiving invasive (any mode where a patient has been intubated endotracheally, or via tracheostomy) or non-invasive (for instance, but not restricted to CPAP, PSV, PCV, SiMV) mechanical ventilation before or upon randomisation
 - * Pregnancy or breastfeeding
 - * Any medical condition that would impose an unacceptable safety hazard by participation to the study
 - * Patients with a documented grade 3 allergic reaction after the administration of FFP (i.e. systemic reaction with cardiovascular and/or respiratory involvement)
 - * Patients that have treatment restriction that excludes mechanical ventilation and/or endotracheal intubation
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

NCT04429854 (Continued)

Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy randomised 2:1 to standard care • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: NR * Number of doses: 4 * Antibody test and antibody-titre: NR * Pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody: NR * Severity of disease: NR * Timing from recovery from disease: 21 days without symptoms from negative PCR test • Treatment details, including time of plasma therapy (e.g. early stage of disease): without non-invasive/invasive ventilation • Comparator: nil • Concomitant therapy: standard of care • Duration of follow-up: 30 days • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Participants requiring mechanical ventilation or death • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: reported * Time to death: reported • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported * WHO ordinal scale: reported * 30-day and 90-day mortality: reported * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR * Virological response: NR • Additional outcomes: nil
Starting date	2 May 2020
Contact information	Geert Meyfroidt, MD, PhD003216332211 geert.meyfroidt@uzleuven.be
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 2 November 2021 • Sponsor/funding: Universitaire Ziekenhuizen Leuven

NCT04432103

Study name	Treatment of severe and critical COVID-19 pneumonia with convalescent plasma
Methods	<ul style="list-style-type: none"> • Trial design: non-randomised parallel assignment • Sample size: 36 • Setting: severe/critical patients • Country: Mexico • Language: English • Number of centres: 1 • Trial registration number: NCT04432103 • Date of registration: 16 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Age: > 18 years * Admitted to the ABC Medical Center facility for the treatment of COVID-19 * Patients with severe or critical COVID-19 * Informed consent provided by the patient or healthcare proxy • Exclusion criteria: <ul style="list-style-type: none"> * Contraindication to transfusion (severe volume overload, history of anaphylaxis to blood products) * Any other not controlled infection * DIC * Patient under dialysis * Patient with recent haemorrhagic stroke * Severe ischaemic heart disease • Donor eligibility criteria: <ul style="list-style-type: none"> * Age: > 18 and < 60 years * Body weight: > 60 kg * Confirmed previous SARS-CoV-2 infection * Negative SARS CoV-2 test result * 21 days without symptoms from the negative SARS CoV2-negative test * Written informed consent to participate in this clinical trial, to donate plasma and to store the specimen for future testing * Positive COVID-19 IgG antibodies * Male donors, or female donors who have not been pregnant, or female donors who have been pregnant tested negative for HLA antibodies * Individuals who meet all regular voluntary donor eligibility requirements by the Mexican legislation • Donor exclusion criteria: nil
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy <ul style="list-style-type: none"> * 2 groups depending on the stage of the disease according to the CDC of China classification severe and critical COVID-19 pneumonia <ul style="list-style-type: none"> <input type="checkbox"/> severe <input type="checkbox"/> critical • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: 200 mL * Number of doses: 1 * Antibody test and antibody-titre: NR * Pathogen inactivated or not: NR * RT-PCR tested: NR

NCT04432103 (Continued)

- Details of donors:
 - * Gender: both, women with prior pregnancy tested for HLA antibodies
 - * HLA and HNA antibody: HLA tested
 - * Severity of disease: NR
 - * Timing from recovery from disease: 21 days without symptoms from negative PCR test
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severe/critical patients
- Comparator: nil
- Concomitant therapy: standard of care
- Duration of follow-up: 28 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * Incidence of critical pneumonia (time frame: 14 days after CP administration)
 - * Mortality rate among critical pneumonia patients
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: incidence and duration of mechanical ventilation

Starting date 19 June 2020

 Contact information Paulina Trápaga, MBE+525511031600 ext 1872 ptrapaga@abchospital.com

 Notes

- Recruitment status: not yet recruiting
- Prospective completion date: 30 September 2020
- Sponsor/funding: Centro Medico ABC

NCT04432272

Study name Antibody-level based analysis of COVID-19 convalescent serum (ABACCuS)

 Methods

- Trial design: 2 arms, both receiving CP
- Sample size: 500
- Setting: hospitalised patients
- Country: USA
- Language: English
- Number of centres: 8

NCT04432272 (Continued)

	<ul style="list-style-type: none"> • Trial registration number: NCT04432272 • Date of registration: 16 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Participants must be ≥ 18 years * Hospitalised with confirmed COVID-19 infection via COVID-19 SARS-CoV-2 RT-PCR testing * Symptoms consistent with COVID-19 infection (fever, acute onset cough, shortness of breath) at time of screening * Patient requires > 6 L nasal cannula oxygen (Group A) or intubated (Group B) * Patient (or their LAR) is willing and able to provide written informed consent and comply with all protocol requirements • Exclusion criteria: <ul style="list-style-type: none"> * For participants in Group A admitted for > 14 days * Female participants with positive pregnancy test, breastfeeding, or planning to become pregnant or breastfeed during the study period * Receipt of pooled immunoglobulin in past 30 days * Contraindication to transfusion or history of prior reactions to transfusion blood products * Patients currently undergoing cancer treatment or those who are presently immunocompromised * Patient who in the opinion of the investigator will not be a good study candidate • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy <ul style="list-style-type: none"> * Participants will be assigned to a study group depending on how sick they are * Group A: those who require > 6 L of supplemental oxygen but are not on a ventilator * Group B: those who require a ventilator to preserve their life • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: 200 mL * Number of doses: 1 * Antibody test and antibody-titre: NR * Pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody: NR * Severity of disease: variable * Timing from recovery from disease: variable <ul style="list-style-type: none"> <input type="checkbox"/> donors either: 1) been symptom-free for 14 days and screen negative via nasopharyngeal swab or 2) symptom-free for at least 28 days or 3) individuals who have never had symptoms of COVID-19 but were found to have elevated anti-SARS-CoV-2 IgG by a serology test deemed to be of acceptable quality and fitting the current guidance by the FDA • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients • Comparator: nil • Concomitant therapy: standard of care • Duration of follow-up: 28 days • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Avoidance of intubation at 28 days (group A) (time frame: 28 days) * Mortality (group B) (time frame: 28 days)

NCT04432272 (Continued)

- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: reported
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: reported (count of participants with presence of SARS-CoV-2 RNA detected by RT-PCR-tested nasopharyngeal swabs)
- Additional outcomes: renal failure, liver failure, presence of ARDS, ventilator-free days

Starting date	14 July 2020
Contact information	Maureen Cooney, RN, BSN248 551-0099 Maureen.Cooney@beaumont.org
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: August 2021 • Sponsor/funding: William Beaumont Hospitals

NCT04433910

Study name	Randomized, prospective, open label clinical trial on the use of convalescent plasma compared to best supportive care in patients with severe COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: randomised • Sample size: 106 • Setting: hospitalised patients with severe disease • Country: Germany • Language: English • Number of centres: 3 • Trial registration number: NCT04433910 • Date of registration: 16 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Patients with SARS-CoV-2 infection * Age \geq 18 years and \leq 75 years * SARS-CoV-2 infection confirmed by PCR (BAL, sputum, nasal and/or pharyngeal swab) * Severe disease defined by at least 1 of the following: <ul style="list-style-type: none"> <input type="checkbox"/> respiratory rate \geq 30 breaths/minute under ambient air <input type="checkbox"/> requirement of any type of ventilation support <input type="checkbox"/> needs ICU treatment * Written informed consent by patient or LAR

NCT04433910 (Continued)

- Exclusion criteria:
 - * Accompanying diseases other than COVID-19 with an expected survival time of < 12 months
 - * Previous treatment with any SARS-CoV-2-CP
 - * In the opinion of the clinical team, progression to death is imminent and inevitable within the next 48 h, irrespective of the provision of treatment
 - * Interval > 72 h since start of ventilation support
 - * Not considered eligible for ECMO support (even in case of severe ARDS according to Berlin classification with Horovitz-Index < 100 mg Hg)
 - * COPD, stage 4
 - * Lung fibrosis with UIP pattern in CT and severe emphysema
 - * Chronic heart failure NYHA ≥ 3 and/or pre-existing reduction of left ventricular ejection fraction to ≤ 30%
 - * Shock of any type requiring ≥ 0.5 µg/kg/min noradrenaline (or equivalent) or requiring > 2 types of vasopressor medication for > 8 h
 - * Liver cirrhosis Child C
 - * Liver failure: bilirubin > 5 x ULN and elevation of ALT/AST (at least one > 10 x ULN)
 - * Any history of adverse reactions to plasma proteins
 - * Known deficiency of IgA
 - * Pregnancy
 - * Breastfeeding women
 - * Volume overload until sufficiently treated
 - * Participation in another clinical trial with an investigational medicinal product
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: (250-325 mL) on days 1, 3 and 5
 - * Number of doses: 3 (transfusion on day 1, 3 and 5)
 - * Antibody test and antibody-titre: NR
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients with severe disease
- Comparator: standard of care
- Concomitant therapy: standard of care
- Duration of follow-up: 60 days
- Treatment cross-overs: yes (cross over for participants with progressive disease on day 14 with CP transfusion on day 15, 17 and 19)

Outcomes

- Primary study outcome:
 - * Composite endpoint of survival and no longer fulfilling criteria of severe COVID-19 (time frame: Day 21)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR

NCT04433910 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - * Number of participants with SAEs: reported (up to 4 h)
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: reported
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: reported (time until negative SARS-CoV-2 PCR (nasopharyngeal sample))
- Additional outcomes:
 - * laboratory parameters (inflammatory markers, thrombotic markers, anti-SARS-CoV-2-antibody titres will be correlated with age; gender; severity of COVID-19; interval between resolution of symptoms and plasmapheresis of plasma donors, correlation of antibody titres with: 1. "Survival and no longer fulfilling criteria of severe COVID-19"; 2. Change in WHO ordinal scale; 3. Time to clinical improvement; 4. Length of hospital stay; 5. Length of ICU stay; 6. Length of mechanical ventilation or ECMO support. Percentage of former COVID-19 patients willing to donate qualifying for plasma donation. (time frame: through study completion, an average of 8 months, amount of plasma units that could be collected for the clinical trial (time frame: through study completion, an average of 8 months), titre of anti-SARS-CoV-2 in transfused plasma units (time frame: any plasmapheresis, through study completion, an average of 8 months), impact of donor characteristics on anti-SARS-CoV-2 humoral response (time frame: up to 60 days), course of anti-SARS-CoV-2 titre in both participant groups at different time points related to transfusion of CP (time frame: up to 60 days)

Starting date	June 2020
Contact information	Sixten Körper, Dr.731150560 ext +49s.koerper@blutspende.de
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: February 2021 • Sponsor/funding: Deutsches Rotes Kreuz DRK-Blutspendedienst Baden-Württemberg-Hessen

NCT04438057

Study name	Evaluating the efficacy of convalescent plasma in symptomatic outpatients infected with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: randomised 2:1 (CP:standard of care) • Sample size: 150 • Setting: mild to moderate symptoms • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04438057 • Date of registration: 18 June 2020

NCT04438057 (Continued)

Participants

- Inclusion criteria:
 - * Laboratory-confirmed diagnosis of infection with SARS-CoV-2
 - * Symptoms of COVID -19 - cough, fever, sore throat, shortness of breath, anosmia, diarrhea, myalgia
 - * Symptoms < 14 days
 - * ID physician determination that the patient does not need hospitalisation
 - * O2 saturation of > 93%
 - * Informed consent provided by the patient or healthcare proxy
 - * Age ≥ 18 years
 - * Ambulatory outpatient when informed consent obtained and study drug is administered
- Exclusion criteria:
 - * Age < 18 years
 - * Patients currently receiving intravenous immunoglobulin
 - * Hypercoagulable state - neoplasia, collagen vascular disease, myelodysplastic syndrome, chronic anticoagulation treatment, etc
 - * Need to be hospitalised
 - * O2 sat < 93%
 - * D-Dimer > 2 x normal
 - * Chronic oxygen therapy
 - * Renal insufficiency with Creatinine clearance < 30
 - * Long-term care or assisted living facility resident
 - * Ongoing usage of hydroxychloroquine for any indication
 - * History of blood or plasma transfusion-related complications
 - * Enrollment into any other investigational drug or device study within the previous 30 days
 - * Any drug, chemical or alcohol dependency as determined by the investigator through history that may affect study procedures and follow-up
 - * Pregnant or breastfeeding
 - * Any acute or chronic medical comorbidity, psychiatric, social or other circumstance that, in the opinion of the investigator, may interfere with study compliance, completion, or accurate assessment of the study outcomes/safety
 - * Admitted to or expected to be admitted to a medical facility
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy (arm 1: 1 dose, arm 2: 2 doses)
- Details of CP:
 - * Type of plasma: CP
 - * Volume: NR
 - * Number of doses: 1
 - * Antibody test and antibody-titre: NR
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): mild to moderate symptoms
- Comparator: standard of care
- Concomitant therapy: standard of care
- Duration of follow-up: 28 days

NCT04438057 (Continued)

	<ul style="list-style-type: none"> Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> Primary study outcome: <ul style="list-style-type: none"> * Time to resolution of symptoms (time frame: 28 days) * SAEs within 24 h of plasma infusion (time frame: 28 days) Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR * Number of participants with SAEs: reported * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported * WHO ordinal scale: NR * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR * Virological response: NR Additional outcomes: laboratory parameters (CRP, D-dimer, LDH, ferritin)
Starting date	6 July 2020
Contact information	<ul style="list-style-type: none"> Nicholas Van Hise, PharmD 630-655-6952 nvanhise@midcusa.com Nathan Skorodin, PharmD nskorodin@midcusa.com
Notes	<ul style="list-style-type: none"> Recruitment status: not yet recruiting Prospective completion date: 6 July 2021 Sponsor/funding: Metro Infectious Disease Consultants

NCT04438694

Study name	Use of convalescent plasma for treatment of patients with COVID-19 infection
Methods	<ul style="list-style-type: none"> Trial design: randomised Sample size: 60 Setting: hospitalised patients requiring supplemental oxygen Country: Egypt Language: English Number of centres: 1 Trial registration number: NCT04438694 Date of registration: 19 June 2020
Participants	<ul style="list-style-type: none"> Inclusion criteria: <ul style="list-style-type: none"> * Must have laboratory-confirmed COVID-19 and admitted to Cairo University isolation hospital * Admitted to acute care facility * Must have severe or immediately life-threatening COVID-19 * age 21-70 years

NCT04438694 (Continued)

- Exclusion criteria:
 - * Pregnancy
 - * Autoimmune disorder
 - * Participated in a CP trial in the past 6 months
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy (arm 1: 1 dose, arm 2: 2 doses)
- Details of CP:
 - * Type of plasma: CP
 - * Volume: NR
 - * Number of doses: 1-2 (if 2, 48 h apart)
 - * Antibody test and antibody-titre: NR
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severe/life-threatening disease
- Comparator: placebo (arm 3)
- Concomitant therapy: standard of care
- Duration of follow-up: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome:
 - * Duration of hospitalisation/recovery status
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: nil

Starting date

1 June 2020

Contact information

Nermeen ElDesouky, MD PhD01006029006nermeen.eldesoukey@kasralainy.edu.eg

Notes

- Recruitment status: recruiting
- Prospective completion date: 31 December 2021

NCT04438694 (Continued)

- Sponsor/funding: Cairo University

NCT04442191

Study name	Infusion of convalescent plasma for the treatment of patients infected with severe acute respiratory syndrome-coronavirus-2 (COVID-19): a double-blinded, placebo-controlled, proof-of-concept study
Methods	<ul style="list-style-type: none"> • Trial design: randomised • Sample size: 50 • Setting: hospitalised patients requiring supplemental oxygen • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04442191 • Date of registration: 22 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Patients \geq 40 years who are admitted to the University of Illinois Hospital (UIC) due to COVID-19 * Positive oropharyngeal and/or nasopharyngeal swab test for SARS-CoV-2 by RT-PCR within the preceding 72 h (performed by University of Illinois Hospital Laboratories or, if performed elsewhere, documented in the patient's UIC medical record) * Symptomatic infection with any of the following: fever, cough, dyspnea, or tachypnoea $>$ 22 breaths/min * Need for supplemental oxygen, between 1-5 L/minute by nasal canula, to maintain O₂ saturations $>$ 92% * Consents to comply with all protocol requirements * Agrees to storage of specimens for future testing • Exclusion criteria: <ul style="list-style-type: none"> * Patients with known IgA deficiency (high risk of severe or fatal anaphylactic reactions) * Patients who are on a ventilator * Patients with past history of severe transfusion reaction including transfusion-related acute lung injury (TRALI) or anaphylaxis * Patients with a baseline requirement for supplemental oxygen due to chronic lung disease or with known history of either moderate-to-severe asthma or emphysema * Women who report that they are pregnant or breastfeeding * Receipt of pooled immunoglobulin in the past 30 days * Patients must be willing to not take any other alternative experimental treatment for COVID-19 from the time they undergo enrolment until the 28-day follow-up phone call * Participants who are being treated with remdesivir and have had their first dose of remdesivir $>$ 24 h prior to the time they will receive their first dose of CP * Patients with severe disease due to COVID-19, as manifested by a need for vasopressors, and/or diagnosis of ARDS • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy

NCT04442191 (Continued)

- Details of CP:
 - * Type of plasma: CP
 - * Volume: NR
 - * Number of doses: NR
 - * Antibody test and antibody-titre: neutralising antibody titres > 1:64
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients requiring supplemental oxygen
- Comparator: standard FFP
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome:
 - * The primary endpoint will be clinical response at 8 days, defined as no need for oxygen supplementation for the previous 24 h
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR (up to 28 days)
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes:
 - * CRP (time frame: 28 days)
 - * Lymphocyte count (time frame: 28 days)
 - * Change in LDH following treatment
 - * LDH (time frame: 28 days)
 - * Ferritin (time frame: 28 days)
 - * D-Dimer (time frame: 28 days)
 - * WBC Count (time frame: 28 days)

 Starting date 5 May 2020

 Contact information Jessica Herrick, Assistant Professor of Clinical Medicine, University of Illinois at Chicago

 Notes

- Recruitment status: recruiting
- Prospective completion date: 5 May 2021

NCT04442191 (Continued)

- Sponsor/funding: University of Illinois at Chicago

NCT04442958

Study name	Effectiveness of convalescent immune plasma therapy in severe COVID-19 patients with acute respiratory distress syndrome
Methods	<ul style="list-style-type: none"> • Trial design: randomised cross-over • Sample size: 60 • Setting: severe with ARDS • Country: Turkey • Language: English • Number of centres: 1 • Trial registration number: NCT04442958 • Date of registration: 23 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * clinical diagnosis of COVID-19 • Exclusion criteria: <ul style="list-style-type: none"> * < 18 * Lower plasma IgA levels * PaO₂/FiO₂ > 300 mmHg * SpO₂ > 90 • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: 200 mL * Number of doses: 1 * Antibody test and antibody-titre: neutralising antibody titres above 1:640 * Pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody: NR * Severity of disease: NR * Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): severe patients with ARDS • Comparator: standard care • Concomitant therapy: NR • Duration of follow-up: NR • Treatment cross-overs: NR

NCT04442958 (Continued)

Outcomes

- Primary study outcome:
 - * Plasma ferritin level (time frame: 7 days)
 - * Lymphocyte count (time frame: 7 days)
 - * D-Dimer level (time frame: 7 days)
 - * CRP level (time frame: 7 days)
 - * Plasma procalcitonin level (time frame: 7 days)
 - * Plasma fibrinogen level (time frame: 7 days)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes:
 - * FiO2 level (time frame: 7 days)
 - * PaO2 level (time frame: 7 days)
 - * Arterial oxygen level (time frame: 7 days)

Starting date 15 May 2020

Contact information Salih SS Sevdi, Mdlstanbul Bagcilar Training and Research Hospital

Notes

- Recruitment status: recruiting
- Prospective completion date: 17 June 2020
- Sponsor/funding: Bagcilar Training and Research Hospital

NCT04445207

Study name Experimental expanded access treatment with convalescent plasma for the treatment of patients with COVID-19

Methods

- Trial design: expanded access
- Sample size: NR
- Setting: NR
- Country: USA
- Language: English
- Number of centres: 1
- Trial registration number: NCT04445207
- Date of registration: 24 June 2020

NCT04445207 (Continued)

Participants

- Inclusion criteria:
 - * At least 12 years of age
 - * COVID-19 CP (CCP) treatment is in line with the patient's current goals of care (i.e. recipient cannot be DNI status)
 - * Laboratory-confirmed diagnosis of infection with SARS-CoV-2 that is severe or life-threatening OR the individual is judged by the treating provider to be at a high risk of progression to severe or life-threatening disease
 - * Severe COVID-19 is defined by one or more of the following:
 - Dyspnoea
 - Respiratory frequency ≥ 30 /min
 - Blood oxygen saturation $\leq 93\%$
 - PaO₂/FiO₂ ratio < 300
 - Lung infiltrates $> 50\%$ within 24-48 h
 - * Life-threatening COVID-19 is defined as one or more of the following:
 - Respiratory failure
 - Septic shock
 - Multiple organ dysfunction or failure
- Exclusion criteria:
 - * History of prior life-threatening reactions to transfusion of blood products
 - * Not receiving other therapies that would preclude plasma transfusion
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: 200 mL
 - * Number of doses: 1-6
 - * Antibody test and antibody-titre: NR
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: nil
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: nil

Outcomes

- Primary study outcome: NR
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR

NCT04445207 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: NR

Starting date	NR
Contact information	<ul style="list-style-type: none"> • Contact: Jonathan Gerber, MD508-856-3216cancerresearch@umassmed.edu • Contact: Cara Gregoire774-455-4458Cara.Gregoire@umassmed.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: available • Prospective completion date: NR • Sponsor/funding: Jonathan Gerber

NCT04452812

Study name	Pilot clinical, statistical and epidemiological study on efficacy and safety of convalescent plasma for the management of patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: pilot, experimental, randomised, prospective, longitudinal, clinical study • Sample size: 15 • Setting: hospitalised patients in ICU • Country: Mexico • Language: English • Number of centres: 1 • Trial registration number: NCT04452812 • Date of registration: 30 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Signed informed consent provided by the patient, legal guardian or the health provider if not available * Patients hospitalised in an ICU dedicated to the treatment of COVID-19 patients * At least positive for 1 q-PCR test for SARS-CoV-2 * Patients with COVID-19 defined as severe or critically ill: <ul style="list-style-type: none"> <input type="checkbox"/> Severe: RF > 30 breaths/min, oxygen saturation <94%, Pa/FiO₂ < 301, bilateral lung infiltrates that extends in > 50% (by chest radiograph or CT scan) in 24-48 h <input type="checkbox"/> Critically ill: RF (PaO₂ < 60 mmHg or SatO₂ < 90% with FiO₂ > 60%) and septic shock (MAP < 65 mmHg with vasoactive requirement, lactate > 2 mmol/L and SOFA score > 1)

NCT04452812 (Continued)

- Exclusion criteria:
 - * Positive pregnancy test
 - * Patients in lactation
 - * Informed consent not signed
 - * Patients involved in other treatment protocols
 - * Patients on immunomodulatory drugs (DMARDs, monoclonal antibodies or small molecule drugs)
- Donor eligibility criteria:
 - * Signed informed consent
 - * At least positive for 1 q-PCR test for SARS-CoV-2
 - * 14 days of COVID-19 clinical remission
 - * Positive serologic test for SARS-CoV-2
 - * Requirements to donate according to NOM-253-SSA1-2012
 - * To accept sample storing for future study
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: 200 mL
 - * Number of doses: 2
 - * Antibody test and antibody-titre: yes
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: yes
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: at least 14 days from resolution of COVID-19-associated symptoms including fevers
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients in ICU
- Comparator: placebo
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * All-cause mortality (time frame: 30 days)
 - * Side effects (time frame: 30 days)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported

NCT04452812 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: reported (30 days)
 - * Admission on the ICU: reported (inclusion criteria)
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes:
 - * Inflammatory biomarkers (d-dimer) (time frame: 21 days)
 - * Inflammatory biomarkers (CRP) (time frame: 21 days)
 - * Inflammatory biomarkers (LDH) (time frame: 21 days)
 - * Inflammatory biomarkers (ferritin) (time frame: 21 days)

Starting date	6 July 2020
Contact information	Julio César Martínez Gallegos, MD, MSc8113852249juliomartinez.18@hotmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 1 April 2021 • Sponsor/funding: Universidad Autonoma de Coahuila

NCT04456413

Study name	Phase II randomized study of convalescent plasma from recovered COVID-19 donors collected by plasmapheresis as treatment for subjects with early COVID-19 infection
Methods	<ul style="list-style-type: none"> • Trial design: randomised • Sample size: 306 • Setting: early stage, high-risk hospitalisation • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04456413 • Date of registration: 2 July 2020

NCT04456413 (Continued)

Participants

- Inclusion criteria:
 - * Patient age > 30 years old, newly diagnosed with a COVID-19 infection with onset of first symptoms < 96 h
 - * And least one other high-risk feature:
 - Age > 65
 - BMI ≥ 3
 - Hypertension, defined as SBP > 140 or DBP > 90, or requiring medication for control
 - Coronary artery disease (history, not ECG changes only)
 - Congestive heart failure
 - Peripheral vascular disease (includes aortic aneurysm ≥ 6 cm)
 - Cerebrovascular disease
 - Dementia
 - Chronic pulmonary disease
 - Liver disease (such as portal hypertension, chronic hepatitis)
 - Diabetes (excludes diet-controlled alone)
 - Moderate or severe renal disease defined as having a GFR < 60 mL/min
 - Cancer (exclude if > 5 years in remission)
 - AIDS (not just HIV-positive)
- Exclusion criteria:
 - * History of severe transfusion reaction to plasma products
 - * Need for oxygen supplementation
 - * Positive test for COVID-19 antibodies
 - * Chemotherapy-induced neutropenia (ANC < 0.5 x 10³/mL)
 - * Immunosuppressive medications except for prednisone (or steroid equivalent) > 10 mg daily
 - * Performance status < 50 by KPS scale
 - * Pneumonia by radiographic evaluation
- Donor eligibility criteria:
 - * Age 18-60
 - * A history of a positive nasopharyngeal swab for COVID-19 or a history of positive antibody titre test
 - * At least 14 days from resolution of COVID-19-associated symptoms including fevers
 - * A negative nasopharyngeal swab (or similar test) for COVID-19
 - * Anti-SARS-CoV2 titres > 1:500
 - * Adequate venous access for apheresis
 - * Meets donor eligibility criteria in accordance to Hackensack University Medical Center (HUMC) Collection Facility at the John Theurer Cancer Center (JTCC) if collecting at the JTCC, and all regulatory agencies as described in SOP 800 01
 - * Required testing of the donor and product must be performed in accordance to FDA regulations (21 CFR 610.40), and the donation must be found suitable (21 CFR 630.30)
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: NR
 - * Number of doses: NR
 - * Antibody test and antibody-titre: > 1:500
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: yes

NCT04456413 (Continued)

- Details of donors:
 - * Gender: both
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: at least 14 days from resolution of COVID-19-associated symptoms including fevers
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator: nil
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * Hospitalisation rate (up to 10 days)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: rate of virologic clearance by nasopharyngeal swab at 2 and 4 weeks

NCT04456413 (Continued)

- Additional outcomes:
 - * Time to symptoms resolution
 - * Rate of nasopharyngeal swab positivity in donors
 - * Rate of donor titres level
 - * Impact of donor titres level on efficacy
 - * Participants' anti-SARS-CoV2 titre assessment pre-infusion for the treatment group, at 2 weeks, 4 weeks and 2 months
 - * Univariate test will be performed in terms of identifying the association between exploratory objective and the hospitalisation rate, Mantel-Haenszel test for categorical variables, and t-test or its non-parametric version for the continuous variables based on the normalised of the data
 - * Plasma product's cytokine level assessment (time frame: Day 0)
 - * Plasma product's mannose-binding lectin (MBL) level assessment (time frame: Day 0)
 - * Plasma product's procalcitonin (PCT) level assessment (time frame: Day 0)
 - * Plasma product's CRP level assessment (time frame: Day 0)
 - * Plasma product's human neutrophil lipocalin (HNL) level assessment (time frame: Day 0)
 - * Plasma product's annexin V level assessment (time frame: Day 0)
 - * Plasma product's surfactant protein D (SP-D) level assessment (time frame: Day 0)
 - * Plasma product's microRNA level assessment (time frame: Day 0)
 - * Plasma product's immunoglobulin level assessment (time frame: Day 0)
 - * Patients' cytokines levels assessment at +2 and +4 weeks post-randomisation (time frame: 2 weeks and 4 weeks)
 - * Patients' chemokines levels assessment at +2 and +4 weeks post-randomisation (time frame: 2 weeks and 4 weeks)

Starting date	July 2020
Contact information	<ul style="list-style-type: none"> • Contact: Mariefel Vendivil551-996-5828 Mariefel.Vendivil@HackensackMeridian.org • Contact: Marlo Kemp551-996-4464 Marlo.Kemp@HackensackMeridian.org
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: July 2021 • Sponsor/funding: University of California, Los Angeles

NCT04458363

Study name	Convalescent plasma to optimize treatment of COVID-19 disease in pediatric patients: a feasibility study
Methods	<ul style="list-style-type: none"> • Trial design: single-arm interventional • Sample size: 50 • Setting: hospitalised • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04458363 • Date of registration: 7 July 2020

NCT04458363 (Continued)

Participants

- Inclusion criteria:
 - * Aged 0-22 years of age
 - * SARS-CoV-2 infection documented by RNA RT-PCR detection
 - * Admitted to an acute care facility
 - * Ability of patient or guardian to provide consent and assent (if applicable); if patient is intubated assent may be waived
 - * Severe COVID-19 disease, OR
 - * Moderate disease with a risk of progression to severe or life threatening disease, OR
 - * Severely immunocompromised patient with any illness attributed to COVID-19 disease requiring inpatient care
- Exclusion criteria:
 - * Pregnancy/breastfeeding
 - * Medical condition that increases the risk of plasma infusion
 - * Contraindication to transfusion (severe volume overload, history of anaphylaxis to blood products)
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: 10 mL/kg/dose (up to 2 units per dose)
 - * Number of doses: 2
 - * Antibody test and antibody-titre: > 1:500
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: yes
- Details of donors:
 - * Gender: both
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: at least 14 days from resolution of COVID-19-associated symptoms including fevers
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator: nil
- Concomitant therapy: NR
- Duration of follow-up: 1 year
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * safety (Grade 3-5 AE over 28 days)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported

NCT04458363 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response:
 - SARS-CoV-2 antibody titre (time frame: up to 28 days)
 - SARS-CoV-2 neutralizing titre (time frame: up to 28 days)
- Additional outcomes:
 - * Number of participants with progression to renal dysfunction and/or multisystem organ failure (time frame: up to 1 year)
 - * IL-6 level (time frame: up to 28 days)
 - * Number of anti-SARS CoV 2-specific T cells (time frame: up to 28 days)
 - * Diversity of circulating T cells (time frame: up to 28 days)

Starting date	July 2020
Contact information	Preeti Jaggi, MD (404) 785-5437 preeti.jaggi@emory.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: June 2022 • Sponsor/funding: Emory University

NCT04462848

Study name	Phase I study of the safety and pharmacokinetics of human convalescent plasma in high risk children exposed or infected with SARS-CoV-2
Methods	<ul style="list-style-type: none"> • Trial design: single-arm interventional • Sample size: 30 • Setting: paediatric patients with underlying medical conditions (cardiovascular disease, lung disease, immunosuppression) who are either infected with SARS-CoV-2 or who have had a high-risk exposure • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04462848 • Date of registration: 8 July 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Age \geq 1 month and < 18 years at the time of consent. * Determined to be at high-risk for severe SARS-CoV-2 disease based on the American Academy of Pediatrics definition of immunocompromised children and reported high-risk paediatric subpopulations. These include the following groups: immunocompromised, haemodynami-

NCT04462848 (Continued)

cally significant cardiac disease (e.g. congenital heart disease), lung disease with chronic respiratory failure, infant, i.e. child \leq 1 year old

- * Confirmed SARS-CoV-2 infection OR high-risk exposure as defined:
 - Confirmed infection: child who tested positive for COVID-19 and is \leq 96 h after onset of symptoms (and within 120 h at the time of receipt of study plasma)
 - High-risk exposure: susceptible child who was not previously infected or otherwise immune to SARS-CoV-2 and exposed within 96 h prior to enrolment (and within 120 h at the time of receipt of study plasma). Both criteria below should be met:
 - A household member or daycare center (same room) exposure to a person with confirmed SARS-CoV-2 OR with clinically compatible disease in areas with widespread ongoing transmission
 - Negative for SARS-CoV-2 (nasopharyngeal or oropharyngeal swab)
- * For women of reproductive potential (defined as having experienced menarche), not pregnant based on testing performed at screening
- * Parent or legal guardian able and willing to provide signed parent permission
- Exclusion criteria:
 - * History of severe reactions (e.g. anaphylaxis) to transfusion of blood products. Individuals with minor reactions such as fever, itching, chills, etc. that resolve spontaneously or respond to pre-medications, and that do not represent more significant allergic reactions, will not be excluded
 - * For women, breastfeeding, or planning to become pregnant/breastfeed during the study period
 - * Participant is unlikely to adhere to the study procedures, keep appointments, or is planning to relocate outside the greater Los Angeles area during the study
 - * Any condition that would, in the opinion of the principal investigator, place the participant at an unacceptable risk of injury or render the participant unable to meet the requirements of the protocol
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: 5 mL/kg up to maximum 500 mL
 - * Number of doses: 1
 - * Antibody test and antibody-titre: NR
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator: nil
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * Cumulative incidence of Grade 3 and Grade 4 AEs, SAEs
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR

NCT04462848 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: reported (Serum concentration at baseline, Day 7, Day 14, and Day 28 for anti-SARS-CoV-2 antibodies, Percentage of participants with a natural antibody response to SARS-CoV-2 infection)
- Additional outcomes: NR

Starting date	August 2020
Contact information	Jaime G Deville, M.D.310-825-9660jdeville@mednet.ucla.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: December 2024 • Sponsor/funding: University of California, Los Angeles

NCT04463823

Study name	"NORPLASMA" COVID-19 convalescent plasma treatment monitoring study
Methods	<ul style="list-style-type: none"> • Trial design: observational prospective • Sample size: 500 • Setting: hospitalised patients • Country: Norway • Language: English • Number of centres: 1 • Trial registration number: NCT04463823 • Date of registration: 9 July 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * patients treated with COVID-19 CP * patients who provided informed consent or where nearest relative gave consent • Exclusion criteria: <ul style="list-style-type: none"> * patients included in other clinical studies of COVID-19 treatment * consent not given • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy

NCT04463823 (Continued)

- Details of CP:
 - * Type of plasma: CP
 - * Volume: NR
 - * Number of doses: NR
 - * Antibody test and antibody-titre: NR
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator: nil
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * observation (time frame: up to 2 years) clinical data and lab results from participants who receive COVID-19 CP on a clinical indication, are being collected for later analysis
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: NR

Starting date 6 July 2020

Contact information

- Contact: Lise Sofie Haug Nissen-Meyer, Ph.D+47 22117828 lisoha@ous-hf.no
- Contact: Tor Audun Hervig, Ph.D tor.audun.hervig@helse-fonna.no

Notes

- Recruitment status: recruiting
- Prospective completion date: 31 May 2025
- Sponsor/funding: Oslo University Hospital

NCT04467151

Study name	A randomized, double-blind, placebo-controlled trial of anti-SARS-CoV-2 plasma in hospitalized non-ICU patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: randomised sequential assignment 2:1 (CP:placebo) • Sample size: 96 • Setting: hospitalised patients, not yet admitted to ICU • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04467151 • Date of registration: 10 July 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Patients ≥ 18 years of age * Hospitalised with COVID-19-related acute respiratory symptoms * Initial COVID-19 severity status on the WHO Ordinal Scale for Clinical Improvement = 3 ("Hospitalized, no oxygen therapy) or 4 ("Hospitalized, on oxygen by mask or nasal prongs") * Laboratory-confirmed COVID-19 * First signs of infection occurring ≤ 14 days prior to enrolment • Exclusion criteria: <ul style="list-style-type: none"> * Receipt of pooled immunoglobulin in the past 30 days * Contraindication to transfusion or history of prior reactions to transfusion blood products * Admission to ICU at any point during hospital course prior to enrolment • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: 250-300 mL * Number of doses: 1 * Antibody test and antibody-titre: NR * Pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody: NR * Severity of disease: NR * Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients, not yet admitted to ICU • Comparator: albumin (placebo) • Concomitant therapy: NR • Duration of follow-up: NR • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Disease progression as measured by WHO scale • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR

NCT04467151 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: reported
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes:
 - * Comparison of maximum WHO score per group
 - * Comparison of decrease of median and maximum WHO score per group
 - * Comparison of time to reach score of "6" or greater on the WHO scale

Starting date	August 2020
Contact information	Contact: Diane F McIntee, MS323-409-5814 mcintee@usc.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: December 2021 • Sponsor/funding: Kashif Khan

NCT04468009

Study name	Treatment of critically ill patients with COVID-19 with convalescent plasma
Methods	<ul style="list-style-type: none"> • Trial design: randomised sequential assignment • Sample size: 36 • Setting: critically ill requiring mechanical ventilation • Country: Argentina • Language: English • Number of centres: 1 • Trial registration number: NCT04468009 • Date of registration: 13 July 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age: ≥ 18 years * Patient with COVID-19 confirmed with nuclear acid testing * Critically ill patients with COVID-19 on mechanical ventilation. Potentially critically ill patients (with ARDS, septic shock and/or multiple organ failure) with COVID-19 * Diagnosed with ARDS * Informed consent

NCT04468009 (Continued)

- Exclusion criteria:
 - * No consent
 - * Symptoms for a period > 20 days
 - * Not detectable by acid nuclear testing within 48 h prior to eligibility
 - * Descompensated congestive heart failure, in which receiving 500 mL of IV volume signifies a life risk
 - * History of severe adverse events or anaphylaxis to plasma components
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: NR
 - * Number of doses: NR
 - * Antibody test and antibody-titre: NR
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): critically ill, requiring mechanical ventilation
- Comparator: standard care
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * ICU mortality (time frame: mortality at 30, 90 days)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR

NCT04468009 (Continued)

- Additional outcomes:
 - * SOFA score of study days 1, 3, 5, 7, 14 and 28 (time frame: study days 1, 3, 5, 7, 14 and 28)
 - * Need for supportive therapy after enrolment (time frame: duration of supportive therapy through study completion, an average of 3 months)
 - * Days without vasopressors after enrolment (time frame: days without vasopressors through study completion, an average of 3 months)
 - * Changes in chest X-ray (time frame: changes in chest X-ray through study completion, an average of 3 months)

Starting date	25 June 2020
Contact information	Contact: Carlos A Gonzalez, MD+54 9 1157233801 carlosgonzalez@buenosaires.gob.ar
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: June 2021 • Sponsor/funding: Hospital de Infecciosas Francisco Javier Muniz

NCT04471051

Study name	An observational cohort trial of outcomes and antibody responses following treatment with COVID-19 convalescent plasma in hospitalized COVID-19 patients
Methods	<ul style="list-style-type: none"> • Trial design: prospective, observational cohort trial • Sample size: 150 • Setting: hospitalised patients • Country: USA • Language: English • Number of centres: 6 • Trial registration number: NCT04471051 (CP from Expanded Access protocol NCT04372368) • Date of registration: 14 July 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age \geq 18 years * Hospitalised with COVID-19 respiratory symptoms and confirmation via COVID-19 SARS-CoV-2 RT-PCR testing * Patient treated with COVID-19 CP * Patient or surrogate designated decision maker is willing and able to provide written informed consent. • Exclusion criteria: <ul style="list-style-type: none"> * Receipt of pooled immunoglobulin in past 30 days * Contraindication to transfusion or history of prior reactions to transfusion blood products • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: NR * Number of doses: NR * Antibody test and antibody-titre: NR * Pathogen inactivated or not: NR * RT-PCR tested: NR

NCT04471051 (Continued)

- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator: nil
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * Inpatient mortality (time frame: hospital admission up to Day 28 or discharge)
 - * Requirement for mechanical ventilation (time frame: hospital admission up to Day 28 or discharge)
 - * Transfer to ICU (time frame: hospital admission up to Day 28 or discharge)
 - * ICU mortality (time frame: hospital admission up to Day 28 or discharge)
 - * ICU length of stay (time frame: hospital admission up to Day 28 or discharge)
 - * Hospital mortality (time frame: hospital admission up to Day 28 or discharge)
 - * Hospital Length of Stay (time frame: hospital admission up to Day 28 or discharge)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: NR

Starting date 30 April 2020

 Contact information Contact: John D Beckham, MD303-724-4927 David.beckham@cuanschutz.edu

- Notes
- Recruitment status: recruiting
 - Prospective completion date: April 2021
 - Sponsor/funding: University of Colorado, Denver

NCT04472572

Study name Expanded access to convalescent plasma for the treatment of patients with COVID-19

NCT04472572 (Continued)

Methods	<ul style="list-style-type: none"> • Trial design: expanded access • Sample size: nil • Setting: severe or life-threatening disease • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04472572 • Date of registration: 15 July 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * provide access to investigational CP for patients at Hackensack University Medical Center infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease * informed consent • Exclusion criteria: NR • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: 200-500 mL of ABO compatible CP * Number of doses: NR * Antibody test and antibody-titre: yes, no details regarding type of test or titre * Pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody: NR * Severity of disease: NR * Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): severe-life-threatening disease • Comparator: No CP • Concomitant therapy: NR • Duration of follow-up: NR • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Safety (SAE) • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: reported * Time to death: reported

NCT04472572 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported (days intubated)
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: NR

Starting date	15 July 2020
Contact information	Principal Investigator: Michele Donato, Hackensack Meridian Health
Notes	<ul style="list-style-type: none"> • Recruitment status: temporarily not available • Prospective completion date: NR • Sponsor/funding: Hackensack Meridian Health

NCT04474340

Study name	COVID-19 convalescent plasma treatment in SARS-CoV-2 infected patients: multicenter interventional study
Methods	<ul style="list-style-type: none"> • Trial design: non-randomised parallel assignment • Sample size: 200 • Setting: moderate or severe cases • Country: Kuwait • Language: English • Number of centres: 1 • Trial registration number: NCT04474340 • Date of registration: 16 July 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Patients aged ≥ 18 years old (those who are younger are involved after case-based discussion) * Confirmed laboratory diagnosis with SARS-CoV-2, and admission diagnosis of SARS-CoV-2 * Patients with moderate or severe COVID-19 (moderate COVID-19 disease defined as the presence of any signs of pneumonia (fever, cough, dyspnoea fast breathing) including SpO₂ > 90 on room air, but no signs of severe pneumonia (severe pneumonia have the above plus one of the following: respiratory rates > 30 breaths/min or SpO₂ < 90% on room air), or admission to ICU for respiratory support (i.e. high-flow nasal cannula, non-invasive mechanical ventilation and intubation) • Exclusion criteria <ul style="list-style-type: none"> * Contraindication to transfusion (volume overload, history of anaphylaxis to blood products) * Patients presenting with acute severe multi-organ failure, haemodynamic instability * DIC, septic shock and those with expected survival of < 48 h • Donor eligibility criteria: NR

NCT04474340 (Continued)

	<ul style="list-style-type: none"> • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: 200-250 mL/h * Number of doses: 1-2 * Antibody test and antibody-titre: yes, no details regarding type of test or titre * Pathogen inactivated or not: yes * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody: negative HLA * Severity of disease: NR * Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): moderate-severe disease • Comparator: no CP • Concomitant therapy: standard care • Duration of follow-up: up to 30 days • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Time to improvement • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: reported (up to 30 days) * Time to death: reported (up to 30 days) • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported * WHO ordinal scale: reported * 30-day and 90-day mortality: reported (30-day) * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR * Virological response: NR • Additional outcomes: NR
Starting date	21 May 2020
Contact information	Contact: Sundos Alsharida, 0096566691663, salsharidah@moh.gov.kw
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 30 December 2020 • Sponsor/funding: Ministry of Health, Kuwait

NCT04476888

Study name	Convalescent plasma treatment in COVID-19 patients at a tertiary care center in Pakistan
Methods	<ul style="list-style-type: none"> • Trial design: non-randomised parallel assignment • Sample size: 100 • Setting: severe or life-threatening cases • Country: Pakistan • Language: English • Number of centres: 1 • Trial registration number: NCT04476888 • Date of registration: 20 July 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Inpatients at Aga Khan University with positive SARS-CoV-2 infection by rRT-PCR and who have provided written informed consent for inclusion in the trial; * Age \geq 18 years; * Severe or immediately life-threatening COVID-19 defined by any of: <ul style="list-style-type: none"> <input type="checkbox"/> Respiratory rate \geq 30/min <input type="checkbox"/> Blood oxygen saturation \leq 93% at room air <input type="checkbox"/> PaO₂/FiO₂ < 300 <input type="checkbox"/> Lung infiltrates > 50% within 24-48 h on radiology (X-ray or CT scan) <input type="checkbox"/> Need for mechanical ventilation <input type="checkbox"/> respiratory failure <input type="checkbox"/> septic shock <input type="checkbox"/> multiple organ dysfunction or failure • Exclusion criteria <ul style="list-style-type: none"> * Negative rRT-PCR from respiratory secretions or blood within 48 h prior to assessment of eligibility * History of allergic reaction to blood or plasma products (as judged by the investigator) * Medical conditions in which receipt of 500 mL IV volume may be detrimental to the patient (e.g. actively decompensated congestive heart failure) * Enrollment in any other clinical trial for an investigational therapy • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: 500 mL * Number of doses: 1 * Antibody test and antibody-titre: NR * Pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody: NR * Severity of disease: NR * Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): severe or life-threatening disease • Comparator: no CP • Concomitant therapy: steroids, tocilizumab, azithromycin and supportive care • Duration of follow-up: up to 1 month

NCT04476888 (Continued)

	<ul style="list-style-type: none"> • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Length of stay, mortality, adverse events • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: reported * Time to death: reported (up to 1 month) • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported * Number of participants with SAEs: reported * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported * WHO ordinal scale: reported * 30-day and 90-day mortality: reported (30-day) * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: reported * QoL: NR * Virological response: NR • Additional outcomes: laboratory parameters (serum ferritin, procalcitonin, CRP, D dimer, full blood exam), chest X-ray findings
Starting date	-
Contact information	<ul style="list-style-type: none"> • Contact: Muhammad Hasan, MBBS, FCPS00923333710453hasan.hayat@aku.edu • Contact: Natasha Ali, FCPS, MSc00923009202079natasha.ali@aku.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: September 2020 • Sponsor/funding: Aga Khan University

NCT04479163

Study name	Prevention of severe COVID-19 in infected elderly by early administration of convalescent plasma with high-titers of antibody against SARS-CoV2
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 210 • Setting: elderly within 48 h of symptoms • Country: Argentina • Language: English • Number of centres: 7 • Trial registration number: NCT04479163 • Date of registration: 21 July 2020

NCT04479163 (Continued)

Participants

- Inclusion criteria
 - * Age \geq 75 or age 65-74 with at least 1 of the following comorbidities: arterial hypertension, diabetes, obesity, COPD, heart disease, chronic kidney disease
 - * Last 48 h: axillary temperature \geq 37.5 °C or febrile equivalent, one or a combination of
 - dry cough
 - breathing difficulty
 - odinophagia
 - anosmia/dysgeusia
 - any of the following symptoms: fatigue, anorexia, myalgias or rhinorrhoea
 - * Confirmed diagnosis SARS-CoV-2 by RT-PCR
 - * Give informed consent
- Exclusion criteria
 - * Severe respiratory disease
 - * Cardiac insufficiency
 - * Chronic renal failure
 - * Primary hypogammaglobulinemias
 - * Myelodysplastic syndromes
 - * Chronic linfoproliferative syndromes
 - * Monoclonal gammopathies
 - * Known hypersensibility
 - * Active cancer
 - * HIV, HBV or HCV infection
 - * Chronic administration of immunosuppressants
 - * Body transplant history
 - * Chronic liver disease
 - * Chronic lung disease with oxygen requirement
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP with an IgG titre against SARS-CoV-2
 - * Volume: 250 mL
 - * Number of doses: 1
 - * Antibody test and antibody-titre: spike (S) protein $>$ 1:1,000 (COVIDAR IgG, Insituto Leloir, Argentina)
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage, within 72 h of symptoms
- Comparator: placebo (normal saline)
- Concomitant therapy: NR
- Duration of follow-up: $>$ 25 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * Development of severe respiratory disease

NCT04479163 (Continued)

- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: yes (up to 25 days)
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: NR

Starting date	4 June 2020
Contact information	<ul style="list-style-type: none"> • Contact: Fernando P Polack, MD, 54 11 4632 8216, fpolack@infant.org.ar • Contact: Romina P Libster, MD, 54 11 4632 8216, rlibster@infant.org.ar
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 30 July 2020 • Sponsor/funding: Fundacion Infant

NCT04483960

Study name	An international multi-centre randomised clinical trial to assess the clinical, virological and immunological outcomes in patients diagnosed with SARS-CoV-2 infection (COVID-19)
Methods	<ul style="list-style-type: none"> • Trial design: RCT (randomised factorial design, participants enrolled into the study have the option of deciding whether to be randomised in one or both (if available) treatment domains concurrently, if they meet the eligibility criteria) • Sample size: 2400 • Setting: hospitalised patients • Country: Australia • Language: English • Number of centres: 77 • Trial registration number: NCT04483960 • Date of registration: 23 July 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age \geq 18 years * Confirmed SARS-CoV-2 by nucleic acid testing in the past 12 days * Able to be randomised within 12 days of symptom onset * Expected to be remain an inpatient for at least 48 h from the time of randomisation • Exclusion criteria <ul style="list-style-type: none"> * Overall exclusions: <ul style="list-style-type: none"> <input type="checkbox"/> Currently receiving acute intensive respiratory support (invasive or noninvasive ventilation) or vasopressor/inotropic support. Note, participants already on non-invasive ventilation

NCT04483960 (Continued)

(either CPAP or BiPAP) in the community can still be recruited if they are continuing on their usual degree of non-invasive ventilation. Humidified high-flow nasal oxygen will not be considered an exclusion criterion

- Previous participation in the trial
- Known pregnancy
- Treating team deems enrolment in the study is not in the best interests of the patient
- Death is deemed to be imminent and inevitable within the next 24 h
- Enrolment to other study protocols that do not allow co-enrolment in ASCOT
- * Domain 2 (CP) specific exclusions:
 - CP not available at trial site
 - Participant has already received treatment with non-trial prescribed SARS-CoV-2-specific immunoglobulin therapy (CP, hyperimmune globulin or monoclonal antibody)
 - Known previous history of TRALI
 - Known previous history of serious allergic reaction to blood product transfusion
 - Known religious objection to receiving blood products
 - Treating team deems enrolment in antibody interventions is not in the best interests of the patient
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: C)
 - * Volume: NR
 - * Number of doses: 2 (days 1, 2)
 - * Antibody test and antibody-titre: NR
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients currently not receiving invasive/noninvasive ventilation
- Comparator: no CP, also antiviral domain (antiviral - standard of care, lopinavir/ritonavir, lopinavir and ritonavir + hydroxychloroquine)
- Concomitant therapy: standard of care, antiviral domain
- Duration of follow-up: 90 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * Proportion of participants alive and not having required new intensive respiratory support (invasive or non-invasive ventilation) or vasopressors/inotropic support in the 28 days after randomisation (time frame: 28 days)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: yes
 - * Time to death: yes

NCT04483960 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: reported
 - * 30-day and 90-day mortality: reported
 - * Admission on the ICU: reported
 - * Length of stay on the ICU: reported
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: viral clearance (at 3 and 7 days)
- Additional outcomes:
 - * Presence of chest infiltrates on chest X-ray or CT (time frame: 3 and 7 days)
 - * Time to defervescence from randomisation (time frame: 28 days)
 - * Biomarker levels (time frame: 28 days)
 - * Antibiotic use (time frame: 10 days)
 - * AEs (time frame: 10 days)
 - * Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital (time frame: 28 days)
 - * Acute kidney injury (time frame: 28 days)
 - * Thrombotic events (-time frame: 28 days)

Starting date	21 July 2020
Contact information	<ul style="list-style-type: none"> • Jocelyn Mora, +61 3 8344 0770, jocelyn.mora@unimelb.edu.au • Naomi Perry, +61 3 8344 0770, naomi.perry@unimelb.edu.au
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 12 June 2022 • Sponsor/funding: University of Melbourne

NCT04492501

Study name	Investigational treatments for COVID-19 in tertiary care hospital of Pakistan
Methods	<ul style="list-style-type: none"> • Trial design: non-randomised factorial assignment • Sample size: 600 • Setting: hospitalised patients • Country: Pakistan • Language: English • Number of centres: 1 • Trial registration number: NCT04492501 • Date of registration: 30 July 2020

NCT04492501 (Continued)

Participants

- Inclusion criteria:
 - * PCR-positive-confirmed COVID-19
 - * Admitted in hospital
 - * Patients willing to participate in trial
 - * Day of illness < 14 days
 - * No contraindications to invasive procedure or novel therapies
- Exclusion criteria:
 - * Comorbidities with life expectancy < 6 months
 - * Multi-organ failure
 - * Septic shock before initiation of treatment
 - * Congestive cardiac failure (ejection fraction < 20%)
 - * Those receiving immunotherapy, anti-thymocyte globulin or hematopoietic stem cell transplant in recent past
 - * Patients of haematological or solid organ malignancies
- Donor eligibility criteria:
 - * After 28 days of illness to 3 months
 - * Symptom-free 2 weeks prior to donation
 - * Negative 2 consecutive PCRs any time between initial positivity and before donation
 - * Anti SARS-CoV-2 IgG-positive, IgM-negative
 - * Fulfills healthy donor criteria as per WHO/AABB guidelines
 - * Volume of plasma to be collected: 900-1200 mL through apheresis OR plasma separated from phlebotomy donation
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - * Type of plasma: CP
 - * Volume: 200-400 mL
 - * Number of doses: 1
 - * Antibody test and antibody-titre: IgG titre of > 1.320
 - * Pathogen inactivated or not: NR
 - * RT-PCR tested: NR
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease:
 - After 28 days of illness to 3 months
 - Symptom-free 2 weeks prior to donation
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients, within 14 days of illness
- Comparator: supportive care, procedure: therapeutic plasma exchange, tocilizumab, remdesivir, mesenchymal stem cell therapy
- Concomitant therapy: supportive care
- Duration of follow-up: 90 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * Survival (time frame: 28 days)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: NR
 - * Time to death: NR

NCT04492501 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - * Number of participants with SAEs: NR
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: viral clearance at 45 days
- Additional outcomes:
 - * Time to resolution of cytokine release storm (time frame: 28 days)
 - * Complications (time frame: 90 days)

Starting date	1 April 2020
Contact information	Study Director: Sumaira Irum, MITUNICEF
Notes	<ul style="list-style-type: none"> • Recruitment status: completed • Prospective completion date: 20 July 2020 • Sponsors: UNICEF, Pak Emirates Military Hospital Rawalpindi

NCT04497324

Study name	PERUCONPLASMA: randomized clinical trial to evaluate safety and efficacy of the use of convalescent plasma in hospitalized patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: multicentre, randomised, open, parallel, controlled trial • Sample size: e.g. 50 in each arm (100) • Setting: Inpatient • Country: Peru • Language: English • Number of centres: 1 • Trial registration number: NCT04497324; PER-016-20 20997 (Registry Identifier: Peruvian Clinical Trial Registry (REPEC))- Prospective • Date of registration: 4 August 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Hospitalised ≥ 18 years patient with COVID-19 disease, confirmed by a molecular test or a serologic test, along with a typical COVID-19 clinical presentation * Severe or critical disease caused by COVID-19. Severe disease is defined as ≥ 2 of the following criteria: <ul style="list-style-type: none"> <input type="checkbox"/> Respiratory frequency > 22 <input type="checkbox"/> O₂ saturation $\leq 93\%$ <input type="checkbox"/> PaO₂ 50 mmHg <input type="checkbox"/> PaO₂/FiO₂ < 300 * Or critical disease with ≥ 1 of the following criteria: <ul style="list-style-type: none"> <input type="checkbox"/> Respiratory insufficiency with requirement of mechanical ventilation within the last 72h <input type="checkbox"/> Shock * Informed consent signed by patient or direct family member

NCT04497324 (Continued)

- Exclusion criteria
 - * Contraindication for transfusion (history of TRALI or TACO, history of anaphylaxis to blood components)
 - * Multi-organ failure, defined by a SOFA score of > 5
 - * haemodynamically unstable, with mean arterial pressure < 60 mmHg, refractory to vasopressors use
 - * Uncontrolled concomitant infection
 - * DIC
 - * Myocardial infarction
 - * Acute coronary disease
 - * Patient on dialysis
 - * Intracranial bleeding active within the last 7 days
 - * Pregnancy

Interventions

- Intervention(s): CP therapy vs standard care
- Details of CP:
- Type of plasma: details or NR
 - * Volume: 200 mL-250 mL per dose
 - * Number of doses: 1 to 2
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy: within 48 h (possible from admission: unclear) with severe or life-threatening disease
- Comparator: standard of care
- Concomitant therapy: standard care
- Treatment cross-overs: yes/no

Outcomes

- Primary study outcome(s):
 - * Transfusion-related SAEs (time frame: 14 days after randomisation)
 - * Incidence of transfusion-related SAEs, according to the Hemovigilance Module Surveillance Protocol v 2.5.2
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: all-cause in-hospital mortality (time frame: 30 days after randomisation) Death during hospitalisation within the first 30 days after enrolment
 - * Time to death: NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction: yes
 - * Transfusion-related SAEs (time frame: 14 days after randomisation). Incidence of transfusion-related SAEs, according to the Hemovigilance Module Surveillance Protocol v 2.5.2
 - * Number of participants with SAEs: yes. Transfusion-related SAEs
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: yes. Duration of mechanical ventilation (time frame: 30 days after randomisation or until hospital discharge, whatever comes first). Number of days from date of intubation to date of successful extubation
 - * 30-day and 90-day mortality: all-cause in-hospital mortality (time frame: 30 days after randomisation). Death during hospitalisation within the first 30 days after enrolment
 - * Admission on ICU: no. Clinical Improvement at 14 days (time frame: At 3, 14 and 30 days after randomisation). Improvement of ≥ 2 points in the WHO progression scale
 - * Length of stay on the ICU: Yes. Length of ICU stay (time frame: 30 days after randomisation or until hospital discharge, whatever comes first)
 - * Number of days from date of admission to the ICU to date of discharge from ICU
 - * Time to discharge from hospital: Yes. Length of hospital stay (time frame: 30 days after randomisation or until hospital discharge, whatever comes first)
 - * Number of days from date of enrolment to date of discharge

NCT04497324 (Continued)

	<ul style="list-style-type: none"> • Additional outcomes <ul style="list-style-type: none"> * Proportion of viral nucleic acid negatives (3 days after transfusion): no * Results of lab tests and vital signs: no
Starting date	20 August 2020
Contact information	Contact: Fiorella Krapp Lopez, MD, MSc (511) 3190000 ext 201353 fiorella.krapp@upch.pe Contact: Patricia Garcia Funegra, MD patricia.garcia@upch.pe
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 31 December 2020 • Sponsor: Universidad Peruana Cayetano Heredia

NCT04497779

Study name	Evaluation of coronavirus disease 19 (COVID-19) convalescent plasma
Methods	<ul style="list-style-type: none"> • Trial design: observational • Sample size: 800 • Setting: not specified • Country: USA • Language: English • Number of centres: 1 • Trial registration number: prospective- NCT04497779 • Date of registration: 4 August 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Be willing to provide blood samples * Permit medical record review * Have documented informed consent * ≥ 18 years • Exclusion criteria: NR • Donor eligibility criteria: <ul style="list-style-type: none"> * COVID-19 CP volunteers must meet all regulatory requirements for conventional plasma and FDA's additional considerations for COVID-19 CP * Be willing to complete a questionnaire * Be willing to donate blood samples * Permit medical record review * Have documented informed consent * If volunteers can't provide evidence of COVID-19, but are otherwise eligible, then we will test them for SARS-CoV-2 antibodies to confirm eligibility • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: NR * Number of doses: NR * Antibody test and antibody-titre: SARS-CoV-2 immunoassay, coronavirus (CoV) PepSeq assay, and SARS-CoV-2 lenti-based neutralising antibody titre * Pathogen inactivated or not: NR * RT-PCR tested: NR

NCT04497779 (Continued)

- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: nil
- Concomitant therapy: NR
- Duration of follow-up: 12 months
- Treatment cross-overs: nil
- Details of donors:
 - * Gender: NR
 - * HLA and HNA antibody: NR
 - * Severity of disease: NR
 - * Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: nil
- Concomitant therapy: NR
- Duration of follow-up: 12 months
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - * CP units infused in COVID-19 patients (time frame: up to 12 months after enrolment)
 - * All-cause mortality (time frame: at day 28 post-CP infusion)
 - * Donor antibody levels (time frame: up to 28 days post-CP infusion)
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: reported
 - * Time to death: reported
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - * WHO ordinal scale: reported
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: reported
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: nil

Starting date 21 August 2020

 Contact information Contact: John Zaia 626-218-1817 jzaia@coh.org

- Notes
- Recruitment status: not yet recruiting
 - Prospective completion date: 21 August 2022
 - Sponsor: City of Hope Medical Center

NCT04502472

Study name	Open-label treatment of severe coronavirus disease 2019 (COVID-19) with convalescent plasma collected from individuals with documented infection and recovery from COVID-19 (SARS-CoV-2)
Methods	<ul style="list-style-type: none"> • Trial design: open-label. Single-group Assignment • Sample size: 200 • Setting: inpatients • Country: USA • Language: English • Number of centres: 1 • Trial registration number: prospective - NCT04502472 • Date of registration: 6 August 2020
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patients in the Inova Health System with confirmed COVID-19 by PCR testing • Age \geq 13 years • All sexes • Currently hospitalised with COVID-19 infection with severe or life-threatening clinical syndrome as follows: <ul style="list-style-type: none"> * Severe COVID-19: (\geq 3 of the following) <ul style="list-style-type: none"> <input type="checkbox"/> Dyspnea <input type="checkbox"/> Respiratory rate \geq 30/min <input type="checkbox"/> Blood oxygen saturation (SpO₂) \leq 94% on room air <input type="checkbox"/> PaO₂/FiO₂ ratio $<$ 300 <input type="checkbox"/> Pulmonary infiltrates $>$ 50% of lung parenchyma within 24-48 h * Life-threatening disease is defined as: (one of the following) <ul style="list-style-type: none"> <input type="checkbox"/> Respiratory failure <input type="checkbox"/> Septic shock, and/or <input type="checkbox"/> Multiple organ dysfunction or failure • Patient must provide informed consent or have healthcare power of attorney/next of kin provide consent if he/she cannot <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Contraindication to receive plasma as deemed by the treating physician • Severe hypercoagulable state (documented in medical chart or by treating physician assessment) • Absolute IgA deficiency • Prior history of TRALI • Inability to tolerate plasma volume due to severe systolic or diastolic heart failure despite slower infusion and diuretic administration • Positive pregnancy test (HCG)
Interventions	<p>Interventions: COVID-19 CP transfusion</p> <ul style="list-style-type: none"> • Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: NR * Number of doses: NR * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, time of plasma therapy: severe COVID-19 or life-threatening clinical syndrome due to infection • Comparator: none • Concomitant therapy: NR

NCT04502472 (Continued)

	<ul style="list-style-type: none"> Treatment cross-overs: N/A
Outcomes	<ul style="list-style-type: none"> Primary study outcome(s): <ul style="list-style-type: none"> * Change in clinical status (time frame: time of plasma infusion (day 0) compared to day 7) * Change in clinical status as captured by 7-point ordinal scale to include <ul style="list-style-type: none"> <input type="checkbox"/> Death <input type="checkbox"/> Hospitalised, requiring mechanical ventilation or ECMO <input type="checkbox"/> Hospitalised, requiring non-invasive ventilation or high-flow oxygen <input type="checkbox"/> Hospitalised, requiring supplemental oxygen <input type="checkbox"/> Hospitalised, not requiring supplemental oxygen--requiring ongoing medical care (COVID-19 related or otherwise) <input type="checkbox"/> Hospitalised, not requiring supplemental oxygen-not requiring ongoing medical care (COVID-19 related or otherwise) <input type="checkbox"/> Not hospitalised • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes. Mortality (time frame: Day 28). All-cause Mortality <ul style="list-style-type: none"> <input type="checkbox"/> Time to death: change in clinical status (time frame: time of plasma infusion (day 0 prior to first infusion) to days 14, 21, and 28) <input type="checkbox"/> Change in 7-point ordinal scale score from time of plasma infusion (day 0-prior to first infusion) to days 14, 21, and 2 • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction: Yes. Transfusion related events (time frame: Within 6 h of infusion) * Presence of any adverse events related to plasma infusion <ul style="list-style-type: none"> <input type="checkbox"/> Number of participants with SAEs: yes. SOFA score at days 0, 7, 14, 21, 28 (time frame: Days 0, 7, 14, 21, 28). Assess change in SOFA score <input type="checkbox"/> Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: yes * Supplemental oxygen (time frame: Days 7, 14, 21, 28) <ul style="list-style-type: none"> <input type="checkbox"/> Time to discontinuation of supplemental oxygen * Mechanical Ventilation (time frame: Days 7, 14, 21, 28) <ul style="list-style-type: none"> <input type="checkbox"/> Need for mechanical ventilation (for those patients not on the ventilator) <input type="checkbox"/> Change in mechanical ventilation status (time frame: Days 7, 14, 21, 28) <input type="checkbox"/> Time to liberation from mechanical ventilation (for patients on a ventilator) * 30-day and 90-day mortality: yes. Mortality (time frame: Day 28) <ul style="list-style-type: none"> <input type="checkbox"/> All-cause Mortality * Admission on ICU: no. Total duration in hospital instead <ul style="list-style-type: none"> <input type="checkbox"/> Length of stay on the ICU: No. Length of Hospital Stay (time frame: Days 7, 14, 21, 28) * Time to discharge from hospital: yes. Length of hospital stay (time frame: Days 7, 14, 21, 28) • Additional outcomes <ul style="list-style-type: none"> * E.g. proportion of viral nucleic acid negatives (3 days after transfusion): no * E.g. results of lab tests and vital signs: yes. Change in inflammatory markers (time frame: Day 0 to days 7, 14, 21, 28) * Change in standard of care inflammatory markers (ferritin, LDH, CRP, D-dimer)
Starting date	6 June 2020
Contact information	<ul style="list-style-type: none"> Merte Lemme-Woldehanna, BS 703-776-2020 Merte.LemmaWoldeHanna@inova.org Edwinia Battle, BSN 703-776-3067 edwinia.battle@inova.org
Notes	<ul style="list-style-type: none"> Recruitment status: recruiting Prospective completion date: 31 December 2021 Sponsor: Inova Health Care Services

NCT04502472 (Continued)

- Principal Investigator: Anne Brown, MD Inova Health System

NCT04513158

Study name	Convalescent plasma in the early treatment of high-risk patients with SARS-CoV-2 (COVID-19) infection
Methods	<ul style="list-style-type: none"> • Trial design: clinical trial • Sample size: 100 • Setting: inpatient • Country: USA • Language: English • Trial registration: NCT04513158 • Date of registration: 14 August 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Diagnosis of SARS-CoV-2 infection via RT-PCR or FDA-approved testing * Patients must also have the following indications for enrolment: <ul style="list-style-type: none"> <input type="checkbox"/> D-Dimer > 1500 ng/mL FEU AND <input type="checkbox"/> IL-6 > 5 pg/mL * With any of the following: <ul style="list-style-type: none"> <input type="checkbox"/> Lymphocytes < 0.8 10³/ul OR <input type="checkbox"/> LDH > 700 U/L OR <input type="checkbox"/> Creatine kinase > 170 U/L OR <input type="checkbox"/> CRP > 1.0 mg/dL OR <input type="checkbox"/> Ferritin > 1000 ng/mL * AND one of the following: <ul style="list-style-type: none"> <input type="checkbox"/> Age > 60 years <input type="checkbox"/> Underlying active malignancy <input type="checkbox"/> Cardiovascular disease <input type="checkbox"/> Active tobacco use <input type="checkbox"/> History of pulmonary volume reduction surgery <input type="checkbox"/> Hypertension * Prior treatment: patients are still eligible for this trial if active antimicrobial agents are in use. Patients are also eligible if they had been treated on COVID-19 clinical trial in the course of their disease * Age ≥ 18 years * The effects of allogeneic plasma infusion on the developing fetus is unknown. For this reason women who are pregnant are not eligible to participate * Agrees to required laboratory data collected which will include the baseline organ function and regular ongoing assessments done as part of routine care * Ability to understand and the willingness to sign a written informed consent document or ability to have consent provided by LAR • Exclusion criteria: <ul style="list-style-type: none"> * Patients who do not meet above inclusion criteria are not eligible * Patients may not be receiving any other investigational agents * History of allergic reactions attributed to previous transfusion history * Respiratory rate > 30/min * Blood oxygen saturation < 93% * PaO₂/FiO₂ ratio < 300 * Diagnosis of respiratory failure, septic shock or multiple organ dysfunction/failure

NCT04513158 (Continued)

Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: approximately 200 mL * Number of doses: one * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised • Comparator: No • Concomitant therapy: NR • Treatment cross-overs: not applicable
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Determine the therapeutic efficacy (response rate) of CP infusion in patients at high risk for mortality when infected by SARS-CoV-2 (COVID-19) (time frame: through study completion, an average of 30 days) * Measured by respiratory rate > 30/min, blood oxygen saturation < 93%, PaO₂/FiO₂ ratio < 300 and received a medical diagnosis of respiratory failure, septic shock or multiple organ dysfunction/failure • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR * 30-day and 90-day mortality: NR * Admission on the ICU: NR * Length of stay on the ICU: NR * Time to discharge from hospital: NR * QoL: NR • Additional study outcomes: <ul style="list-style-type: none"> * Determine the immunologic effects of CP infusion (time frame: Through study completion, an average of 14 days) * Absolute lymphocyte count (10³/uL) (time frame: Through study completion, an average of 14 days) * Creatinine kinase (mg/dL) (time frame: Through study completion, an average of 14 days) * C-reactive protein (mg/dl) (time frame: Through study completion, an average of 14 days) * D-Dimer (ng/mL FEU) (time frame: Through study completion, an average of 14 days) * Interleukin-6 (pg/mL) (time frame: Through study completion, an average of 14 days) * Ferritin (ng/mL) (time frame: Through study completion, an average of 14 days)
Starting date	14 August 2020
Contact information	Joseph M Flynn, DO, MPH502-272-5001 Joseph.flynn@nortonhealthcare.org Marti Gardner, MSN, APRN502-629-3550 Marti.Gardner@nortonhealthcare.org
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 31 December 2021 • Sponsor/funding: Joseph M Flynn, DO, MPH Norton Healthcare

NCT04516811

Study name	A prospective, randomized, placebo-controlled, double-blinded, phase III clinical trial of the therapeutic use of convalescent plasma in the treatment of patients with moderate to severe COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: randomised, double-blinded, placebo-controlled, phase III clinical trial • Sample size: 600 • Setting: inpatient • Country: South Africa • Language: English • Number of centres: 1 • Trial registration: NCT04516811 • Date of registration: 18 August 2020
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Laboratory-confirmed SARS-CoV-2 by positive RT-PCR on any respiratory sample • Age \geq 18 years • Require hospital admission for COVID-19 pneumonia as defined by the presence of pulmonary infiltrates on chest X-ray • Moderate to severe COVID-19 disease, defined as: SpO₂ \leq 93% on room air; plus requiring non-invasive oxygen therapy (WHO R&D BOSCI 4 or 5) • Signed informed consent • Pregnant women will be allowed to participate <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Current participation in another therapeutic clinical trial for COVID-19 • Invasive mechanical ventilation • Expected survival < 24 h based on clinical assessment (however, the study does not exclude critically ill patients who are not, due to resource limitations, candidates for critical care admission and/or mechanical ventilation) • Known hypersensitivity to immunoglobulin or any components of the formulation
Interventions	<ul style="list-style-type: none"> • Intervention(s): standard care and CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: 200-250 mL * Number of doses: 1 * Antibody test and antibody-titre: NR * Pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: NR * HLA and HNA antibody: NR * Severity of disease: NR * Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): moderate or severe COVID-19 • Comparator: standard care and Saline (200 mL) • Concomitant therapy: NR • Duration of follow-up: NR • Treatment cross-overs: nil

NCT04516811 (Continued)

Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Clinical Improvement (time frame: Day 28). Proportion of participants with successful treatment outcome, defined as clinical improvement (≥ 2 points on WHO R&D BOSCI 1) by Day 28 post-randomisation • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: reported * Time to death: reported • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported * Number of participants with SAEs: reported * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported * WHO ordinal scale: NR * 30-day and 90-day mortality: NR * Admission on the ICU: reported * Length of stay on the ICU: reported * Time to discharge from hospital: reported * QoL: NR * Virological response: reported • Additional outcomes: <ul style="list-style-type: none"> * Inflammatory markers (time frame: Day 28) * Radiography (time frame: Day 28) * Fever and hypoxia (time frame: Day 28) * Participants with HIV infection and other comorbidities (time frame: Day 28) * Timing of IP and efficacy outcome (time frame: Day 28) * Neutralising Ab (time frame: Day 28) * SARS-CoV antibody titre (time frame: Day 28)
Starting date	3 September 2022
Contact information	Contact: Cynthia Nyoni, +27117619279 ext 9279, Cynthia.Nyoni@sanbs.org.za Contact: Mpumi Maxebengula, BCom, +27214066497 ext 6497, mpumi.maxebengula@uct.ac.za
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 31 July 2022 • Sponsor/funding: Karin vandenBerg, Dr, South African National Blood Service

NCT04516954

Study name	Assessment of the safety of convalescent plasma to treat COVID-19 patients with moderate and above illness
Methods	<ul style="list-style-type: none"> • Trial design: single-group interventional trial • Sample size: 10 • Setting: medium stage • Country: Vietnam • Language: English • Number of centres: multi-centre • Trial registration number: prospective - NCT04516954

NCT04516954 (Continued)

	<ul style="list-style-type: none"> • Date of registration: 18 August 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> * Age 18-75 years * SARS-CoV-19 PCR-positive * Medium stage * Time from onset to screening \leq 21 days, the SARS-CoV-2 test is still positive • Exclusion criteria: <ul style="list-style-type: none"> * Patients with a history of autoimmune disease or IgA deficiency * Patients with a history of allergy * Multi-organ/system failure * Pregnant or breastfeeding at the time of study * Cancer, history of heart failure, stroke, bronchial asthma * Multi-organ/system failure with indications for dialysis, severe hypoxia, failure with conventional treatment methods, indications for ECMO * The patient is infected with multidrug-resistant bacteria * The patient is participating in another study * Time from onset to screening $>$ 21 days • Donor eligibility criteria: male donors, nulliparous females, or female donors negative for HLA antibodies at least 14 days following recovery from COVID-19 infection • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: 500 mL * Number of doses: NR * Antibody test and antibody-titre: NR * Pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> * Gender: male donors, nulliparous females, or female donors negative for HLA antibodies * HLA and HNA antibody: female donors negative for HLA antibodies * Severity of disease: NR * Timing from recovery from disease: at least 14 days following recovery from COVID-19 infection • Treatment details, including time of plasma therapy (e.g. early stage of disease): moderate and above severity • Comparator: nil • Concomitant therapy: NR • Duration of follow-up: 28 days • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: evaluate safety (time frame: at Day 28) • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: NR * Time to death: NR

NCT04516954 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - * Number of participants with SAEs: reported
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - * 30-day and 90-day mortality: NR
 - * Admission on the ICU: NR
 - * Length of stay on the ICU: NR
 - * Time to discharge from hospital: NR
 - * QoL: NR
 - * Virological response: NR
- Additional outcomes: change in requirement for mechanical ventilatory support (time frame: at Day 28)

Starting date	1 August 2020
Contact information	Vinmec Research Institute of Stem cell and Gene Technology, Hanoi, Vietnam, 10000
Notes	<ul style="list-style-type: none"> • Recruitment status: enrolling by invitation • Prospective completion date: 30 December 2020 • Sponsor: <ul style="list-style-type: none"> * Vinmec Research Institute of Stem Cell and Gene Technology * National Institute of Hygiene and Epidemiology, Vietnam * National Hospital for Tropical Diseases, Hanoi, Vietnam * National Institute of Hematology and Blood Transfusion, Vietnam

NL8633

Study name	A randomized, double blinded clinical trial of convalescent plasma compared to standard plasma for treatment of hospitalized non-ICU patients with COVID-19 infections (COV-PLAS)
Methods	<ul style="list-style-type: none"> • Trial design: randomised, prospective, multicenter, double-blinded phase 2/3 trial • Sample size: 215 each arm (430) • Setting: inpatient • Country: Netherlands • Language: English • Number of centres: multi-centre • Trial registration number: prospective - NL8633 • Date of registration: 13 May 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Maximal 3 days hospitalised at plasma infusion * Age \geq 18 years and \leq 85 years * SARS-CoV-2 infection: confirmed by PCR (BAL, sputum, nasal and/or pharyngeal swap) < 7 days before * Symptoms not expected to lead to IC transfer within 6 h of study plasma administration * Written informed consent including storing of specimen for future testing

NL8633 (Continued)

- Exclusion criteria
 - * A potential participant who meets any of the following criteria will be excluded from participation in this study:
 - Accompanying diseases other than COVID-19 with an expected survival time of < 6 months
 - Chronic severe pulmonary dysfunction like COPD, Gold stage 4; severe emphysema; or lung fibrosis with usual interstitial pneumonia pattern
 - Chronic heart failure NYHA ≥ 3 and/or pre-existing reduction of left ventricular ejection fraction to $\leq 30\%$ for which among others e.g. strict fluid restriction is needed
 - Clinical diagnosis of circulatory overload for which active therapy (like increased doses of diuretics) is initiated
 - Clinical judgement of deterioration in oxygenation (e.g. > 2 L increase in additional O₂ by nose tube), respiratory rates (e.g. > 5 / min increase) in the 2 h before the planned randomisation/plasma infusion
 - Signs of severe coagulopathy: thrombocytopenia by consumption (< 100 x 10⁹/L) or prolongation of the PT (+3 sec) , PTT (+ 5 sec)
 - Any history of severe adverse reactions to plasma proteins
 - Known deficiency of IgA
 - Pregnancy
 - Breastfeeding women
 - Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator, would affect subject safety and/or compliance

Interventions

- Intervention(s): CP therapy vs standard plasma
- Details of CP:
 - * Type of plasma: convalescent thawed FFP
 - * Volume: 1 unit (250-325 mL)
 - * Number of doses: 1 unit
 - * Antibody-titre: NR
 - * Pathogen inactivated: NR
- Treatment details, including time of plasma therapy:
 - * Early. Maximally 3 days hospitalised COVID-19 patients that are not at or bound to be referred to the ICU or expected to go to the ICU within 6 h of first plasma administration. Patients with COVID-19 that are sick enough to warrant hospitalisation but have not (yet) experienced overwhelming disease including a systemic inflammatory response, sepsis, and/or ARDS warranting ventilation and (eminent) ICU referral
- Comparator: standard thawed FFP 1 unit (250-325 mL)
- Concomitant therapy: NR
- Treatment cross-overs: no - parallel

Outcomes

- Primary study outcome(s):
 - * Ordinal outcome at day 14 of all cause mortality, mechanical ventilation, ICU admission and long duration of hospital stay (6 days or more), with < 6 hospitalised days as reference category
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: ordinal outcome of all-cause mortality at day 6, 14, 21, 18 and 56
 - * Length of ICU mortality
 - * Time to death: ordinal outcome of all-cause mortality at day 14, 21, 18 and 56
 - * ICU mortality

NL8633 (Continued)

- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction: yes. Deterioration of respiratory, circulatory or otherwise the clinical status during transfusion; transfusion transmitted infections
 - * Number of participants with SAEs: numbers not mentioned: "The following safety parameters will be assessed during this trial: deterioration of respiratory, circulatory or otherwise the clinical status during transfusion; transfusion transmitted infections."
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: maybe. Ordinal outcome includes mechanical ventilation, ICU admission and long duration of hospital stay day 6, 14, 21, 28
 - * 30-day and 90-day mortality: yes. Ordinal outcome of all-cause mortality, mechanical ventilation, ICU admission and long duration of hospital stay day 21, 28 and 56
 - * Admission on ICU: yes within ordinal outcome of all-cause mortality, mechanical ventilation, ICU admission and long duration of hospital stay day 6, 14, 21, 28 and 56
 - * Length of stay on the ICU: Yes. "Length of stay in ICU."
 - * Time to discharge from hospital: yes. "duration of hospitalisation in days"
- Additional outcomes
 - * E.g. proportion of viral nucleic acid negatives (3 days after transfusion): yes. "The time until negative SARS-CoV-2 PCR (nasal/ pharyngeal swab)"
 - * E.g. results of lab tests and vital signs: NR

Starting date	13 May 2020
Contact information	Name: Jaap Jan Zwaginga Email: j.j.zwaginga@lumc.nl Phone: 0715264006
Notes	<ul style="list-style-type: none"> • Recruitment status: open for patient inclusion • Prospective completion date: 1 May 2021 • Sponsor: Leiden University Medical Center • www.trialregister.nl/trial/8633

RBR-4vm3yy

Study name	Use of convalescent plasma submitted to pathogen inactivation for the treatment of patients with severe COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: single-arm intervention; historic control • Sample size: 20 • Setting: inpatient • Country: Brazil • Language: Portuguese • Number of centres: 1 • Trial registration: RBR-4vm3yy • Date of Registraton: 11 May 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Age ≥ 18 years * Severe or critical-19 COVID-19 * Length of stay < 3 days * Laboratory confirmation of COVID-19 by detection of the viral genome in respiratory secretions, collected by swab * Signature, by the patient or a relative, of the informed consent form

RBR-4vm3yy (Continued)

	<ul style="list-style-type: none"> Exclusion criteria <ul style="list-style-type: none"> Allergic reactions prior to plasma transfusion Donor eligibility criteria NR Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> Intervention(s): CP therapy Details of CP: <ul style="list-style-type: none"> Type of plasma: hyperimmune plasma anti-SARS-CoV-2 Volume: NR Number of doses: NR Antibody-titre: NR Pathogen inactivated: NR Treatment details, including time of plasma therapy (e.g. early stage of disease): NR Comparator: historic control Concomitant therapy: NR Treatment cross-overs: not applicable
Outcomes	<ul style="list-style-type: none"> Primary study outcome: <ul style="list-style-type: none"> Temporal improvement in inflammatory biomarkers and organ dysfunction scores during ICU admission, measured by the daily reduction in 10% of biomarkers in plasma and respiratory secretions, per day for 14 days Primary review outcomes reported <ul style="list-style-type: none"> All-cause mortality at hospital discharge: yes Time to death: NR Secondary review outcomes reported <ul style="list-style-type: none"> Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: <ul style="list-style-type: none"> Number of participants with SAEs: NR Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes 30-day and 90-day mortality: yes Admission on the ICU: yes Length of stay on the ICU: yes Time to discharge from hospital: yes QoL: NR Additional outcomes: NR
Starting date	19 April 2020
Contact information	<ul style="list-style-type: none"> Pedro Kurtz Address: Rua do Resende 156 City: Ro de Janeiro / Brazil Zip Code: 20231092 Telephone: 2122779352 E-mail: kurtzpedro@mac.com
Notes	<ul style="list-style-type: none"> Recruitment status: recruiting Prospective completion date: NR Sponsor/funding: primary sponsor: Instituto Estadual de Hematologia Arthur Siqueira Cavalcanti; Secondary Sponsors: Institution: Paulo Niemeyer State Brain Institute; Source(s) of Monetary or Material Support: Institution: Instituto Estadual de Hematologia Arthur Siqueira Cavalcanti

RBR-7jqpnw

Study name	Therapeutic effectiveness of COVID-19 convalescent plasma produced by HEMOPE: a multicenter, randomized and controlled clinical trial
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 220 • Setting: hospitalised patients • Country: Brazil • Language: Portuguese/English • Number of centres: 77 • Trial registration number: U1111-1254-0612 • Date of registration: 22 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> * Adults > 18 years with diagnosis of COVID-19, who are hospitalised; and considered as having a condition that increases the risk of a worse prognosis: obesity; diabetes mellitus; systemic arterial hypertension; chronic lung disease, obesity, diseases that alter immunity (AIDS, neoplasms or autoimmune diseases in immunosuppressive therapy), chronic liver disease • Exclusion criteria <ul style="list-style-type: none"> * History of anaphylactic reaction related to blood transfusion • Donor eligibility criteria NR • Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> * Type of plasma: CP * Volume: NR * Number of doses: NR * Antibody-titre: NR * Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: standard of care • Concomitant therapy: standard of care • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> * Mortality • Primary review outcomes reported <ul style="list-style-type: none"> * All-cause mortality at hospital discharge: yes * Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR * Number of participants with SAEs: NR * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes * 30-day and 90-day mortality: yes * Admission on the ICU: yes * Length of stay on the ICU: yes * Time to discharge from hospital: yes * QoL: NR * Virological response: NR

RBR-7jqpnw (Continued)

	<ul style="list-style-type: none"> Additional outcomes: NR
Starting date	1 July 2020
Contact information	<ul style="list-style-type: none"> Full Name: Democritus of Barros Miranda Filho Zip Code: 55100-130 City: Recife / Brazil Address: Rua Arnóbio Marques, 310, Santo Amaro Telephone: +55 081 999764712 Email: demofilho@gmail.com
Notes	<ul style="list-style-type: none"> Recruitment status: not yet recruiting Prospective completion date: NR Sponsor/funding: University of Pernambuco

RPCEC00000323

Study name	Plasma treatment to asymptomatic patient with COVID-19 infection
Methods	<ul style="list-style-type: none"> Trial design: single-arm study. Masking: Open. Control group: Uncontrolled. Assignment: Single group. Purpose: treatment Target Sample size: All patients who meet the criteria until 30 September 2020 Setting: Inpatient Country: Cuba Language: English (translated at rpcec.sld.cu/en/trials/RPCEC00000323-En) Number of centres: NR Trial registration number. RPCEC00000323: Not prospective. Date of registration 03 July 2020
Participants	<ul style="list-style-type: none"> Gender: male/female Inclusion criteria <ul style="list-style-type: none"> * Adult with SARS-CoV2 infection diagnosed by RT-PCR (19-74 years) * Remain asymptomatic with SARS-CoV2 positive PCR for > 30 days * That the antibody kit tests do not detect antibodies * That there is no history of anaphylaxis reactions with blood products * That at the clinical evaluation by the attending physician there are no contraindications for plasma transfusion * That the patient or their relatives give their informed consent to receive this donation Exclusion criteria <ul style="list-style-type: none"> * None
Interventions	<ul style="list-style-type: none"> Intervention(s): CP therapy Details of CP: <ul style="list-style-type: none"> * Type of plasma: NR * Volume: 1-4 bags (300 mL) * Number of doses: 1-4 on days 1, 3, 7 and 12 * Antibody-titre: NR * Pathogen inactivated: NR Treatment details, including time of plasma therapy (e.g. early stage of disease): patients are asymptomatic and remain PCR-positive without symptoms past 30 days Comparator: N/A Concomitant therapy: NR

RPCEC00000323 (Continued)

- Treatment cross-overs: N/A

Outcomes

- Primary study outcome(s):
 - * Improvement of respiratory failure (measured as increase in the PaO₂ > 60 mmHg or oxygen saturation > 90.7%). Measurement time: 48 h after treatment
 - * Clinical improvement (measured through change in classification from severe to from care and from care to open room). Measurement time: 72 h after treatment
 - * Improvement of at least 2 complete blood count parameters (measured as any positive difference in haemoglobin levels, differential WBC and platelet value). Measurement time: 48 and, 72 h after treatment
 - * Negativisation of the PCR (yes, no). Measurement time: 7 days after the treatment
- Primary review outcomes reported
 - * All-cause mortality at hospital discharge: (give details e.g. 28-day mortality)
 - * Time to death: yes/NR
- Secondary review outcomes reported
 - * Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI),
 - * Number of participants with SAEs: yes
 - AE (occurrence of any AE in the participant (yes, no),
 - Type of AE (name of the adverse event)
 - Location (local, systemic), time of onset (immediate, late)
 - Duration of AE (< a day, > a day)
 - Previous knowledge (expected, unexpected)
 - AE intensity (mild, moderate, severe)
 - AE severity (serious, not serious)
 - AE result (recovered, improved, persists, sequelae)
 - Causal relationship (very probable, probable, possible, unlikely, not related, not evaluable)
 - Outcome of the AE (recovered, not recovered, recovered with sequelae, death, unknown)
 - * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: NR
 - * 30-day and 90-day mortality: no
 - * Admission on ICU: maybe. "Clinical improvement (It will measure through the change in the classification from Severe to From Care and From Care to Open Room). Measurement time: 72 h after treatment"
 - * Length of stay on the ICU: no
 - * Time to discharge from hospital: no
 - * Time to discharge from hospital: no
- Additional outcomes
 - * Proportion of viral nucleic acid negatives (3 days after transfusion): yes. Negativisation of the PCR (yes, no). Measurement time: 7 days after the treatment
 - * Results of lab tests and vital signs: yes. Improvement of at least two complete blood count parameters (measured as any positive difference in haemoglobin levels, differential WBC and platelet value) Measurement time: 48 and 72 h after treatment
 - * Attitude towards treatment of study (continuation, definitive interruption). Measurement time: at the end of treatment

Starting date 5 May 2020

Contact information Consuelo Macias Abraham
Telephone: +53-78465555; +53-78465554
Email address: cmabraham@infomed.sld.cu

Notes Sponsor: Institute of Hematology and Immunology "Dr. Jose Manuel Ballester Santovenia"
apps.who.int/trialsearch/Trial2.aspx?TrialID=RPCEC00000323

RPCEC00000323 (Continued)

rpcec.sld.cu/en/trials/RPCEC00000323-En

AE: adverse event; **ALT:** alanine transaminase; **ANC:** absolute neutrophil count; **ARDS:** acute respiratory distress syndrome; **AST:** aspartate transaminase; **BAL:** bronchoalveolar lavage; **BAT:** best available therapy; **B(i)PAP:** bi-level positive airway pressure; **BMI:** body mass index; **CDC:** Centers for Disease Control and Prevention; **COI:** conflict of interest; **COPD:** chronic obstructive pulmonary disease; **CAP:** community-acquired pneumonia; **CP:** convalescent plasma; **CPAP:** continuous positive airway pressure; **CPK:** creatine phosphokinase; **CRP:** C-reactive protein; **CT:** computed tomography; **DBP:** diastolic blood pressure; **DFPP:** double-filtration plasmapheresis; **DIC:** disseminated intravascular coagulation; **DMARD:** disease-modifying anti-rheumatic drug; **DVT:** deep vein thrombosis; **ECG:** electrocardiogram; **ECMO:** extracorporeal membrane oxygenation; **ED:** emergency department; **FDA:** US Food and Drug Administration; **FFP:** fresh frozen plasma; **FiO₂:** fractional inspired oxygen; **GFR:** glomerular filtration rate; **HBV/HCV:** hepatitis B/C; **HCPOA:** healthcare power of attorney; **HLA:** human leukocyte antigen; **ICU:** intensive care unit; **IgA (B/G/M):** immunoglobulin A (B/G/M); **IL-6:** interleukin-6; **IV:** intravenous; **IVIG:** intravenous immunoglobulin; **LAR:** legal authorised representative; **LDH:** lactate dehydrogenase; **NR:** not reported; **NYHA:** New York Heart Association; **PaO₂:** arterial blood oxygen partial pressure; **PCR:** polymerase chain reaction; **PE:** pulmonary embolism; **QoL:** quality of life; **RCT:** randomised controlled trial; **RF:** respiratory failure; **RNA:** ribonucleic acid; **RRT:** renal replacement therapy; **RT-PCR:** reverse transcription polymerase chain reaction; **SAE:** serious adverse event; **SARS:** severe acute respiratory syndrome; **SBP:** systolic blood pressure; **SC:** subcutaneous; **SOFA:** Sequential Organ Failure Assessment; **SpO₂:** peripheral capillary oxygen saturation; **SRD:** severe respiratory disease; **TACO:** transfusion-associated circulatory overload; **TAD:** transfusion-associated dyspnoea; **TB:** tuberculosis; **TRALI:** transfusion-related acute lung injury; **TTP:** thrombotic thrombocytopenic purpura; **UIP:** usual interstitial pneumonia; **ULN:** upper limit of normal; **WBC:** white blood count; **WHO:** World Health Organization

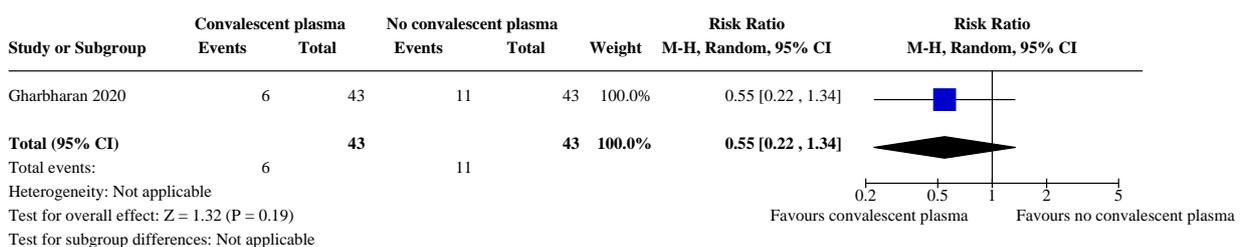
DATA AND ANALYSES

Comparison 1. Results from RCTs

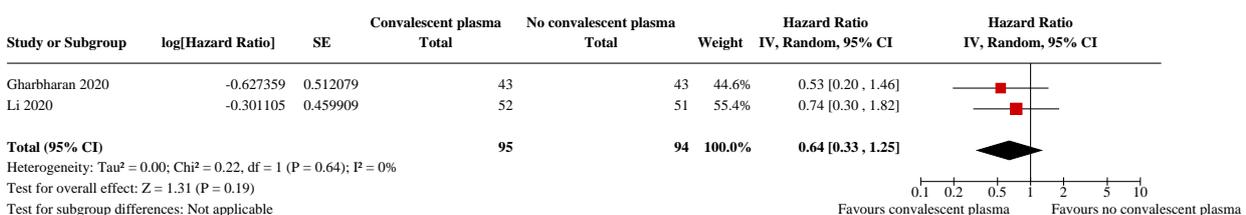
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality at hospital discharge	1	86	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.22, 1.34]
1.2 Mortality (time to event)	2	189	Hazard Ratio (IV, Random, 95% CI)	0.64 [0.33, 1.25]
1.3 Time to death: subgroup severity of disease	1	103	Hazard Ratio (IV, Random, 95% CI)	0.86 [0.32, 2.29]
1.3.1 Severe disease	1	45	Hazard Ratio (IV, Random, 95% CI)	Not estimable
1.3.2 Life-threatening disease	1	58	Hazard Ratio (IV, Random, 95% CI)	0.86 [0.32, 2.29]
1.4 Improvement of clinical symptoms at up to 7 days (assessed by need for respiratory support)	1	103	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.30, 3.19]
1.5 Improvement of clinical symptoms at 8 to 15 days (assessed by need for respiratory support)	2	189	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.85, 2.11]
1.6 Improvement of clinical symptoms at 16 to 30 days (assessed by need for respiratory support)	2	188	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.88, 1.43]
1.7 Improvement of clinical symptoms at up to 7 days (assessed by need for respiratory support): subgroup severity of disease	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.7.1 Severe disease	1	45	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.18, 2.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.2 Life-threatening disease	1	58	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.19, 20.86]
1.8 Improvement of clinical symptoms at 8 to 15 days (assessed by need for respiratory support): subgroup severity of disease	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.8.1 Severe disease	1	45	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.05, 4.76]
1.8.2 Life-threatening disease	1	58	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.22, 4.55]
1.9 Improvement of clinical symptoms at 16 to 30 days (assessed by need for respiratory support): subgroup severity of disease	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.9.1 Severe disease	1	45	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.98, 1.83]
1.9.2 Life-threatening disease	1	58	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.33, 2.24]
1.10 30-day mortality	1	101	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.29, 1.46]
1.11 Time to discharge from hospital	2	189	Hazard Ratio (IV, Random, 95% CI)	1.44 [0.98, 2.11]
1.12 Virological response at 24h (post-hoc analysis)	1	87	Risk Ratio (M-H, Random, 95% CI)	2.98 [1.33, 6.65]
1.13 Virological response at 48h (post-hoc analysis)	1	87	Risk Ratio (M-H, Random, 95% CI)	2.09 [1.29, 3.41]
1.14 Virological response at 72h	1	87	Risk Ratio (M-H, Random, 95% CI)	2.33 [1.54, 3.52]

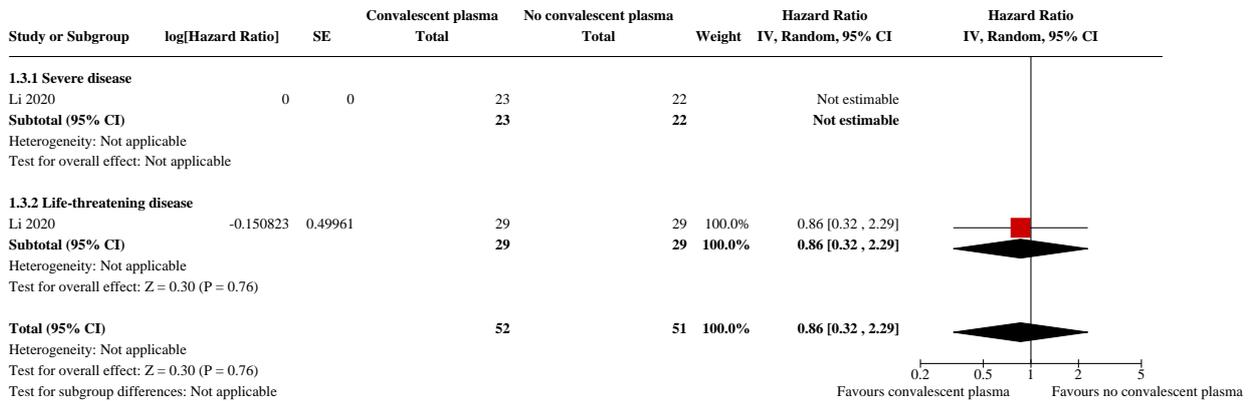
Analysis 1.1. Comparison 1: Results from RCTs, Outcome 1: All-cause mortality at hospital discharge



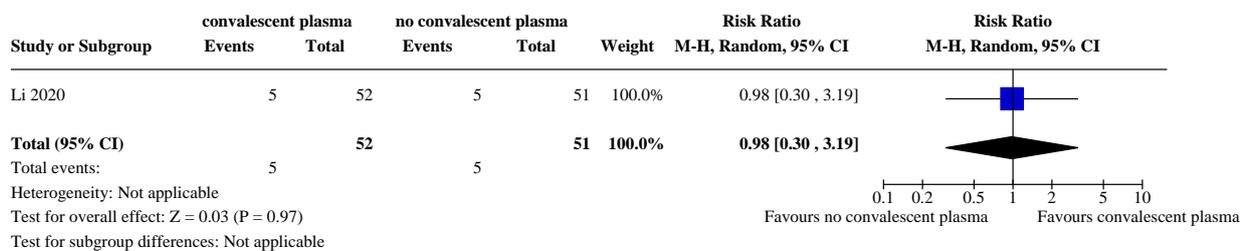
Analysis 1.2. Comparison 1: Results from RCTs, Outcome 2: Mortality (time to event)



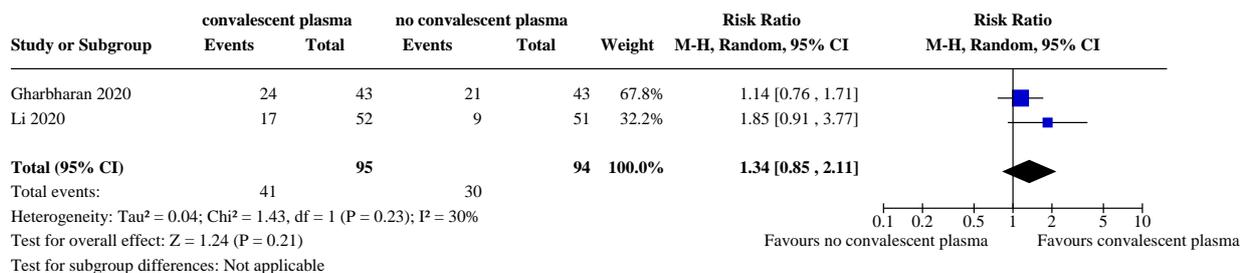
Analysis 1.3. Comparison 1: Results from RCTs, Outcome 3: Time to death: subgroup severity of disease



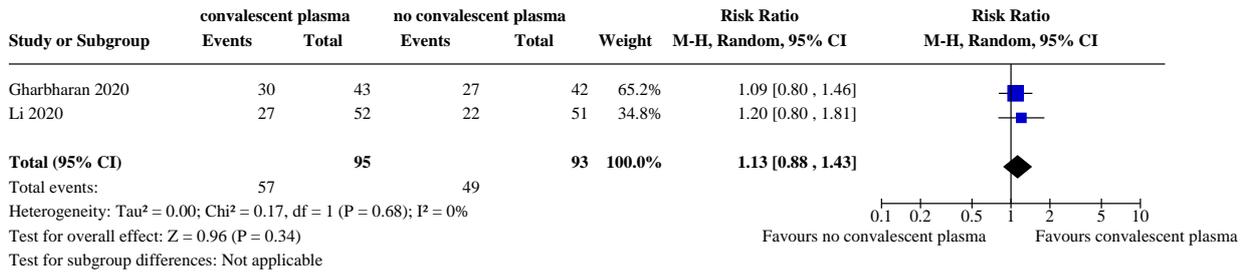
Analysis 1.4. Comparison 1: Results from RCTs, Outcome 4: Improvement of clinical symptoms at up to 7 days (assessed by need for respiratory support)



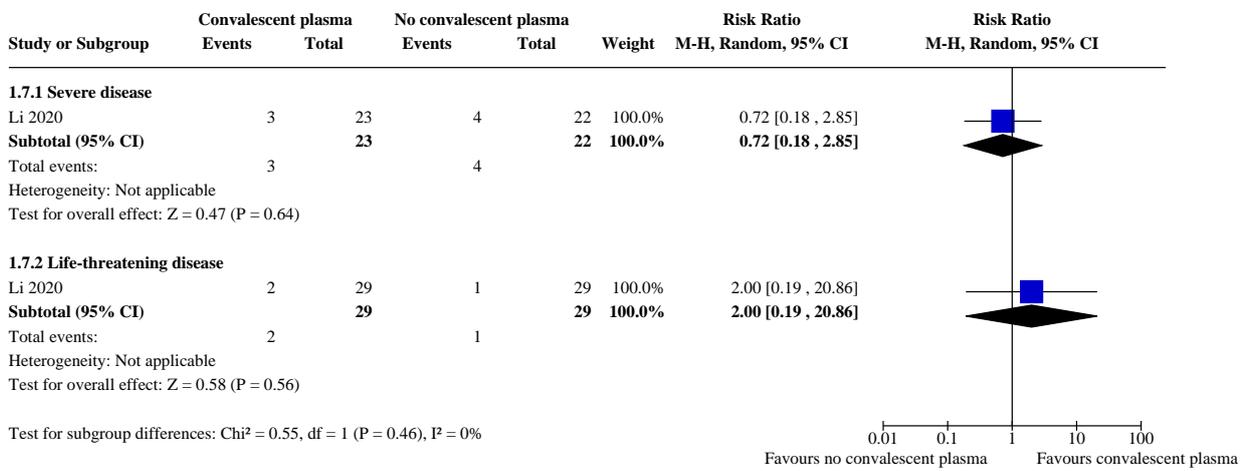
Analysis 1.5. Comparison 1: Results from RCTs, Outcome 5: Improvement of clinical symptoms at 8 to 15 days (assessed by need for respiratory support)



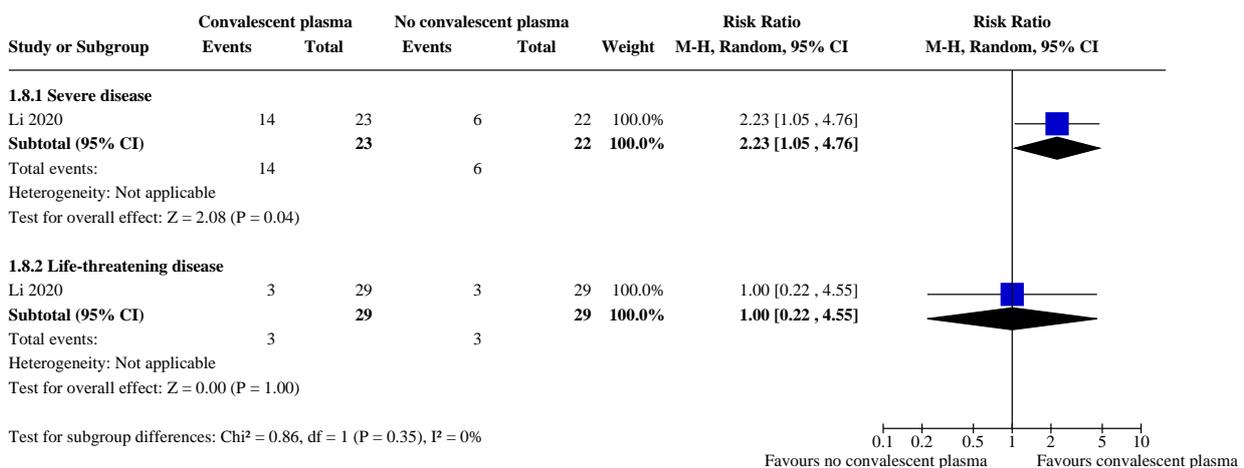
Analysis 1.6. Comparison 1: Results from RCTs, Outcome 6: Improvement of clinical symptoms at 16 to 30 days (assessed by need for respiratory support)



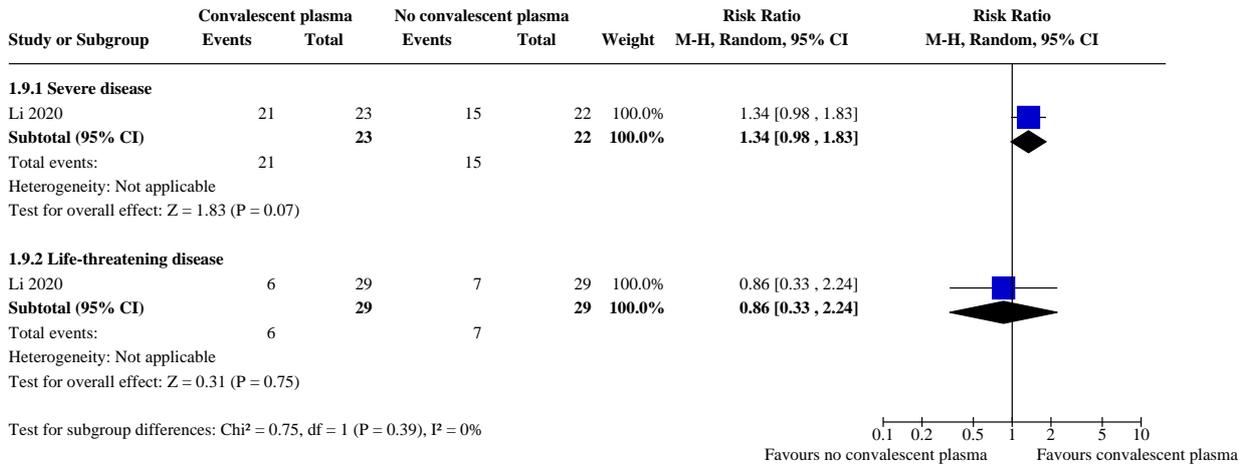
Analysis 1.7. Comparison 1: Results from RCTs, Outcome 7: Improvement of clinical symptoms at up to 7 days (assessed by need for respiratory support): subgroup severity of disease



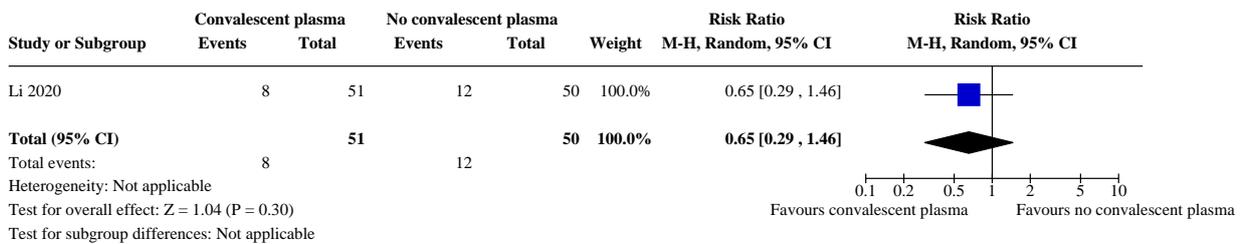
Analysis 1.8. Comparison 1: Results from RCTs, Outcome 8: Improvement of clinical symptoms at 8 to 15 days (assessed by need for respiratory support): subgroup severity of disease



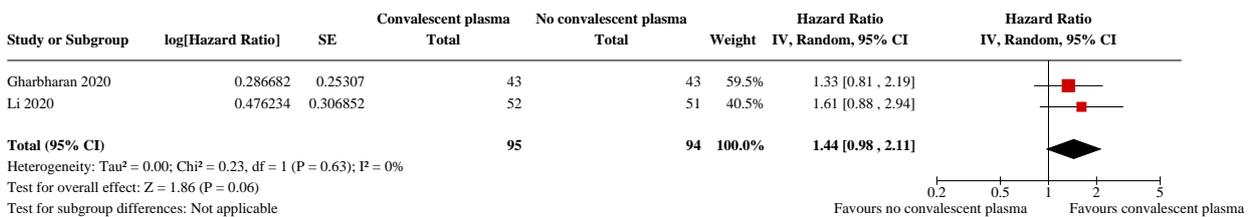
Analysis 1.9. Comparison 1: Results from RCTs, Outcome 9: Improvement of clinical symptoms at 16 to 30 days (assessed by need for respiratory support): subgroup severity of disease



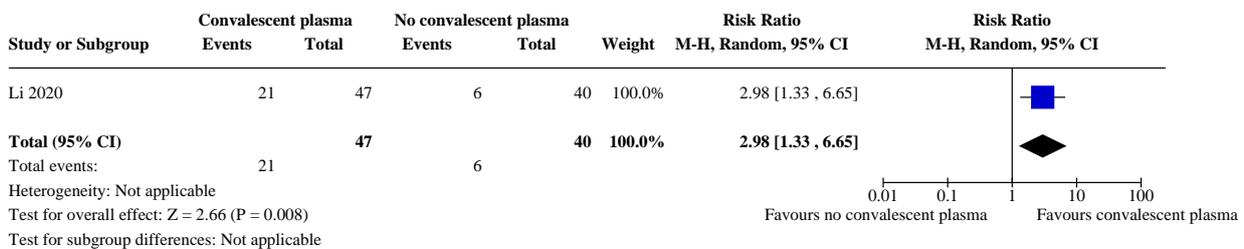
Analysis 1.10. Comparison 1: Results from RCTs, Outcome 10: 30-day mortality



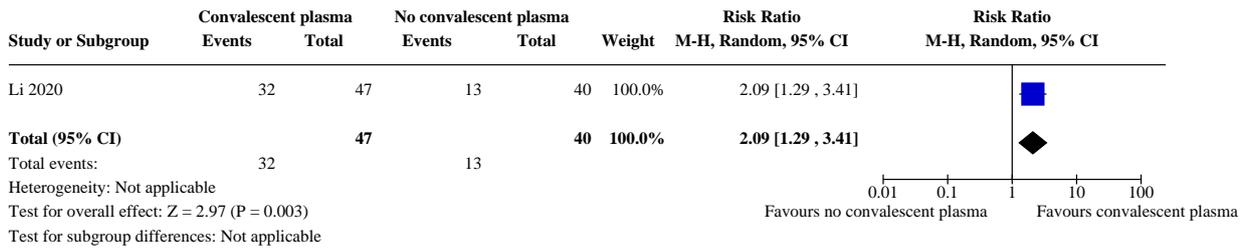
Analysis 1.11. Comparison 1: Results from RCTs, Outcome 11: Time to discharge from hospital



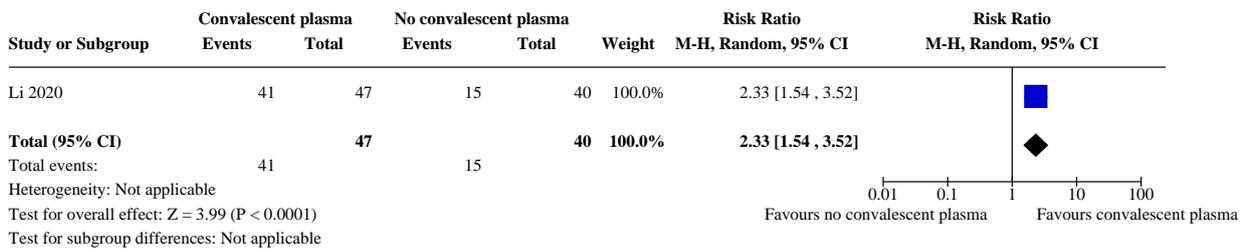
Analysis 1.12. Comparison 1: Results from RCTs, Outcome 12: Virological response at 24h (post-hoc analysis)



Analysis 1.13. Comparison 1: Results from RCTs, Outcome 13: Virological response at 48h (post-hoc analysis)



Analysis 1.14. Comparison 1: Results from RCTs, Outcome 14: Virological response at 72h



ADDITIONAL TABLES

Table 5. Improvement of clinical symptoms (assessed by need for respiratory support)

Study	Number of participants		Baseline		At day 7		At day 15		Up to day 30		From baseline to longest follow-up	
	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group
Randomised controlled trials (RCTs)												
Gharbharan 2020	43	43	WHO COVID-19 ordinal disease severity score (WHO 2020f) <ul style="list-style-type: none"> • ≤ 2: 0 • 3: 7 (16%) • 4-5: 31 (72%) • 6-7: 5 (12%) 	WHO COVID-19 disease severity score (WHO 2020f) <ul style="list-style-type: none"> • ≤ 2: 0 • 3: 1 (2%) • 4-5: 34 (79%) • 6-7: 8 (19%) 	NR	NR	24/43 (55.8%) showed a 2-point improvement ^a	21/43 (48.8%) showed a 2-point improvement ^a	27/43 (70%) showed a 2-point improvement ^a	27/42 ^b (64%) showed a 2-point improvement ^a	Longest follow-up: day 30 30/43 improved	Longest follow-up: day 30 27/42 ^b improved
Li 2020	52	51	<ul style="list-style-type: none"> • 14 on invasive mechanical ventilation and/or ECMO • 21 high-flow oxygen and/or NIV • 15 supplemental oxygen but no high-flow oxygen or NIV • 2 no supplemental oxygen 	<ul style="list-style-type: none"> • 11 on invasive mechanical ventilation and/or ECMO • 23 high-flow oxygen and/or NIV • 15 supplemental oxygen but no high-flow oxygen or NIV • 1 no supplemental oxygen • 1 excluded/unknown 	5/52 improved (9.6%)	5/51 improved (9.8%)	17/52 improved (32.7%)	9/51 improved (17.6%)	27/52 improved (51.9%)	22/51 improved (43.1%)	After 28 days: 27/52 improved (51.9%)	After 28 days: 22/51 improved (43.1%)
CP: convalescent plasma; ECMO: extracorporeal membrane oxygenation; NIV: non-invasive ventilation; NR: not reported; RCT: randomised controlled trial; WHO: World Health Organization												

^aTo increase the comparability of results, we used the individual patient data provided on the WHO COVID-19 disease severity score ([WHO 2020f](#)) and transferred the scale into the 6-point scale used by [Li 2020](#).

^bData for one participant were missing.

Table 6. Adverse events: grade 3 or 4

Study	Number of participants	Grade 3 or 4 adverse events ^a
Abolghasemi 2020 ^b	115 (CP group)	0
Donato 2020	47	0
Duan 2020 ^c	10 (CP group)	0
Dulipsingh 2020 ^d	46	0
Hegerova 2020	20 (CP group)	0
Jin 2020	6	0
Li 2020	52 (CP group)	3 (in 2 participants) <ul style="list-style-type: none"> • 1 possible severe transfusion-associated dyspnoea (participant had "shortness of breath, cyanosis, and severe dyspnoea within 6 hours of transfusion. The patient was given dexamethasone, aminophylline, and other supportive care immediately and gradually improved after 2 hours"). • 1 non-severe allergic transfusion reaction and 1 probable non-severe febrile non-haemolytic transfusion reaction (participant developed chills and rashes within 2 hours of transfusion but recovered fully after treatment with dexamethasone and promethazine).
Liu 2020	39 (CP group)	0
Madariaga 2020	10	0
Olivares-Gazca 2020	10	0
Perotti 2020	46	5 (in 4 participants) <ul style="list-style-type: none"> • Chills and fever during transfusion (relation likely) • Urticaria (relation likely) • Anaphylaxis/hypersensitivity (relation possible) • Transfusion-related acute lung injury (relation possible) • Subsegmental pulmonary embolism (relation unlikely/excluded)
Rasheed 2020 ^e	21 (CP group)	0
Xia 2020 ^f	138 (CP group)	0
Zeng 2020	6 (CP group)	0

CP: convalescent plasma

^aWe assume that these adverse events were grade 3 or 4, but the studies did not specify the degree of severity.

^bOne participant with transient mild fever and chill (grade 2).

^cOne participant with evanescent red face (grade unclear).

^dOne participant with transfusion reaction (grade unclear, event unclear).

^eOne participant with mild skin redness and itching that lasted for one hour after taking convalescent plasma (grade unclear).

^fThree participants with minor allergic reactions (grade unclear).

Table 1. 'Risk of bias' assessment criteria for observational studies

Heading	Internal validity	External validity
Study group	<p>Selection bias (representative: yes/no)</p> <ul style="list-style-type: none"> if the described study group consisted of > 80% of individuals with COVID-19 treated with convalescent plasma therapy or hyperimmune globulin in the original cohort <p>or</p> <ul style="list-style-type: none"> if it was a random sample with respect to the treatment and important prognostic factors 	<p>Reporting bias (well defined: yes/no)</p> <ul style="list-style-type: none"> if the study population was well described (e.g. severity of disease, age, risk factors) <p>and</p> <ul style="list-style-type: none"> the intervention was well described (e.g. number of doses, volume)
Follow-up	<p>Attrition bias (adequate: yes/no)</p> <ul style="list-style-type: none"> if the outcome was assessed for > 90% of the study group of interest (++) <p>or</p> <ul style="list-style-type: none"> if the outcome was assessed for 60% to 90% of the study group of interest (+) 	<p>Reporting bias (well defined: yes/no)</p> <ul style="list-style-type: none"> if the length of follow-up was mentioned
Outcome	<p>Detection bias (blind: yes/no)</p> <ul style="list-style-type: none"> if the outcome assessors were blinded to the investigated determinant 	<p>Reporting bias (well defined: yes/no)</p> <ul style="list-style-type: none"> if the outcome definition was objective and precise, and the method of detection was provided
Risk estimation	<p>Confounding (adjustment for other factors: yes/no)</p> <ul style="list-style-type: none"> if important prognostic factors (i.e. age, co-treatment, comorbidities) or follow-up were taken adequately into account 	<p>Analyses (well defined: yes/no)</p> <ul style="list-style-type: none"> if a risk ratio, odds ratio, attributable risk, linear or logistic regression model, mean difference or Chi² statistic was calculated

Table 2. Summary: design and planned completion date of ongoing studies

Study ID	Title	Design	Planned number of participants	Planned completion date	Completed/terminated	Results available	Other study ID
ChiC-TR2000029850	Efficacy and safety of convalescent plasma treatment for severe patients with novel coronavirus pneumonia (COVID-19): a prospective cohort study	Controlled NRS www.chic-tr.org.cn/show-pro-j.as-px?proj=49533	20	15 February 2022			
ChiC-TR2000030010	A randomized, double-blind, parallel-controlled trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia patients (COVID-19)	RCT www.chic-tr.org.cn/show-pro-j.as-px?proj=49777	100	31 May 2020			
ChiC-TR2000030039	Clinical study for infusing convalescent plasma to treat patients with new coronavirus pneumonia (COVID-19)	Controlled NRS www.chic-tr.org.cn/show-pro-j.as-px?proj=49544	60	1 February 2020			
ChiC-TR2000030179	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19)	RCT www.chic-tr.org.cn/show-pro-j.as-px?proj=50059	100	24 February 2020			
ChiC-TR2000030627	Study on the application of convalescent plasma therapy in severe COVID-19	RCT www.chic-tr.org.cn/show-pro-j.as-px?proj=50727	30	30 May 2020			
ChiC-TR2000030702	Convalescent plasma for the treatment of common COVID-19: a prospective RCT	RCT www.chic-tr.org.cn/show-pro-j.as-px?proj=50537	30	15 August 2020			
ChiC-TR2000030929	A randomized, double-blind, parallel-controlled trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated	RCT www.chic-tr.org.cn/show-pro-j.as-px?proj=50537	30	16 June 2020			

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

	plasma in the treatment of severe novel coronavirus pneumonia (COVID-19)	j.as-px?proj=50696			
ChiC-TR2000031501	The efficacy of convalescent plasma in patients with critical novel coronavirus pneumonia (COVID-19): a pragmatic, prospective cohort study	ControlledTrials.org/cttrials/2020/01/01/proj=50254	20	17 July 2020	
ChiC-TR2000033798	The efficacy and safety of convalescent plasma therapy in novel coronavirus pneumonia (COVID-19): a medical records based retrospective cohort study	ControlledTrials.org/cttrials/2020/01/01/proj=55194	150	11 June 2021	
EUC-TR2020-001310-01	A randomized, prospective, open label clinical trial on the use of convalescent plasma compared to best supportive care in patients with severe COVID-19	www.clinicaltrials.gov/ct2/show/study?term=EUC-TR2020-001310-01&rank=1	106	NR	
IRC-T20151228025710-193	Therapeutic effects of plasma of recovered people from COVID-19 on hospitalized patients with this disease	ControlledTrials.org/cttrials/2015/12/28/025710-193	12	20 June 2020	
IRC-T20200310046746-193	Comparison of the therapeutic effect of convalescent plasma and plasma-derived immunoglobulin-enriched solution on COVID-19 patients	ClinicalTrials.gov/cttrials/2020/03/10/046746-193	45	24 July 2020	
IRC-T20200404046946-193	Efficacy and safety of convalescent plasma in the treatment of COVID-19	ClinicalTrials.gov/cttrials/2020/04/04/046946-193	60	20 June 2020	

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

IRC- T202004090470	Effect of COVID 19 survivors plasma in COVID 19 patients with ARDS	RCT ten.irc-t.ir/trial/47058	32	15 August 2020	
IRC- T202004130470	Comparison between the efficacy of intravenous immunoglobulin and convalescent plasma in COVID-19	RCT ten.irc-t.ir/trial/47212	15	19 June 2020	
IRC- T20200525047562N1	Treatment of COVID-19 patients with convalescent plasma	Non-controlled NRSI clinicaltrials.gov/ct2/show/study/NCT048493	100	26 July 2020	x
ISRCTN85216856	Using blood plasma to develop passive immunity to coronavirus in Ecuador	RCT isrctn.com/ISRCTN85216856	200	31 December 2020	
NCT02735707	Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP)	RCT clinical-trials.gov/ct2/show/study/NCT02735707	7100	31 December 2021	
NCT04264858	An exploratory clinical study on the treatment of acute severe 2019-nCoV pneumonia with immunoglobulin from cured 2019-nCoV pneumonia patients	Non-controlled NRSI clinical-trials.gov/show/study/NCT04264858	10	31 May 2020	ChiC-TR2000030841
NCT04292340	The efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of novel coronavirus pneumonia patient (COVID-19): an observational study	Non-controlled NRSI clinical-trials.gov/show/study/NCT04292340	15	31 July 2020	
NCT04327349	Investigating effect of convalescent plasma on COVID-19 patients outcome: a clinical trial	Non-controlled NRSI clinical-trials.gov/show/study/NCT04327349	30	30 September 2020	

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

		tri- al- s.gov/show/ NCT04327349			
NCT04332380	Convalescent plasma for patients with COVID-19: a pilot study	Non-con- trolled NRSI cal- tri- al- s.gov/show/ NCT04332380	10	31 Decem- ber 2020	
NCT04332835	Convalescent plasma for patients with COVID-19: a randomized, open label, parallel, controlled clinical study	RCTclin- i- cal- tri- al- s.gov/show/ NCT04332835	80	31 Decem- ber 2020	
NCT04333251	Evaluating convalescent plasma to decrease coronavirus associated complications. A phase I study comparing the efficacy and safety of high-titre anti-Sars-CoV-2 plasma versus best supportive care in hospitalised patients with interstitial pneumonia due to COVID-19	RCTclin- i- cal- tri- al- s.gov/show/ NCT04333251	115	31 Decem- ber 2022	
NCT04333355	Phase 1 study to evaluate the safety of convalescent plasma as an adjuvant therapy in patients with SARS-CoV-2 infection	Non-con- trolled NRSI cal- tri- al- s.gov/show/ NCT04333355	20	30 April 2021	
NCT04338360	Expanded access to convalescent plasma for the treatment of patients with COVID-19	Expanded access cal- Tri- al-	NR	NR	Preprint, subset of data

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

			s.gov/show/ NCT04338360			
NCT04344535	Convalescent plasma versus standard plasma for COVID-19	RCT Clinical Trial	s.gov/show/ NCT04344535	500	31 August 2021	
NCT04345289	Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia (CCAP)	RCT Clinical Trial	s.gov/show/ NCT04345289	1500	15 June 2021	EUC- TR2020-001367-88
NCT04345523	Convalescent plasma therapy versus SOC for the treatment of COVID-19 in hospitalized patients (ConPlas-19)	RCT Clinical Trial	s.gov/show/ NCT04345523	278	1 July 2020	
NCT04345679	Anti COVID-19 convalescent plasma therapy	Non- Random- Controlled NRSI Clinical Trial	s.gov/show/ NCT04345679	20	1 April 2021	
NCT04345991	Efficacy of convalescent plasma to treat COVID-19 patients, a nested trial in the CORIMUNO-19 cohort	RCT Clinical Trial	s.gov/show/ NCT04345991	120	1 June 2020	
NCT04346446	Efficacy of convalescent plasma therapy in severely sick COVID-19 patients	RCT Clinical Trial		20	20 June 2020	

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

		cal- Tri- al- s.gov/show/ NCT04346446			
NCT04346589	Convalescent antibodies infusion in critically ill COVID 19 patients	Non- con- trolled NRSI cal- Tri- al- s.gov/ct2/ show/ NCT04346589	10	1 July 2020	
NCT04347681	Potential efficacy of convalescent plasma to treat severe COVID-19 and patients at high risk of developing severe COVID-19	Non- con- trolled NRSI cal- Tri- al- s.gov/show/ NCT04347681	40	11 April 2021	
NCT04348656	Convalescent plasma for hospitalized adults with COVID-19 respiratory illness (CONCOR-1)	RCT clin- i- cal- Tri- al- s.gov/show/ NCT04348656	1200	31 December 2020	
NCT04348877	Plasma rich antibodies from recovered patients from COVID19	Non- con- trolled NRSI cal- Tri- al- s.gov/show/ NCT04348877	20	1 December 2020	
NCT04352751	Experimental use of convalescent plasma for passive immunization in current COVID-19 pandemic in Pakistan in 2020	Non- con- trolled NRSI cal- Tri- al-	2000	1 April 2021	

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

NCT04352751		Non- controlled NRSI	90	1 May 2021
NCT04353206	Convalescent plasma in ICU patients with COVID-19-induced respiratory failure	Non- controlled NRSI cal- Tri- al- s.gov/show/ NCT04353206	90	1 May 2021
NCT04354831	A study evaluating the efficacy and safety of high-titre anti-SARS-CoV-2 plasma in hospitalised patients with COVID-19 infection	Non- controlled NRSI cal- Tri- al- s.gov/ct2/ show/ NCT04354831	106	1 May 2023
NCT04355767	Convalescent plasma versus placebo in emergency room patients with COVID-19	RCT Clinical- cal- Tri- al- s.gov/ct2/ show/ NCT04355767	206	1 December 2022
NCT04355897	CoVID-19 plasma in treatment of COVID-19 patients	Non- controlled NRSI cal- Tri- al- s.gov/ct2/ show/ NCT04355897	100	1 August 2020
NCT04356482	Determination of the dose and effectiveness of convalescent plasma in severely and very severely ill patients with COVID-19	Non- controlled NRSI cal- Tri- al-	90	1 December 2020

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

			s.gov/show/ NCT04356482		
NCT04356534	Convalescent plasma trial in COVID-19 patients	RCTClinical-trial	s.gov/show/ NCT04356534	40	30 June 2020
NCT04358211	Expanded access to convalescent plasma to treat and prevent pulmonary complications associated with COVID-19	Expanded access	s.gov/show/ NCT04358211	NR	NR
NCT04358783	Phase II, randomized, double-blind, controlled clinical trial evaluating the efficacy and safety of plasma from patients cured of COVID-19 compared to the best available therapy in subjects with SARS-CoV-2 pneumonia	RCTClinical-trial	s.gov/show/ NCT04358783	30	30 May 2020
NCT04359810	A phase 2, randomized clinical trial to evaluate the efficacy and safety of human anti-SARS-CoV-2 convalescent plasma in severely ill adults with COVID-19	RCTClinical-trial	s.gov/show/ NCT04359810	105	1 April 2021
NCT04360486	Treatment of COVID-19 with anti-SARS-CoV-2 convalescent plasma (ASCoV2CP)	Expanded access	s.gov/show/ NCT04360486	NR	NR
NCT04361253	A prospective, randomized, double-masked, placebo-controlled trial of high-titer COVID-19 convalescent plasma (HT-CCP) for the	RCTClinical-trial		220	1 December 2021

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

	treatment of hospitalized patients with COVID-19 of moderate severity	cal-Tri-al- s.gov/show/NCT04361253			
NCT04362176	A randomized, controlled clinical trial to test the safety and efficacy of convalescent donor plasma to treat COVID-19 in hospitalized adults	RCTClinical-Trial- s.gov/show/NCT04362176	500		1 April 2021
NCT04363034	Arkansas expanded access COVID-19 convalescent plasma treatment program	Expanded access cal-Tri-al- s.gov/ct2/show/NCT04363034	NR		NR
NCT04364737	Convalescent plasma to limit COVID-19 complications in hospitalized patients	RCTClinical-Trial- s.gov/show/NCT04364737	300		30 April 2023
NCT04365439	Convalescent plasma for the treatment of moderate-severe COVID-19: a proof-of-principle study	Controlled Non-Randomized Clinical-Trial- s.gov/show/NCT04365439	10		30 June 2020
NCT04366245	Phase I/II multicentre, randomized and controlled clinical trial to evaluate the efficacy of treatment with hyperimmune plasma obtained from convalescent antibodies of COVID-19 infection	RCTClinical-Trial- s.gov/show/NCT04366245	72		1 December 2021

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

			s.gov/show/ NCT04366245		
NCT04372368	Convalescent plasma for the treatment of patients with COVID-19	Expanded access	NR	NR	
		cal-Tri-al- s.gov/show/ NCT04372368			
NCT04372979	Evaluation of efficacy of COVID-19 convalescent plasma versus standard plasma in the early care of COVID-19 patients hospitalized outside intensive care units	RCT	80	1 May 2021	
		lin-i- cal- Tri- al- s.gov/show/ NCT04372979			
NCT04373460	Comparison of the efficacy and safety of human coronavirus immune plasma (HCIP) vs. control (SARS-CoV-2 non-immune) plasma among outpatients with symptomatic COVID-19	RCT	1344	31 January 2023	
		lin-i- cal- Tri- al- s.gov/show/ NCT04373460			
NCT04374370	Severe acute respiratory syndrome coronavirus 2 of the genus betacoronavirus (SARSCoV2) convalescent plasma (CP) expanded access protocol (EAP)	Expanded access	NR	NR	
		cal- Tri- al- s.gov/show/ NCT04374370			
NCT04374487	A phase II, open label, RCT to assess the safety and efficacy of convalescent plasma to limit COVID-19 associated complications	RCT	100	9 May 2021	
		lin-i- cal- Tri- al- s.gov/show/ NCT04374487			
NCT04374526	Early transfusion of convalescent plasma in elderly COVID-19 patients	RCT	182	30 June 2021	
		lin-i-			

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

	to prevent disease progression	cal- Tri- al- s.gov/show/ NCT04374526		
NCT04374565	Efficacy and safety of high-titer anti-SARS-CoV-2 (COVID19) convalescent plasma for hospitalized patients with infection due to COVID-19 to decrease complications: a phase II trial	Non- Con- trolled NRSI cal- Tri- al- s.gov/show/ NCT04374565	29	5 April 2021
NCT04375098	Efficacy and safety of early anti-SARS-COV-2 convalescent plasma in patients admitted for COVID-19 infection: a randomized phase II trial	RCT Clin- i- cal- Tri- al- s.gov/show/ NCT04375098	30	1 December 2021
NCT04376034	Convalescent plasma collection from individuals that recovered from COVID19 and treatment of critically ill individuals with donor convalescent plasma	Non- Con- trolled NRSI cal- Tri- al- s.gov/show/ NCT04376034	240	30 Mar 2021
NCT04376788	Exchange transfusion versus plasma from convalescent patients with methylene blue in patients with COVID-19	RCT Clin- i- cal- Tri- al- s.gov/show/ NCT04376788	15	1 June 2020
NCT04377568	CONCOR-KIDS: a randomized, multicentered, open-label phase 2 clinical trial of the safety and efficacy of human coronavirus-immune convalescent plasma for the treatment of COVID-19 disease in hospitalized children	RCT Clin- i- cal- Tri- al-	100	1 May 2022

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

			s.gov/show/ NCT04377568		
NCT04377672	Human convalescent plasma for high risk children exposed or infected with SARS-CoV-2	Non-controlled NRSI	30	18 May 2022	
		cal-Tri-al- s.gov/show/ NCT04377672			
NCT04380935	Effectiveness and safety of convalescent plasma therapy on COVID-19 patients with acute respiratory distress syndrome	RCTClinical	60	31 August 2020	
		cal-Tri-al- s.gov/show/ NCT04380935			
NCT04381858	Convalescent plasma vs human immunoglobulin to treat COVID-19 pneumonia	RCTClinical	500	30 September 2020	
		cal-Tri-al- s.gov/show/ NCT04381858			
NCT04381936	Randomised evaluation of COVID-19 therapy (RECOVERY)	RCTClinical	12000	30 June 2021	ISRCTN50189673
		cal-Tri-al- s.gov/ct2/ show/ NCT04381936			
NCT04383535	Convalescent plasma and placebo for the treatment of COVID-19 severe pneumonia	RCTClinical	333	20 August 2020	
		cal-Tri-al- s.gov/show/ NCT04383535			

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

NCT04383548	Clinical study for efficacy of anti-corona VS2 immunoglobulins prepared from COVID19 convalescent plasma prepared by VIPS mini-pool IVIG medical devices in prevention of SARS-CoV-2 infection in high risk groups as well as treatment of early cases of COVID	Non-controlled NRSI cal-Trial- s.gov/show/NCT04383548	100	1 January 2021
NCT04384497	Convalescent plasma for treatment of COVID-19: an exploratory dose identifying study	Non-controlled NRSI cal-Trial- s.gov/show/NCT04384497	50	1 December 2020
NCT04384588	COVID19-convalescent plasma for treating patients with active symptomatic COVID 19 infection (FALP-COVID)	Controlled NRSI cal-Trial- s.gov/show/NCT04384588	400	6 April 2021
NCT04385043	Phase 2b/3 trial to evaluate the safety and efficacy of plasma transfusion from convalescent patients with SARS-CoV-2 infection on severity and mortality of COVID-19 in hospitalized patients	RCTClinical-Trial- cal-Trial- s.gov/show/NCT04385043	400	15 May 2021
NCT04385186	Inactivated convalescent plasma as a therapeutic alternative in patients with CoViD-19	RCTClinical-Trial- cal-Trial- s.gov/show/NCT04385186	60	30 November 2020
NCT04385199	The use of convalescent plasma for patients hospitalized with COVID-19 disease	RCTClinical-Trial- cal-Trial-	30	1 August 2020

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

			al- s.gov/show/ NCT04385199		
NCT04388410	Phase 2b/3 trial to evaluate the safety and efficacy of plasma transfusion from convalescent patients with SARS-CoV-2 infection on severity and mortality of COVID-19 in hospitalized patients.	RCT Clinical- Trial- al- s.gov/show/ NCT04388410	250	31 Decem- ber 2020	
NCT04388527	An open-label, single arm, phase 1, safety and exploratory efficacy study of convalescent plasma for severely ill mechanically ventilated participants with COVID-19 caused by SARS-CoV-2	Non- Clinical- controlled NRSI cal- Tri- al- s.gov/show/ NCT04388527	50	30 Septem- ber 2020	
NCT04389710	Convalescent plasma for the treatment of patients with COVID-19	Non- Clinical- controlled NRSI cal- Tri- al- s.gov/show/ NCT04389710	100	14 April 2021	
NCT04389944	Amotosalen-ultraviolet a pathogen-inactivated convalescent plasma in addition to best supportive care and antiviral therapy on clinical deterioration in adults presenting with moderate to severe COVID-19	Non- Clinical- controlled NRSI cal- Tri- al- s.gov/show/ NCT04389944	15	30 June 2020	
NCT04390178	Convalescent plasma as treatment for acute coronavirus disease (COVID-19)	Non- Clinical- controlled NRSI cal- Tri- al- s.gov/show/ NCT04390178	10	1 December 2020	

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

NCT04390503	A phase 2 randomized, double-blinded trial to evaluate the efficacy and safety of human anti-SARS-CoV-2 plasma in close contacts of COVID-19 cases	RCT Clinical Trial s.gov/ct2/show/NCT04390503	200	1 April 2021
NCT04391101	Efficacy of convalescent plasma for the treatment of severe SARS-CoV-2 infection: a randomized, open label clinical trial	RCT Clinical Trial s.gov/show/NCT04391101	231	31 December 2021
NCT04392232	A phase 2 study of COVID 19 convalescent plasma in high risk patients with COVID 19 infection	Non- Randomized Controlled NRSI Clinical Trial s.gov/show/NCT04392232	100	31 December 2020
NCT04392414	Randomized, open label, prospective study of the safety and efficacy of hyperimmune convalescent plasma in moderate and severe COVID-19 disease	RCT Clinical Trial s.gov/show/NCT04392414	60	15 September 2020
NCT04393727	Transfusion of convalescent plasma for the early treatment of pneumonia due to SARSCoV2	RCT Clinical Trial s.gov/show/NCT04393727	126	30 August 2020
NCT04395170	A multicenter randomized clinical trial to evaluate the efficacy and safety of the use of convalescent plasma (PC) compared to	RCT Clinical Trial	75	1 June 2021

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

	anti-COVID-19 human immunoglobulin and standard treatment in hospitalized patients	Tri- al- s.gov/show/ NCT04395170		
NCT04397523	Efficacy and safety of COVID-19 convalescent plasma	Non- controlled NRSI cal- Tri- al- s.gov/show/ NCT04397523	20	29 April 2021
NCT04397757	COVID-19 convalescent plasma for the treatment of hospitalized patients with pneumonia caused by SARS-CoV-2	Clin- i- cal- Tri- al- s.gov/show/ NCT04397757	80	13 Novem- ber 2020
NCT04403477	Convalescent plasma transfusion therapy in severe COVID-19 patients - a tolerability, efficacy and dose-response phase II RCT	Clin- i- cal- Tri- al- s.gov/show/ NCT04403477	20	30 October 2020
NCT04404634	Convalescent plasma to limit coronavirus associated complications	RCT Clin- i- cal- Tri- al- s.gov/show/ NCT04404634	300	31 January 2023
NCT04405310	Convalescent plasma of COVID-19 to treat SARS-COV-2 a randomized double blind 2 center trial	Clin- i- cal- Tri- al- s.gov/show/ NCT04405310	80	20 July 2020

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

NCT04407208	Convalescent plasma therapy in patients with COVID-19	Non- controlled NRSI	10	1 August 2020
		cal- Tri- al- s.gov/show/ NCT04407208		
NCT04408040	Use of convalescent plasma collected from donors recovered from COVID-19 virus disease for transfusion, as an empirical and preemptive treatment during viral pandemic outbreak	Non- controlled NRSI	700	1 June 2022
		cal- Tri- al- s.gov/show/ NCT04408040		
NCT04408209	Convalescent plasma for the treatment of patients with severe COVID-19 infection	Non- controlled NRSI	60	15 September 2021
		cal- Tri- al- s.gov/show/ NCT04408209		
NCT04411602	Feasibility study of anti-SARS-CoV-2 plasma transfusions in COVID-19 patients with SRD	Non- controlled NRSI	90	31 December 2020
		cal- Tri- al- s.gov/show/ NCT04516954		
NCT04412486	COVID-19 Convalescent Plasma (CCP) Transfusion	Non- controlled NRSI	100	31 May 2022
		cal- Tri- al- s.gov/show/ NCT04412486		
NCT04415086	Treatment of patients with COVID-19 with convalescent plasma	RCT Clinical- Tri-	120	22 May 2022

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

			al- s.gov/show/ NCT04415086		
NCT04418518	CONCOR-1: a randomized open-label trial of convalescent plasma for hospitalized adults with acute COVID-19 respiratory illness	RCTClinical-Trial	al- s.gov/show/ NCT04418518	1200	31 December 2021
NCT04418531	A pilot study to explore the efficacy and safety of rescue therapy with antibodies from convalescent patients obtained with double-filtration plasmapheresis (DFPP) and infused in patients with coronavirus disease 2019 (COVID-19) and need of oxygen support without mechanical ventilation	Non-controlled NRSI	al- s.gov/show/ NCT04418531	10	30 September 2020
NCT04420988	Investigational COVID-19 convalescent plasma infusion for severely or life-threateningly ill COVID-19 patients	Expanded access	al- s.gov/show/ NCT04420988	NR	NR
NCT04421404	A randomized controlled adaptive study comparing COVID-19 convalescent plasma (CCP) to non-immune plasma to limit coronavirus-associated complications in hospitalized patients	RCTClinical-Trial	al- s.gov/show/ NCT04421404	30	30 April 2021
NCT04425837	Effectiveness and safety of convalescent plasma in patients with high-risk COVID-19	RCTClinical-Trial	al- s.gov/show/ NCT04425837	235	28 February 2021

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

NCT04425915	Efficacy of convalescent plasma therapy in patients with COVID-19	RCTClinical-trial- s.gov/show/NCT04425915	400	31 May 2021
NCT04428021	Effectiveness of adding standard plasma or COVID-19 convalescent plasma to standard treatment, versus standard treatment alone, in patients with recent onset of COVID-19 respiratory failure. A randomized, three-arms, phase 2 trial	RCTClinical-Trial- s.gov/show/NCT04428021	180	15 December 2021
NCT04429854	A randomized, open-label, adaptive, proof-of-concept clinical trial of donated antibodies working against with COVID-19: DAWN-PLASMA	RCTClinical-Trial- s.gov/show/NCT04429854	483	2 November 2021
NCT04432103	Treatment of severe and critical COVID-19 pneumonia with convalescent plasma	Controlled NRSI s.gov/show/NCT04432103	36	30 September 2020
NCT04432272	Antibody-level based analysis of COVID convalescent serum (ABACCuS)	Non-controlled NRSI s.gov/show/NCT04432272	500	31 August 2021
NCT04433910	Randomized, prospective, open label clinical trial on the use of convalescent plasma compared to best supportive care in patients with severe COVID-19	RCTClinical-trial-	106	28 February 2021

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

		Tri- al- s.gov/show/ NCT04433910				
NCT04438057	Evaluating the efficacy of convalescent plasma in symptomatic outpatients infected with COVID-19	RCTClin- i- cal- Tri- al- s.gov/show/ NCT04438057	150	6 July 2021		
NCT04438694	Use of convalescent plasma for treatment of patients with COVID-19 infection	RCTClin- i- cal- Tri- al- s.gov/show/ NCT04438694	60	31 December 2021		
NCT04442191	Infusion of convalescent plasma for the treatment of patients infected with severe acute respiratory syndrome-coronavirus-2 (COVID-19): a double-blinded, placebo-controlled, proof-of-concept study	RCTClin- i- cal- tri- al- s.gov/show/ NCT04442191	50	31 May 2021		
NCT04442958	Effectiveness of convalescent immune plasma therapy	RCTClin- i- cal- Tri- al- s.gov/show/ NCT04442958	60	17 June 2020	x	
NCT04445207	Experimental expanded access treatment with convalescent plasma for the treatment of patients with COVID-19	Expanded access cal- Tri- al- s.gov/show/ NCT04445207	NR	NR		

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

NCT04452812	Pilot clinical, statistical and epidemiological study on efficacy and safety of convalescent plasma for the management of patients with COVID-19	RCT Clinical- i- cal- Tri- al- s.gov/show/ NCT04452812	15	1 April 2021
NCT04456413	Phase II randomized study of convalescent plasma from recovered COVID-19 donors collected by plasmapheresis as treatment for subjects with early COVID-19 infection	RCT Clinical- i- cal- tri- al- s.gov/show/ NCT04456413	306	31 July 2021
NCT04458363	Convalescent plasma to optimize treatment of COVID-19 disease in pediatric patients: a feasibility study	Non- Clinical- controlled NRSI cal- tri- al- s.gov/ct2/ show/ NCT04458363	50	30 June 2022
NCT04462848	Phase I study of the safety and pharmacokinetics of human convalescent plasma in high risk children exposed or infected with SARS-CoV-2	Non- Clinical- controlled NRSI cal- Tri- al- s.gov/show/ NCT04462848	30	31 Decem- ber 2024
NCT04463823	"NORPLASMA" COVID-19 convalescent plasma treatment monitoring study	Non- Clinical- controlled NRSI cal- Tri- al- s.gov/show/ NCT04463823	500	31 May 2025
NCT04467151	A randomized, double-blind, placebo-controlled trial of anti-SARS-CoV-2 plasma in hospitalized non-ICU patients with COVID-19	RCT Clinical- i- cal-	96	31 Decem- ber 2021

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

		Tri- al- s.gov/show/ NCT04467151		
NCT04468009	Treatment of critically ill patients with COVID-19 with convalescent plasma	RCT Clinical- Trial- s.gov/show/ NCT04468009	36	30 June 2021
NCT04471051	An observational cohort trial of outcomes and antibody responses following treatment with COVID19 convalescent plasma in hospitalized COVID-19 patients	Non- Controlled Clinical- Trial- s.gov/show/ NCT04471051	150	30 April 2021
NCT04472572	Expanded access to convalescent plasma for treatment of COVID-19	Expanded access Clinical- Trial- s.gov/show/ NCT04472572	NR	NR
NCT04474340	COVID-19 convalescent plasma treatment in SARS-CoV-2 infected patients: multicenter interventional study	Controlled Clinical- Trial- s.gov/show/ NCT04474340	300	30 Decem- ber 2020
NCT04476888	Convalescent plasma treatment in COVID-19 patients at a tertiary care center in Pakistan	Controlled Clinical- Trial- s.gov/show/ NCT04476888	100	30 Septem- ber 2020

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

NCT04479163	Prevention of severe COVID-19 in infected elderly by early administration of convalescent plasma with high-titres of antibody against SARS-CoV2	RCT Clinical- trial- s.gov/show/ NCT04479163	210	31 July 2020	
NCT04483960	An international multi-centre randomised clinical trial to assess the clinical, virological and immunological outcomes in patients diagnosed with SARS-CoV-2 infection (COVID-19)	RCT Clinical- trial- s.gov/show/ NCT04483960	2400	12 July 2022	
NCT04492501	Investigational treatments for COVID-19 in tertiary care hospital of Pakistan	Non- randomised controlled NRSI trial- s.gov/show/ NCT04492501	600	20 July 2020	x
NCT04497324	PERUCONPLASMA: randomized clinical trial to evaluate safety and efficacy of the use of convalescent plasma in hospitalized patients with COVID-19	RCT Clinical- trial- s.gov/ct2/ show/ NCT04497324	100	31 December 2020	
NCT04497779	Evaluation of coronavirus disease 19 (COVID-19) convalescent plasma	Non- randomised controlled NRSI trial- s.gov/show/ NCT04497779	800	31 December 2022	
NCT04502472	Open-label treatment of severe coronavirus disease 2019 (COVID-19) with convalescent plasma	Non- randomised controlled NRSI trial- s.gov/show/ NCT04502472	200	31 December 2021	

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

		Tri- al- s.gov/show/ NCT04502472			
NCT04513158	Convalescent plasma in the early treatment of high-risk patients with SARS-CoV-2 (COVID-19) infection	Non- Con- trolled NRSI cal- Tri- al- s.gov/show/ NCT04513158	100	31 Decem- ber 2021	
NCT04516811	A prospective, randomized, placebo-controlled, double-blinded, RCT phase III clinical trial of the therapeutic use of convalescent plasma in the treatment of patients with moderate to severe COVID-19	Clin- i- cal- Tri- al- s.gov/show/ NCT04516811	600	31 July 2022	
NCT04516954	Assessment of the safety of convalescent plasma to treat COVID-19 patients with moderate and above illness	Non- Con- trolled NRSI cal- Tri- al- s.gov/show/ NCT04516954	10	30 Decem- ber 2020	
NL8633	A randomized, double blinded clinical trial of convalescent plasma compared to standard plasma for treatment of hospitalized non-ICU patients with COVID-19 infections	RCT www.tri- al- reg- is- ter.nl/tri- al/8633	430	1 May 2021	
RBR-4vm3yy	Use of convalescent plasma submitted to pathogen inactivation for the treatment of patients with severe COVID-19	Non- con- en- rolled NRSI i- cos.gov.br/rg/ RBR-4vm3yy/	20	31 May 2020	
RBR-7jqpnw	Therapeutic effectiveness of COVID-19 convalescent plasma produced by HEMOPE: a multicenter, randomized and controlled clinical trial	RCT www.en- saioclin- i-	110	30 July 2021	

Table 2. Summary: design and planned completion date of ongoing studies (Continued)

		cos.gov.br/rg/RBR-7jqp-nw/	
RPCEC00000323	Plasma treatment to asymptomatic patient with COVID-19 infection	rpcec.sld.cu22-en/trials/RPCEC00000323-En	12 December 2020

NR: not reported; **NRSI:** non-randomised study of intervention; **RCT:** randomised controlled trial

Table 3. Overview of effectiveness outcomes for randomised controlled trials

Outcomes		Randomised controlled trials	
		Gharbharan 2020	Li 2020
Mortality	All-cause mortality at hospital discharge	NR	NR
	Mortality (time to event)	NR	HR reported (time from randomisation)
	30-day mortality	NR	Events and OR reported (28-day mortality)
	90-day mortality	NR	NR
	Other reporting of mortality	OR of overall mortality (follow-up between 15-60 days)	NR
Improvement of clinical symptoms assessed with need for respiratory support	WHO Clinical Progression Scale		NR
	WHO Ordinal Scale	Day 15: number of participants with improvement and OR reported	NR
	Other ordinal Scale	NR	Events and OR at 7, 14 and 28 days, assessed with 6-point ordinal scale Improvement defined as 2-point improvement or discharge alive
	Other reporting of clinical improvement assessed with need for respiratory support	NR	Time to clinical improvement
Discharge from hospital	Time to discharge	HR reported	HR reported <ul style="list-style-type: none">• Time from randomisation• Time from hospitalisation
	Other reporting of hospital discharge:	NR	Discharge rate at day 28
Admission and length of stay on ICU	Admission to the ICU	NR	NR
	Length of stay on the ICU	NR	NR
	Other reporting of ICU stay and duration	Number of patients on ICU at baseline	NR
Virological response	Time to viral clearance	NR	NR
	Viral clearance	NR	Rates of negative SARS-CoV-2 viral PCR at 24 h, 48 h, and 72 h

Table 3. Overview of effectiveness outcomes for randomised controlled trials *(Continued)*

Other reporting of virological response		Test for antibodies at baseline	NR
Quality of life	Assessed with standardised scales	NR	NR

CP: convalescent plasma; **ECMO:** extracorporeal membrane oxygenation; **HR:** hazard ratio; **ICU:** intensive care unit; **IgG:** immunoglobulin G; **IgM:** immunoglobulin M; **IQR:** interquartile range; **NR:** not reported; **OR:** odds ratio; **PCR:** polymerase chain reaction; **SD:** standard deviation

Table 4. Overview of effectiveness outcomes for controlled non-randomised studies of intervention

Controlled non-randomised studies of intervention									
Outcomes	Abol-ghasemi 2020	Duan 2020	Hegerova 2020	Liu 2020	Rasheed 2020	Salazar 2020a	Xia 2020	Zeng 2020	
Mortality									
All-cause mortality at hospital discharge	Number of deaths, all other participants discharged alive	NR	NR	Nr	NR	NR	NR	NR	Number of deaths, all other participants discharged alive
Mortality (time to event)	NR	NR	NR	Survival curve (30-day follow-up)	NR	HR (28-day follow-up)	NR	NR	NR
30-day mortality	NR	NR	NR	NR	NR	Events reported (28-day mortality)	NR	NR	NR
90-day mortality	NR	NR	NR	NR	NR	NR	NR	NR	NR
Other reporting of mortality	NR	Number of deaths; follow-up not reported	7- and 14-day mortality <ul style="list-style-type: none"> • CP given prior to 7 days of hospitalisation • CP given after 7 days of hospitalisation 	Mortality at end of follow-up (median of 11 days for CP group and 9 days for control group)	Death rate (follow-up unclear)	Subgroups of 28-day mortality, and mortality at longest follow-up reported <ul style="list-style-type: none"> • Transfused within 72 h of admission • Transfused > 72 h after admission • Transfused within 72 h of admission, titre \geq 1350 	Mortality at end of follow-up	NR	NR

Table 4. Overview of effectiveness outcomes for controlled non-randomised studies of intervention (Continued)

Improvement of clinical symptoms assessed with need for respiratory support	WHO Clinical Progression Scale	NR	NR	NR	NR	NR	NR	NR	NR	NR
	WHO Ordinal Scale	NR	NR	Median (IQR), and mean (SD) reported at 7, and 14 days	NR	NR	NR	NR	NR	NR
	Other ordinal Scale	NR	NR	NR	NR	NR	NR	NR	NR	NR
Other reporting of clinical improvement assessed with need for respiratory support	Participants requiring intubation	<ul style="list-style-type: none"> Clinical status (death, stable, improved, discharged); follow-up not reported Improvement within 3 days reported for CP group 	<ul style="list-style-type: none"> Duration of mechanical ventilation Extubated survivors 	Worsening of clinical symptoms at day 14	Mean recovery time from critical illness; defined as improvement in the signs and symptoms of the critical infection, namely relief of severe dyspnoea, no need for ventilators or oxygen therapy, declining in fever if any, declining in respiratory rate to < 30/min, and increased oxygen saturation to > 93% at rest, so that participants can be discharged from respiratory care unit to the infectious disease ward	Subgroups of mechanical ventilation requirement, and supplemental oxygen requirement in days; ventilation status (room air, low flow, high flow, mechanical ventilation, ECMO, death) at day 0, 7, 14, and 28; clinical improvement relative to day 0 at day 7, 14, and 28. <ul style="list-style-type: none"> Transfused within 72 h of admission Transfused > 72 h after admission Transfused within 72 h of admission, titre ≥ 1350 	<ul style="list-style-type: none"> Highest 6-category scale score (SCSS) Time to clinical improvement, defined as a 2-point decrease in SCSS; reported for CP group only 	NR		

Table 4. Overview of effectiveness outcomes for controlled non-randomised studies of intervention (Continued)

Discharge from hospital	Time to discharge	Mean days (SD)	NR	Median days (IQR) of stay, at 7, and 14 days after CP transfusion	NR	NR	NR	NR	NR
		<ul style="list-style-type: none"> Time from plasma transfusion Time from hospitalisation 							
	Other reporting of hospital discharge	People discharged from hospital ≤ 5 days post admission	NR	Median length of stay in days (IQR) at 7, and 14 days after CP transfusion: <ul style="list-style-type: none"> survivors nonsurvivors Discharges alive	NR	NR	Subgroups of discharge rate at 28-day follow-up <ul style="list-style-type: none"> Transfused within 72 h of admission Transfused > 72 h after admission Transfused within 72 h of admission, titre ≥ 1350 	Discharge rate at end of follow-up	NR
Admission and length of stay on ICU	Admission to the ICU	NR	NR	NR	NR	NR	Subgroups of admission rate after day 0 <ul style="list-style-type: none"> Transfused within 72 h of admission Transfused > 72 h after admission Transfused within 72 h of admission, titre ≥ 1350 	Non-ICU patients before CP therapy, that were then admitted to the ICU	Admission rate
	Length of stay on the ICU	NR	NR	NR	NR	NR	Subgroups of length of ICU stay after day 0 <ul style="list-style-type: none"> Transfused within 72 h of admission 	NR	NR

Table 4. Overview of effectiveness outcomes for controlled non-randomised studies of intervention (Continued)

- Transfused > 72 h after admission
- Transfused within 72 h of admission, titre \geq 1350

	Other reporting of ICU stay and duration	NR	NR	NR	NR	NR	NR	NR	NR
Virological response	Time to viral clearance	NR	NR	NR	NR	Mean duration of detectable COVID-19 infection	NR	NR	Median duration of viral shedding
	Viral clearance	NR	NR	NR	NR	NR	NR	SARS-CoV-2 viral clearance reported for CP group only 1-3, 1-7, 1-14 days	SARS-CoV-2 clearance <ul style="list-style-type: none"> • in the whole group • among deaths
	Other reporting of virological response	NR	NR	NR	NR	SARS-CoV-2 IgG and IgM at baseline, day 3	NR	NR	NR
Quality of life	Assessed with standardised scales	NR	NR	NR	NR	NR	NR	Nr	NR

CP: convalescent plasma; **ECMO:** extracorporeal membrane oxygenation; **HR:** hazard ratio; **ICU:** intensive care unit; **IgG:** immunoglobulin G; **IgM:** immunoglobulin M; **IQR:** interquartile range; **NR:** not reported; **OR:** odds ratio; **PCR:** polymerase chain reaction; **SD:** standard deviation

Table 7. Serious adverse events

Study	Number of participants	Serious adverse events
Abolghasemi 2020	115 (CP group)	0
Bradfute 2020 ^a	13	0
Donato 2020	47	0
Duan 2020	10 (CP group)	0
Dulipsingh 2020	46	0
Gharbharan 2020	43 (CP group)	0
Hegerova 2020	20 (CP group)	0
Jin 2020	6	0
Joyner 2020a	35,322 (20,000 included in safety analysis)	<p>Total events within 7 days after transfusion: 1282</p> <p>Within 4 h after transfusion: 146 events reported</p> <ul style="list-style-type: none"> • 63 dead (12 possibly, 1 probably, 0 definitely related) • 37 TACO (37 potentially, probably, or definitely related) • 20 TRALI (20 potentially, probably, or definitely related) • 26 severe allergic reaction (26 potentially, probably, or definitely related) <p>Within 7 days after transfusion: additional 1136 events reported</p> <ul style="list-style-type: none"> • 87 thrombotic or thromboembolic complication (32 potentially, probably, or definitely related) • 406 sustained hypotension (54 potentially, probably, or definitely related) • 643 cardiac events (74 potentially, probably, or definitely related)
Li 2020	52 (CP group)	1 possible severe transfusion-associated dyspnoea (patient had "shortness of breath, cyanosis, and severe dyspnoea within 6 hours of transfusion. The participant was given dexamethasone, aminophylline, and other supportive care immediately and gradually improved after 2 hours)."
Liu 2020	39 (CP group)	0
Madariaga 2020	10	0
Olivares-Gazca 2020	10	0

Table 7. Serious adverse events (Continued)

Perotti 2020	46	3	<ul style="list-style-type: none"> Anaphylaxis/hypersensitivity (relation possible) TRALI (relation possible) Subsegmental pulmonary embolism (relation unlikely/excluded)
Rasheed 2020	21 (CP group)	0	
Xia 2020	138 (CP group)	0	
Zeng 2020	6 (CP group)	0	

CP: convalescent plasma; **TACO:** transfusion-associated circulatory overload; **TRALI:** transfusion-related acute lung injury

^aStudy-related serious adverse events only; one participant developed non-transfusion-related shock and acute kidney injury.

APPENDICES

Appendix 1. Search strategy MEDLINE

1. Coronavirus Infections/
2. Coronavirus/
3. "Betacoronavirus"/
4. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kf.
5. (coronavirus* or coronovirus* or coron?virinae* or "2019-nCoV" or 2019nCoV or 2019-CoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCov or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or SARSr-cov or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or Wuhan virus* or novel CoV or CoV 2 or CoV2 or betacoron?vir*).tw,kf.
6. (((respiratory* adj2 (acute* or symptom* or disease* or illness* or condition*)) or "sea-food market*" or "seafood market*" or "food market*" or "foodmarket*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).tw,kf.
7. ((outbreak* or wildlife* or wild-life or pandemic* or epidemic*) adj3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).tw,kf.
8. (anti-flu* or anti-influenza* or antifu* or antinfluenza*).tw,kf.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. Plasma/
11. Immunoglobulins/
12. Immunoglobulins, Intravenous/
13. Immune Sera/
14. ((convalesc* or recovered or cured or rehabilitat* or survivor* or survived or virus-positive or virus neutrali* or virus inactivated or antibod* or high-titre* or high-titer*) adj6 (plasma or blood or serum or sera)).mp.
15. ((plasma adj1 therap*) or gamma-globulin* or "γ-Globulin" or hyper-Ig).tw,kf.

16. ((hyperimmune or hyper-immune or high-dos*) adj3 (plasma or immunoglobulin* or IVIG* or immune globulin* or globulin* or IgG)).tw,kf.
17. (plasma adj5 (immun* or antibod* or exchange* or donor* or donat* or transfus* or infus*)).mp.
18. ((convalesc* or recovered or cured or rehabilitat* or survivor* or survived or virus-positive or virus inactivated or antibody-positive) adj5 (donor* or donat*)).mp.
19. (((serum or sera) adj2 (therap* or treatment*)) or serotherap* or sero-therap*).tw,kf.
20. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 9 and 20
22. Covid-19 Serotherapy.px
23. (Flu-IVIG or ((anti-flu* or anti-influenza* or antifu* or antinfluenza*) adj5 plasma)).mp.
24. 21 or 22 or 23
25. (exp Animals/ or exp Animal Experimentation/ or exp Models, Animal/) not Humans/
26. 24 not 25
27. limit 26 to yr="2019 -Current"

Appendix 2. Search strategy Embase

Searches

1. "Coronavirus Infections"/ or "Coronavirus Infection"/
2. Coronavirinae/ or Coronavirus/ or exp Betacoronavirus/
3. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kw.
4. (coronavirus* or coronovirus* or coron?virinae* or "2019-nCoV" or 2019nCoV or 2019-CoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCov or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or SARSr-cov or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese* or Wuhan virus* or novel CoV or CoV 2 or CoV2 or betacoron?vir*).tw,kw.
5. (((respiratory* adj2 (acute* or symptom* or disease* or illness* or condition*)) or "sea-food market*" or "seafood market*" or "food market*" or "foodmarket*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).tw,kw.
6. ((outbreak* or wildlife* or wild-life* or pandemic* or epidemic*) adj3 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).tw,kw.
7. (anti-flu* or anti-influenza* or antifu* or antinfluenza*).tw,kw.
8. or/1-7
9. Plasma Transfusion/
10. exp Immunoglobulin/
11. ((convalesc* or recovered or cured or survivor* or survived or rehabilitat* or virus-positive or virus-neutrali* or virusinactivated or antibody-rich or high-tire* or high-titer*) adj6 (plasma or blood or serum or sera)).mp.
12. ((plasma adj1 therap*) or gamma-globulin or "y-Globulin" or hyper-Ig).tw,kw.
13. (plasma adj5 (immun* or antibod* or exchange* or donor* or donat* or transfus* or infus*)).mp.
14. ((convalesc* or recovered or cured or survivor* or rehabilitat* or survived or virus-positive or virus inactivated or antibody-positive) adj5 (donor* or donat*)).mp.
15. (plasma adj5 (immun* or antibod* or exchange* or donor* or donat* or transfus* or infus*)).mp.

16. ((hyperimmune or hyper-immune or high-dos*) adj3 (plasma or immunoglobulin* or IVIG* or immune globulin* or globulin* or IgG)).tw,kw.
17. (plasma adj5 (immun* or antibod* or exchange* or donor* or donat* or transfus* or infus*)).mp.
18. ((convalesc* or recovered or cured or rehabilitat* or survivor* or survived or virus-positive or virus inactivated or antibody-positive) adj5 (donor* or donat*)).mp.
19. (((serum or sera) adj2 (therap* or treatment*)) or serotherap* or sero-therap*).tw,kw.
20. or/9-19
21. (Flu-IVIG or ((anti-flu* or antifu*) adj5 plasma)).mp.
22. (8 and 20) or 21
23. (exp animal/ or nonhuman/) not exp human/
24. a nimal experiment/ not (human experiment/ or human/)
25. 23 or 24
26. 22 not 25

Appendix 3. Search strategy PubMed

- #1 (corona-virus* OR corono-virus* OR coronavirus* OR coronovirus* OR coronavirinae* OR coronavirinae* OR betacoronavirus OR Wuhan* OR Hubei* OR Huanan OR "2019 nCoV" OR 2019nCoV OR 2019 CoV OR nCoV2019 OR "nCoV 2019" OR "COVID 19" OR COVID19 OR "CORVID 19" OR CORVID19 OR "WN CoV" OR WNCov OR "HCoV 19" OR HCoV19 OR CoV OR "2019 novel*" OR Ncov OR "n cov" OR "SARS CoV 2" OR "SARSCoV 2" OR "SARS-CoV-2" OR "SARSCoV-2" OR "SARSCoV2" OR "SARS CoV2" OR „SARS-Cov2“ OR SARSCov19 OR "SARS Cov19" OR "SARSCov 19" OR "SARS Cov 19" OR Ncovor OR Ncorona* OR Ncorono* OR NcovWuhan* OR NcovHubei* OR NcovChina* OR NcovChinese* OR novel CoV OR CoV2 OR SARSr-cov)v 19" OR "SARS Cov 19" OR Ncovor OR Ncorona* OR Ncorono* OR NcovWuhan* OR NcovHubei* OR NcovChina* OR NcovChinese* OR SARSr-cov)
- #2 (((respiratory* AND (acute* OR symptom* OR disease OR diseases OR diseased OR illness* OR condition*)) OR "seafood market*" OR "sea food market*" OR "food market*" OR "foodmarket*") AND (Wuhan* OR Hubei* OR China OR "China's" OR Chinese* OR Huanan*))
- #3 ((outbreak* OR wildlife* OR wild-life* OR pandemic* OR epidemic*) AND (China OR "China's" OR Chinese* OR Huanan* OR Wuhan OR Hubei*))
- #4 (anti-flu* OR anti-influenza* OR antifu* OR antinfluenza*)
- #5 #1 OR #2 OR #3 OR #4
- #7 (((convalesc*[TIAB] OR recovered[TIAB] OR cured[TIAB] OR survivor*[TIAB] OR survived[TIAB] OR virus-positive[TIAB] OR virus-neutrali*[TIAB] OR "virus inactivated"[TIAB] OR antibod*[TIAB] OR high-titre*[TIAB] OR high-titer*) AND (plasma[TIAB] OR blood[TIAB] OR donor*[TIAB] OR donat*[TIAB]))
- #8 ("therapeutic plasma" OR "plasma therapy" OR "immune plasma" OR "plasma exchange" OR gamma-globulin* or "γ-Globulin" or hyper-Ig)
- #9 (plasma[TI] AND (immun*[TIAB] OR transfus*[TIAB] OR infus*[TIAB]))
- #10 ((hyperimmune OR hyper-immune OR high-dos*) AND (plasma OR immunoglobulin* OR IVIG* OR immune globulin* OR globulin*))
- #11 #7 OR #8 OR #9 OR #10
- #12 #6 AND #11
- #13 (Flu-IVIG OR ((anti-flu* or anti-influenza* or antifu* or antinfluenza*) AND plasma))
- #14 #12 OR #13
- #15 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
- #16 #13 AND #15: Publication date from 2019/11/01 to present

Appendix 4. Search strategy CDC COVID-19 Database (for searching in Endnote)

Any Field: plasma or hyperimmune or hyper-immune or IVIG or immunoglobulin* or immune-globulin* or globulin* or gamma-globulin or γ-Globulin or hyper-Ig or serum or convalesc* or sera or donor or donat* or sero* or flu-IVIG or antifu* or anti-flu*

Appendix 5. Search strategy Cochrane COVID-19 Study Register

plasma OR hyperimmune OR hyper-immune OR IVIG OR immunoglobulin OR globulin OR gamma-globulin OR γ-Globulin OR hyper-Ig OR serum OR sera OR donor OR donation OR sero* OR flu-IVIG OR antifu* OR anti-flu

Appendix 6. Planned subgroups for the next update

We will add subgroup analyses for the following characteristics in an update of this review.

- Level of antibody titre in donors
- Level of antibody titre in recipients at baseline

Considering the currently available evidence, we decided to add these subgroups, because their role in the effectiveness of convalescent plasma is currently discussed and needs to be further investigated.

Appendix 7. ROBINS-I assessment for: treatment with convalescent plasma compared to treatment without convalescent plasma for people with COVID-19 (per study)

We assessed methodological quality and risk of bias using the Risk Of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool (Sterne 2016).

'Risk of bias' assessment of Abolghasemi 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Bias due to confounding	Mortality Clinical improvement Adverse events	Moderate	Quote: "Treatment and control groups, except for their number of patients, were matched based on gender, age and presence of two main co-morbidities including hypertension and diabetes of mellitus (...). Their chest CT scan scores was also statistically matched indicating that both patient groups had similar clinical conditions on their entrance into the study."
Bias in selection of participants into the study	Mortality Clinical improvement Adverse events	Critical	Quote: "Due to ethical consideration, responsible physicians were reluctant to deprive COVID-19 patients from convalescent plasma therapy. Therefore, patients in control group were mainly comprises of patients with mild clinical presentation who did not have blood group convalescent plasma match on their hospital admission or in the next 3 days."
Bias in classification of interventions	Mortality Clinical improvement Adverse events	Critical	Unclear when assignment to control group was done. Very few details of treatment in control group are provided, and it is unclear whether participants were treated during the same period or at a time when less was known about the disease and the treatment options. Knowledge of patients' outcomes at the time of assignment to the control group could have had a major impact on the selection.
Bias due to deviations from intended interventions	Mortality Clinical improvement Adverse events	Low	All participants received the intended intervention.
Bias due to missing data	Mortality	Critical	All-cause mortality is reported for all participants, but follow-up period is not described

(Continued)

	Clinical improvement	Critical	Need for intubation is reported for all participants, but follow-up period is not described
	Adverse events	Critical	No safety data for control group reported
Bias in measurement of outcomes	Mortality	Moderate	Observation reported from hospitalisation and transfusion for convalescent plasma group, and from hospitalisation for control group
	Clinical improvement		Outcome assessors were aware of the intervention received by study participants.
	Adverse events	Critical	Only transfusion-related adverse events reported
Bias in selection of the reported results	Mortality	Critical	Only primary study outcome was defined in trial registry:
	Clinical improvement		Quote: "Improving respiratory function of patients. Timepoint: Every 24 hours. Method of measurement: Clinical and, para-clinical." Different outcomes were reported in journal publication and those are poorly defined. Quote: "The primary outcomes were the patient survival and length of hospital stay. Secondary outcomes included patients' needs for intubation, improvements in clinical symptoms such as tachypnea and para clinical measured of the patients and frequency of adverse effects resulting from plasma transfusion."
	Adverse events	Critical	Observation period unclear; only transfusion-related adverse events assessed and reported
Overall bias	Mortality	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
	Clinical improvement	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
	Adverse events	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

'Risk of bias' assessment of Duan 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Bias due to confounding	Mortality	Serious	Quote: "Historic control group was formed by random selection of 10 patients from the cohort treated in the same hospitals and matched by age, gender, and severity of the diseases to the 10 cases in our trial." Not adjusted for co-morbidities, previous treatments, time of disease onset, etc.
	Clinical improvement		
	Adverse events		
Bias in selection of participants into the study	Mortality	Critical	Small sample size, unclear how participants were selected into intervention group, unclear how long participants of historical control group were followed
	Clinical improvement		

(Continued)

Adverse events			
Bias in classification of interventions	Mortality	Critical	Assignment to control group was done retrospectively. Treatment details of control group are not provided, and it is unclear whether participants were treated during the same period or at a time when less was known about the disease and the treatment options. Knowledge of patients' outcomes at the time of assignment to the control group could have had a major impact on the selection.
	Clinical improvement		
	Adverse events		
Bias due to deviations from intended interventions	Mortality	Low	All participants received the intended intervention.
	Clinical improvement		
	Adverse events		
Bias due to missing data	Mortality	Serious	Mortality is reported for participants in intervention group until day 3 of follow-up. Unclear how long control group was followed and how clinical status was assessed
	Clinical improvement	Critical	Unclear how long control group was followed and clinical status in terms of respiratory support was not assessed
	Adverse events	Critical	No safety data for control group reported
Bias in measurement of outcomes	Mortality	Critical	Unclear whether follow-up was comparable between groups
	Clinical improvement	Critical	Clinical course is reported for participants in intervention group until day 3 of follow-up
	Adverse events	Critical	Only transfusion-related adverse events reported
Bias in selection of the reported results	Mortality	Critical	Study was registered as single-arm trial and control group was retrospectively selected
	Clinical improvement		
	Adverse events	Critical	
Overall bias	Mortality	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
	Clinical improvement	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
	Adverse events	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

Risk of bias assessment of Hegerova 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement

(Continued)

Bias due to confounding	Mortality	Moderate	Adjusted for age, number of comorbidities, WHO clinical symptoms score, sequential organ failure assessment score, and severity of illness. But with regard to this domain, the study cannot be considered comparable to a well-performed randomised trial.
	Clinical improvement		
	Adverse events		
Bias in selection of participants into the study	Mortality	Critical	Intervention arm is part of US Expanded Access Program (Joyner 2020a). Unclear how and why 20 participants were selected. Also unclear out of which pool control group was selected. Selection into the study may have been related to intervention and outcome.
	Clinical improvement		
	Adverse events		
Bias in classification of interventions	Mortality	Critical	Assignment to control group was done retrospectively. Scant details of control group treatments are provided. Knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.
	Clinical improvement		
	Adverse events		
Bias due to deviations from intended interventions	Mortality	Low	All participants received the intended intervention.
	Clinical improvement		
	Adverse events		
Bias due to missing data	Mortality	Low	Data were reasonably complete
	Clinical improvement		
	Adverse events	Critical	No safety data for control group available
Bias in measurement of outcomes	Mortality	Moderate	Retrospective study; baseline day 0 for matched controls corresponds to equivalent hospital day as convalescent plasma transfusion
	Clinical improvement		
	Adverse events	Critical	Only transfusion-related adverse events assessed and reported
Bias in selection of the reported results	Mortality	Critical	Retrospective study; selection of all reported results are likely biased
	Clinical improvement		
	Adverse events		
Overall bias	Mortality	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient
	Clinical improvement	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
	Adverse events	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

Risk of bias assessment of Liu 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Bias due to confounding	Mortality	Serious	Only adjusted for hydroxychloroquine and azithromycin, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion. Not adjusted for e.g. age and gender
	Clinical improvement		
	Adverse events		
Bias in selection of participants into the study	Mortality	Moderate	<p>Selection into the study may have been related to intervention and outcome, but the study authors used appropriate methods to adjust for the selection bias.</p> <p>Quote: "propensity score-matched analysis using The Mount Sinai Hospital's COVID-19 confirmed patient pool from the same calendar period (24 March 2020 105 to 8 April 2020). A logistic regression was fit to predict the potential for plasma therapy based on time series data obtained at baseline upon admission, prior to transfusion, and the day of 107 transfusion."</p>
	Clinical improvement		
	Adverse events		
Bias in classification of interventions	Mortality	Critical	Assignment to control group was done retrospectively. Treatment details of control group are not provided. Knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.
	Clinical improvement		
	Adverse events		
Bias due to deviations from intended interventions	Mortality	Low	All participants received the intended intervention. Most common co-interventions (hydroxychloroquine and azithromycin, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion) were propensity score-matched. Other co-interventions were administered too infrequently to enforce exact matching
	Clinical improvement		
	Adverse events		
Bias due to missing data	Mortality	Low	Data were reasonably complete
	Clinical improvement		
Bias in measurement of outcomes	Mortality	Moderate	<p>Quote: "For controls patients, the day of transfusion was defined by the length of stay on which their respective recipient received their transfusion."</p> <p>Median follow-up comparable between groups. However, outcome assessors were not blinded to intervention and the study was performed retrospectively.</p>
	Clinical improvement		
	Adverse events		
Bias in selection of the reported results	Mortality	Critical	Retrospective study; selection of all reported results are likely biased
	Clinical improvement		

(Continued)

	Adverse events	Critical	Observation period unclear, non-occurrence of transfusion-related adverse events only reported in discussion section
Overall bias	Mortality	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
	Clinical improvement	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
	Adverse events	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

Risk of bias assessment of Rasheed 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Bias due to confounding	Mortality	Serious	Only adjusted for age and gender. Other confounders not considered
	Clinical improvement		
	Adverse events		
Bias in selection of participants into the study	Mortality	Serious	Study registered after recruitment was completed. Unclear whether inclusion criteria were defined based on available participants or whether inclusion criteria had been defined before recruitment
	Clinical improvement		
	Adverse events		
Bias in classification of interventions	Mortality	Low	Intervention and control group well-defined. All participants received hydroxychloroquine with azithromycin. Participants in the intervention group received additional convalescent plasma Quote: "Forty nine critically-ill COVID-19 patients were included in the current study. All of the patients were with pneumonia and residing in RCU; As a result of ABO compatibility and limited plasma, 21 of the patients were randomly chosen to take CP, while other age- and sex- matched 28 patients were under the conventional therapy as control group"
	Clinical improvement		
	Adverse events		
Bias due to deviations from intended interventions	Mortality	Low	All participants received the intended intervention.
	Clinical improvement		
	Adverse events		
Bias due to missing data	Mortality	Low	Data were reasonably complete
	Clinical improvement		
	Adverse events	Critical	No safety data for control group available

(Continued)

Bias in measurement of outcomes	Mortality	Serious	Outcome assessors were probably aware of the received intervention, and it was unclear when observation period for control group started; but observation probably starts after enrolment into the study
	Clinical improvement		
			Quote: "Forty nine critically-ill COVID-19 patients were included in the current study. ... As a result of ABO compatibility and limited plasma, 21 of the patients were randomly chosen to take CP, while other age- and sex- matched 28 patients were under the conventional therapy as control group."
			Quote: "The CP group was compared to the age- and sex- matched control group in terms of recovery time from critical illness (RTCI), days of infection before inclusion to the study, and the whole duration of infection."
			Comment: no statistical differences between days of infection
	Adverse events	Critical	Only transfusion-related adverse events reported
Bias in selection of the reported results	Mortality	Serious	Follow-up defined as up to 8 weeks in trials registry, but actual follow-up not mentioned in preprint article
	Clinical improvement		
	Adverse events	Critical	No safety data for control group reported
Overall bias	Mortality	Serious	The study has some important problems, however better evidence is still insufficient.
	Clinical improvement		
	Adverse events		

Risk of bias assessment of [Salazar 2020a](#)

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Bias due to confounding	Mortality	Moderate	Quote: "one-to-many nearest neighbor propensity score matching without replacement using an initial ratio of case:control = 1:3 and caliper of 1 between patients having plasma transfusion (cases) versus patients who did not have plasma transfusion (controls). The primary matching criteria included age (categorical, <30, 30-39, 40-49, 50-59, 60-69, 70-79, ≥80), sex, BMI (</>=30), diabetes, hypertension, chronic pulmonary disease, chronic kidney disease, hyperlipidaemia, coronary disease, and baseline ventilation requirement within 48 h from admission. A secondary propensity score matching the ratio of case:control of either 1:2 or 1:1 and caliper <1 was conducted based on the ventilation status at Day 0, which was defined as the day of transfusion for cases and the corresponding day in the hospitalization course for controls"
	Clinical improvement		
	Adverse events	Not applicable	Outcome not reported

(Continued)

Bias in selection of participants into the study	Mortality	Moderate	Selection into the study may have been related to intervention and outcome, but the study authors used appropriate methods to adjust for the selection bias (propensity score-matched).
	Clinical improvement		
Adverse events		Not applicable	Outcome not reported
Bias in classification of interventions	Mortality	Critical	Assignment to control group was done retrospectively. Scant details of control group treatments are provided. Knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.
	Clinical improvement		
Adverse events		Not applicable	Outcome not reported
Bias due to deviations from intended interventions	Mortality	Low	All participants received the intended intervention.
	Clinical improvement		
Adverse events		Not applicable	Outcome not reported
Bias due to missing data	Mortality	Low	Data were reasonably complete
	Clinical improvement		
Adverse events		Not applicable	Outcome not reported
Bias in measurement of outcomes	Mortality	Critical	Observation period different across groups. Intervention group observed and assessed 28 days post-transfusion, control group observed and assessed 28 days post-admission
	Clinical improvement		
Adverse events		Not applicable	Outcome not reported
Bias in selection of the reported results	Mortality	Critical	Retrospective study, selection of all reported results are likely biased
	Clinical improvement	Critical	Not reported for whole groups; reported for subcohorts only: <ul style="list-style-type: none"> • secondary matched, transfused within 72 h of admission • secondary matched, transfused > 72 h after admission • secondary matched, transfused within 72 h of admission, titre ≥ 1350
Adverse events		Not applicable	Outcome not reported
Overall bias	Mortality	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
	Clinical improvement	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
Adverse events		Not applicable	Outcome not reported

'Risk of bias' assessment of Xia 2020

Domain	Assessed out-comes	Authors' judgement	Support for judgement
Bias due to con- founding	Mortality Clinical improve- ment Adverse events	Serious	Not adjusted, cohort of all patients admitted to Wuhan Huoshenshan Hospital (China) from 4 February 2020 to 30 March 2020
Bias in selec- tion of partici- pants into the study	Mortality Clinical improve- ment Adverse events	Critical	Unclear how participants were allocated to receive convalescent plas- ma or not.
Bias in classifi- cation of inter- ventions	Mortality Clinical improve- ment Adverse events	Moderate	Quote: "All patients received standard treatments, including anti-virus therapy, traditional Chinese medicine, and respiratory support" Intervention group received additional 200-1200 mL convalescent plas- ma.
Bias due to de- viations from intended inter- ventions	Mortality Clinical improve- ment Adverse events	Low	All assessed participants received intended intervention
Bias due to missing data	Mortality Clinical improve- ment Adverse events	Low	Data were reasonably complete
		Critical	No safety data for control group available
Bias in mea- surement of outcomes	Mortality Clinical improve- ment Adverse events	Critical	Unclear when observation period started for control group. Outcome assessors were not blinded to intervention and the study was per- formed retrospectively.
		Critical	Only adverse events after plasma transfusion reported
Bias in selec- tion of the re- ported results	Mortality Clinical improve- ment Adverse events	Critical	Retrospective study, selection of all reported results are likely biased
		Critical	Retrospective study; selection of all reported results are likely biased; only transfusion-related adverse events reported; no safety data for control group available
Overall bias	Mortality	Critical	The study is too problematic to provide any useful evidence, however- better evidence is still insufficient.

(Continued)

Clinical improvement	Critical	The study is too problematic to provide any useful evidence, however-better evidence is still insufficient.
Adverse events	Critical	The study is too problematic to provide any useful evidence, however-better evidence is still insufficient.

'Risk of bias' assessment of Zeng 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Bias due to confounding	Mortality	Serious	Not adjusted for confounding factors
	Clinical improvement		
	Adverse events		
Bias in selection of participants into the study	Mortality	Moderate	Allocation to intervention and control group based on donor availability Quote: "A total of 21 contemporaneous critically ill patients with COVID-19 were enrolled in the current study (Table 1), and all of them required intensive care unit admission. Six of the patients received convalescent plasma treatment based on the limited availability of convalescent plasma and ABO compatibility. Five of 6 patients in the convalescent plasma treatment group and 11 of 15 in the non-convalescent plasma treatment (control) group were male."
	Clinical improvement		
	Adverse events		
Bias in classification of interventions	Mortality	Critical	Retrospective study design. Despite missingness of donors, unclear how control group was selected. Treatment details of control group are provided, but knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.
	Clinical improvement		
	Adverse events		
Bias due to deviations from intended interventions	Mortality	Low	All participants received intended intervention. Co-interventions (e.g. antiviral therapy, traditional Chinese medicine, etc.) seem to be balanced across treatment groups.
	Clinical improvement		
	Adverse events		
Bias due to missing data	Mortality	Low	Data were reasonably complete
	Clinical improvement		Living participants discharged
	Adverse events	Critical	No safety data for control group available
Bias in measurement of outcomes	Mortality	Low	Quote: "The duration of illness was calculated from the onset of illness to the date of discharge or death"
	Clinical improvement		Follow-up until death or discharge
	Adverse events	Critical	Only adverse events after plasma transfusion reported

(Continued)

Bias in selection of the reported results	Mortality	Critical	Retrospective study; selection of all reported results are likely biased
	Clinical improvement		
	Adverse events	Critical	Retrospective study; selection of all reported results are likely biased; only transfusion-related adverse events reported; no safety data for control group available
Overall bias	Mortality	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
	Clinical improvement	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
	Adverse events	Critical	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

Appendix 8. ROBINS-I assessment for: treatment with convalescent plasma compared to treatment without convalescent plasma for people with COVID-19 (per outcome)

ROBINS-I assessment for: treatment with convalescent plasma compared to treatment without convalescent plasma for people with COVID-19 (mortality)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Abolghase-mi 2020	Moderate	Critical	Critical	Low	Critical	Moderate	Critical	Critical
	Quote: "Treatment and control groups, except for their number of patients, were matched based on gender, age and presence of two main co-morbidities including hypertension and diabetes of mellitus (...). Their chest CT scan scores was also statistically matched indicating that both patient groups had similar clinical conditions on their entrance into the study."	Quote: "Due to ethical consideration, responsible physicians were reluctant to deprive COVID-19 patients from convalescent plasma therapy. Therefore, patients in control group were mainly comprises of patients with mild clinical presentation who did not have blood group convalescent plasma match on their hospital admission or in the next 3 days."	Unclear when assignment to control group was done. Scant details of control group treatments are provided, and it is unclear whether participants were treated during the same period or at a time when less was known about the disease and the treatment options. Knowledge of patients' outcomes at the time of assignment to the control group could have had a major impact on the selection.	All participants received the intended intervention.	All-cause mortality is reported for all participants, but follow-up period is not described	Observation reported from hospitalisation and transfusion for convalescent plasma group, and from hospitalisation for control group Outcome assessors were aware of the intervention received by study participants.	Only primary study outcome was defined in trials registry: Quote: "Improving respiratory function of patients. Time-point: Every 24 hours. Method of measurement: Clinical and, para-clinical." Different outcomes were reported in	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

journal publication and those are poorly defined.

Quote: "The primary outcomes were the patient survival and length of hospital stay. Secondary outcomes included patients' needs for intubation, improvements in clinical symptoms such as tachypnea and paraclinical measured of the patients and frequency of adverse

(Continued)

effects resulting from plasma transfusion."

(Continued)

Duan 2020	Serious	Critical	Critical	Low	Serious	Critical	Critical	Critical
	Quote: "Historic control group was formed by random selection of 10 patients from the cohort treated in the same hospitals and matched by age, gender, and severity of the diseases to the 10 cases in our trial." Not adjusted for comorbidities, previous treatments, time of disease onset, etc.	Small sample size, unclear how participants were selected into intervention group, unclear how long participants of historical control group were followed	Assignment to control group was done retrospectively. Treatment details of control group are not provided, and it is unclear whether participants were treated during the same period or at a time when less was known about the disease and the treatment options. Knowledge of patients' outcomes at the time of assignment to the control group could have had a major impact on the selection.	All participants received the intended intervention.	Mortality is reported for participants in intervention group until day 3 of follow-up. Unclear how long control group was followed and how clinical status was assessed	Unclear whether follow-up was comparable between groups	Study was registered as single-arm trial and control group was retrospectively selected	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
Hegerova 2020	Moderate	Critical	Critical	Low	Low	Moderate	Critical	Critical
	Adjusted for age, number of comorbidities, WHO clinical symptoms score, sequential organ failure assessment score, and severity of illness. But with regard to this domain, the study cannot be considered comparable to a well-per-	Intervention arm is part of US Expanded Access Program (Joyn-er 2020a). Unclear how and why 20 participants were selected. Also unclear out of which pool control group was selected. Selection into the study may have been related to intervention and outcome.	Assignment to control group was done retrospectively. Scant details of control group treatments are provided. Knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.	All participants received the intended intervention.	Data were reasonably complete	Retrospective study; baseline day 0 for matched controls corresponds to equivalent hospital day as convalescent plasma transfusion	Retrospective study; selection of all reported results are likely biased	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

(Continued)

	formed randomised trial.								
Liu 2020	Serious	Moderate	Critical	Low	Low	Moderate	Critical	Critical	
	<p>Only adjusted for hydroxychloroquine and azithromycin, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion. Not adjusted for e.g. age and gender</p>	<p>Selection into the study may have been related to intervention and outcome, but the study authors used appropriate methods to adjust for the selection bias.</p> <p>Quote: "propensity score-matched analysis using The Mount Sinai Hospital's COVID-19 confirmed patient pool from the same calendar period (24 March 2020 105 to 8 April 2020). A logistic regression was fit to predict the potential for plasma therapy based on time series data obtained at baseline upon admission, prior to transfusion, and the day of 107 transfusion."</p>	<p>Assignment to control group was done retrospectively. Treatment details of control group are not provided. Knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.</p>	<p>All participants received the intended intervention. Most common co-interventions (hydroxychloroquine and azithromycin, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion) were propensity score-matched. Other co-interventions were administered too infrequently to enforce exact matching</p>	<p>Data were reasonably complete</p>	<p>Quote: "For controls patients, the day of transfusion was defined by the length of stay on which their respective recipient received their transfusion."</p> <p>Median follow-up comparable between groups. However, outcome assessors were not blinded to intervention and the study was performed retrospectively.</p>	<p>Retropective study; selection of all reported results are likely biased</p>	<p>The study is too problematic to provide any useful evidence, however better evidence is still insufficient.</p>	
Rasheed 2020	Serious	Serious	Low	Low	Low	Serious	Serious	Serious	

<p>The study has some important problems, however better evidence is still insufficient.</p>	<p>Follow-up defined as up to 8 weeks in trials registry, but actual follow-up not mentioned in preprint article</p>	<p>Outcome assessors were probably aware of the received intervention, and it was unclear when observation period for control group started; but observation probably starts after enrolment into the study</p> <p>Quote: "Forty nine critically-ill COVID-19 patients were included in the current study. ... As a result of ABO compatibility and limited plasma, 21 of the patients were randomly chosen to take CP, while other age- and sex-matched 28 patients were under the conventional therapy as control group."</p> <p>Quote: "The CP group was compared to the age- and sex- matched control group in terms of recovery time from critical illness (RTCI), days of infection before inclusion to the study, and the whole duration of infection."</p>	<p>Data were reasonably complete</p>	<p>All participants received the intended intervention.</p>	<p>Intervention and control group well-defined. All participants received hydroxychloroquine with azithromycin. Participants in the intervention group received additional convalescent plasma</p> <p>Quote: "Forty nine critically-ill COVID-19 patients were included in the current study. All of the patients were with pneumonia and residing in RCU; As a result of ABO compatibility and limited plasma, 21 of the patients were randomly chosen to take CP, while other age- and sex-matched 28 patients were under the conventional therapy as control group"</p>	<p>Study registered after recruitment was completed. Unclear whether inclusion criteria were defined based on available participants or whether inclusion criteria had been defined before recruitment.</p>	<p>Only adjusted for age and gender. Other confounders not considered.</p>
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(Continued)

Comment: no statistical differences between days of infection

(Continued)

Salazar 2020a	Moderate	Moderate	Critical	Low	Low	Critical	Critical	Critical
	Quote: "one-to-many nearest neighbor propensity score matching without replacement using an initial ratio of case:control = 1:3 and caliper of 1 between patients having plasma transfusion (cases) versus patients who did not have plasma transfusion (controls). The primary matching criteria included age (categorical, < 30, 30-39, 40-49, 50-59, 60-69, 70-79, ≥ 80), sex, BMI (< / >= 30), diabetes, hypertension, chronic pulmonary disease, chronic kidney disease, hyperlipidaemia, coronary disease, and baseline ventilation requirement within 48 h from admission. A secondary propensity score matching the ratio of case:control of either 1:2 or 1:1 and caliper < 1 was conducted based on the	Selection into the study may have been related to intervention and outcome, but the study authors used appropriate methods to adjust for the selection bias (propensity-score matched).	Assignment to control group was done retrospectively. Scant details of control group treatments are provided. Knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.	All participants received the intended intervention.	Data were reasonably complete	Observation period different across groups. Intervention group observed and assessed 28 days post-transfusion, control group observed and assessed 28 days post-admission	Retro-spective study, selection of all reported results are likely biased	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

(Continued)

ventilation status at Day 0, which was defined as the day of transfusion for cases and the corresponding day in the hospitalization course for controls"

	Serious	Critical	Moderate	Low	Low	Unclear	Critical	Critical
Xia 2020	Not adjusted, cohort of all patients admitted to Wuhan Huoshenshan Hospital (China) from 4 February 2020 to 30 March 2020	Unclear how participants were allocated to receive convalescent plasma or not.	Quote: "All patients received standard treatments, including anti-virus therapy, traditional Chinese medicine, and respiratory support" Intervention group received additional 200-1200 mL convalescent plasma.	All assessed participants received intended intervention	Data were reasonably complete	Unclear when observation period started for control group. Outcome assessors were not blinded to intervention and the study was performed retrospectively.	Retro-spective study, selection of all reported results are likely biased	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
Zeng 2020	Not adjusted for confounding factors	Allocation to intervention and control group based on donor availability Quote: "A total of 21 contemporaneous critically ill patients with COVID-19 were enrolled in the current study (Table 1), and all of them required intensive care unit admission. Six of the patients received convalescent plasma treatment based on the limited availability of convalescent plasma and ABO compatibility.	Retrospective study design. Despite missingness of donors, unclear how control group was selected. Treatment details of control group are provided, but knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.	All participants received intended intervention. Co-interventions (e.g. antiviral therapy, traditional Chinese medicine, etc.) seem to be balanced across treatment groups.	Data were reasonably complete	Quote: "The duration of illness was calculated from the onset of illness to the date of discharge or death" Follow-up until death or discharge	Retro-spective study; selection of all reported results are likely biased	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

Five of 6 patients in the convalescent plasma treatment group and 11 of 15 in the non-convalescent plasma treatment (control) group were male."

(Continued)

ROBINS-I assessment for: treatment with convalescent plasma compared to treatment without convalescent plasma for people with COVID-19 (clinical improvement)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Abolghasemi 2020	Moderate	Critical	Critical	Low	Critical	Moderate	Critical	Critical
	Quote: "Treatment and control groups, except for their number of patients, were matched based on gender, age and presence of two main co-morbidities including hypertension and diabetes mellitus (...). Their chest CT scan scores were also statistically matched indicating that both patient groups had similar clinical conditions on their entrance into the study."	Quote: "Due to ethical consideration, responsible physicians were reluctant to deprive COVID-19 patients from convalescent plasma therapy. Therefore, patients in control group were mainly comprises of patients with mild clinical presentation who did not have blood group convalescent plasma match on their hospital admission or in the next 3 days."	Unclear when assignment to control group was done. Scant details of control group treatments are provided, and it is unclear whether participants were treated during the same period or at a time when less was known about the disease and the treatment options. Knowledge of patients' outcomes at the time of assignment to the control group could have had a major impact on the selection.	All participants received the intended intervention.	Need for intubation is reported for all participants, but follow-up period is not described	Observation reported from hospitalisation and transfusion for convalescent plasma group, and from hospitalisation for control group Outcome assessors were aware of the intervention received by study participants.	Only primary study outcome was defined in trial registry: Quote: "Improving respiratory function of patients. Time-point: Every 24 hours. Method of measurement: Clinical and, para-clinical." Different outcomes were reported in journal publication and those are poorly defined.	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

Quote:
"The primary outcomes were the patient survival and length of hospital stay. Secondary outcomes included patients' needs for intubation, improvements in clinical symptoms such as tachypnea and para clinical measured of the patients and frequency of adverse effects resulting from plasma transfusion."

(Continued)

Duan 2020	Serious	Critical	Critical	Low	Critical	Critical	Critical	Critical
	Quote: "Historic control group was formed by random selection of 10 patients from the cohort treated in the same hospitals and	Small sample size, unclear how participants were selected into intervention group, unclear how long participants of historical	Assignment to control group was done retrospectively. Treatment details of control group are not provided, and it is unclear whether	All participants received the intended intervention.	Unclear how long control group was followed and clinical status in terms of	Clinical course is reported for participants in intervention group until day 3 of follow-up	Study was registered as single-arm trial and control group was	The study is too problematic to provide any useful evidence, however better

(Continued)	matched by age, gender, and severity of the diseases to the 10 cases in our trial." Not adjusted for comorbidities, previous treatments, time of disease onset, etc.	control group were followed	participants were treated during the same period or at a time when less was known about the disease and the treatment options. Knowledge of patients' outcomes at the time of assignment to the control group could have had a major impact on the selection.		respiratory support was not assessed	retrospectively selected	evidence is still insufficient.		
Hegerova 2020	Moderate	Critical	Critical	Low	Low	Moderate	Critical	Critical	
	Adjusted for age, number of comorbidities, WHO clinical symptoms score, sequential organ failure assessment score, and severity of illness. But with regard to this domain, the study cannot be considered comparable to a well-performed randomised trial.	Intervention arm is part of US expanded access program (Joyn-er 2020a). Unclear how and why 20 participants were selected. Also unclear out of which pool control group was selected. Selection into the study may have been related to intervention and outcome.	Assignment to control group was done retrospectively. Scant details of control group treatments are provided. Knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.	All participants received the intended intervention.	Data were reasonably complete	Retrospective study; Baseline day 0 for matched controls corresponds to equivalent hospital day as CP transfusion	Retrospective study; selection of all reported results are likely biased	The study is too problematic to provide any useful evidence, however better evidence is still insufficient	
Liu 2020	Serious	Moderate	Critical	Low	Low	Moderate	Critical	Critical	
	Only adjusted for hydroxychloroquine and azithromycin, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion. Not adjusted	Selection into the study may have been related to intervention and outcome, but the study authors used appropriate methods to adjust for the selection bias.	Assignment to control group was done retrospectively. Treatment details of control group are not provided. Knowledge of participants' outcomes at the time of assignment to the control group could	All participants received the intended intervention. Most common co-interventions (hydrox-	Data were reasonably complete	Quote: "For controls patients, the day of transfusion was defined by the length of stay on which their respective recipient received their transfusion."	Retrospective study; selection of all reported results are likely biased	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.	

(Continued)

for e.g. age and gender	Quote: "propensity score-matched analysis using The Mount Sinai Hospital's COVID-19 confirmed patient pool from the same calendar period (24 March 2020 to 8 April 2020). A logistic regression was fit to predict the potential for plasma therapy based on time series data obtained at baseline upon admission, prior to transfusion, and the day of 107 transfusion."	have had a major impact on the selection.	hydrochloroquine and azithromycin, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion) were propensity score-matched. Other co-interventions were administered too infrequently to enforce exact matching	Median follow-up comparable between groups. However, outcome assessors were not blinded to intervention and the study was performed retrospectively.
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Rasheed 2020	Serious	Serious	Low	Low	Low	Serious	Serious	Serious
	Only adjusted for age and gender. Other confounders not considered.	Study registered after recruitment was completed. Unclear whether inclusion criteria were defined based on available participants or whether inclusion criteria had been defined before recruitment.	Intervention and control group well-defined. All participants received hydroxychloroquine with azithromycin. Participants in the intervention group received additional convalescent plasma Quote: "Forty nine critically-ill COVID-19 patients were included in the current study. All of the	All participants received the intended intervention.	Data were reasonably complete	Outcome assessors were probably aware of the received intervention, and it was unclear when observation period for control group started; but observation probably starts after enrolment into the study Quote: „Forty nine critically-ill COVID-19 patients were	Follow-up defined as up to 8 weeks in trials registry, but actual follow-up not mentioned in preprint article.	The study has some important problems, however better evidence is still insufficient.

(Continued)

patients were with pneumonia and residing in RCU; As a result of ABO compatibility and limited plasma, 21 of the patients were randomly chosen to take CP, while other age- and sex- matched 28 patients were under the conventional therapy as control group"

included in the current study. ... As a result of ABO compatibility and limited plasma, 21 of the patients were randomly chosen to take CP, while other age- and sex- matched 28 patients were under the conventional therapy as control group."

Quote: "The CP group was compared to the age- and sex- matched control group in terms of recovery time from critical illness (RTCI), days of infection before inclusion to the study, and the whole duration of infection."

Comment: no statistical differences between days of infection

Salazar 2020a	Moderate	Moderate	Critical	Low	Low	Critical	Critical	Critical
	Quote: "one-to-many nearest neighbor propensity score matching without replacement using an initial ratio of case:control = 1:3 and caliper of 1 between patients hav-	Selection into the study may have been related to intervention and outcome, but the study authors used appropriate methods to adjust for the selection bias (propensity score-matched).	Assignment to control group was done retrospectively. Scant details of control group treatments are provided. Knowledge of participants' outcomes at the time of assign-	All participants received the intended intervention.	Data were reasonably complete	Observation period different across groups. Intervention group observed and assessed 28 days post-transfusion, control group observed and as-	Not reported for whole groups; reported for subcohorts only:	The study is too problematic to provide any useful evidence, however better evidence is

(Continued)

ing plasma transfusion (cases) versus patients who did not have plasma transfusion (controls). The primary matching criteria included age (categorical, < 30, 30-39, 40-49, 50-59, 60-69, 70-79, ≥ 80), sex, BMI (</>= 30), diabetes, hypertension, chronic pulmonary disease, chronic kidney disease, hyperlipidaemia, coronary disease, and baseline ventilation requirement within 48 h from admission. A secondary propensity score matching the ratio of case:control of either 1:2 or 1:1 and caliper < 1 was conducted based on the ventilation status at Day 0, which was defined as the day of transfusion for cases and the corresponding day in the hospitalization course for controls"

ment to the control group could have had a major impact on the selection.

essed 28 days post-admission

- secondary matched, transfused within 72 h of admission
- secondary matched, transfused > 72 h after admission
- secondary matched, transfused within 72 h of admission, titre ≥ 1350

still insufficient.

Xia 2020	Serious	Critical	Moderate	Low	Low	Critical	Critical	Critical
	Not adjusted, cohort of all patients admitted to Wuhan Huoshenshan Hospital (China) from 4 Febru-	Unclear how participants were allocated to receive convalescent plasma or not.	Quote: "All patients received standard treatments, including anti-virus therapy, traditional Chi-	All assessed participants received intended intervention	Data were reasonably complete	Unclear when observation period started for control group. Outcome assessors were not blinded	Retrospective study, selection of all reported results are	The study is too problematic to provide any useful evidence, how-

Zeng 2020	Serious	Moderate	Critical	Low	Low	Low	Critical	Critical
(Continued)	ary 2020 to 30 March 2020		nese medicine, and respiratory support" Intervention group received additional 200 mL to 1200 mL convalescent plasma.			to intervention and the study was performed retrospectively.	likely biased	ever better evidence is still insufficient.
	Not adjusted for confounding factors	Allocation to intervention and control group based on donor availability Quote: "A total of 21 contemporaneous critically ill patients with COVID-19 were enrolled in the current study (Table 1), and all of them required intensive care unit admission. Six of the patients received convalescent plasma treatment based on the limited availability of convalescent plasma and ABO compatibility. Five of 6 patients in the convalescent plasma treatment group and 11 of 15 in the non-convalescent plasma treatment (control) group were male."	Retrospective study design. Despite missingness of donors, unclear how control group was selected. Treatment details of control group are provided, but knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.	All participants received intended intervention. Co-interventions (e.g. antiviral therapy, traditional Chinese medicine, etc.) seem to be balanced across treatment groups.	Living participants discharged	Quote: "The duration of illness was calculated from the onset of illness to the date of discharge or death" Follow-up until death or discharge	Retrospective study; selection of all reported results are likely biased	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

ROBINS-I assessment for: treatment with convalescent plasma compared to treatment without convalescent plasma for people with COVID-19 (safety)

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from the intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Abolghasemi 2020	Moderate	Critical	Critical	Low	Critical	Critical	Critical	Critical
	Quote: "Treatment and control groups, except for their number of patients, were matched based on gender, age and presence of two main co-morbidities including hypertension and diabetes of mellitus (...). Their chest CT scan scores was also statistically matched indicating that both patient groups had similar clinical conditions on their entrance into the study."	Quote: "Due to ethical consideration, responsible physicians were reluctant to deprive COVID-19 patients from convalescent plasma therapy. Therefore, patients in control group were mainly comprises of patients with mild clinical presentation who did not have blood group convalescent plasma match on their hospital admission or in the next 3 days."	Unclear when assignment to control group was done. Scant details of control group treatments are provided, and it is unclear whether participants were treated during the same period or at a time when less was known about the disease and the treatment options. Knowledge of patients' outcomes at the time of assignment to the control group could have had a major impact on the selection.	All participants received the intended intervention.	No safety data for control group reported	Only transfusion-related adverse events reported	Observation period unclear; only transfusion-related adverse events assessed and reported	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
Duan 2020	Serious	Critical	Critical	Low	Critical	Critical	Critical	Critical
	Quote: "Historic control group	Small sample size, unclear how participants were selected into intervention	Assignment to control group was done retrospectively. Treatment details	All participants received the	No safety data for control	Only transfusion-related adverse	Observation period unclear; on-	The study is too problematic to

(Continued)	<p>was formed by random selection of 10 patients from the cohort treated in the same hospitals and matched by age, gender, and severity of the diseases to the 10 cases in our trial."</p> <p>Not adjusted for comorbidities, previous treatments, time of disease onset, etc.</p>	<p>group, unclear how long participants of historical control group were followed</p>	<p>of control group are not provided, and it is unclear whether participants were treated during the same period or at a time when less was known about the disease and the treatment options. Knowledge of patients' outcomes at the time of assignment to the control group could have had a major impact on the selection.</p>	<p>intended intervention.</p>	<p>group reported</p>	<p>events reported</p>	<p>ly transfusion-related adverse events assessed and reported</p>	<p>provide any useful evidence, however better evidence is still insufficient.</p>
Hegerova 2020	Moderate	Critical	Critical	Low	Critical	Critical	Critical	Critical
	<p>Adjusted for age, number of comorbidities, WHO clinical symptoms score, sequential organ failure assessment score, and severity of illness. But with regard to this domain, the study cannot be considered comparable to a well-per-</p>	<p>Intervention arm is part of US Expanded Access Program (Joyner 2020a). Unclear how and why 20 participants were selected. Also unclear out of which pool control group was selected. Selection into the study may have been related to intervention and outcome.</p>	<p>Assignment to control group was done retrospectively. Scant details of control group treatments are provided. Knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.</p>	<p>All participants received the intended intervention.</p>	<p>No safety data for control group available</p>	<p>Only transfusion-related adverse events assessed and reported.</p>	<p>Retrospective study; selection of all reported results are likely biased</p>	<p>The study is too problematic to provide any useful evidence, however better evidence is still insufficient</p>

(Continued)

formed randomised trial.

Liu 2020	Serious	Moderate	Critical	Low	Critical	Critical	Critical	Critical
<p>Only adjusted for hydroxychloroquine and azithromycin, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion. Not adjusted for e.g. age and gender</p>	<p>Selection into the study may have been related to intervention and outcome, but the study authors used appropriate methods to adjust for the selection bias.</p> <p>Quote: "propensity score-matched analysis using The Mount Sinai Hospital's COVID-19 confirmed patient pool from the same calendar period (24 March 2020 105 to 8 April 2020). A logistic regression was fit to predict the potential for plasma therapy based on time series data obtained at baseline upon admission, prior to transfusion, and the day of 107 transfusion."</p>	<p>Assignment to control group was done retrospectively. Treatment details of control group are not provided. Knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.</p>	<p>All participants received the intended intervention. Most common co-interventions (hydroxychloroquine and azithromycin, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion) were propensity score-matched. Other co-interventions were administered too infrequently to enforce exact matching</p>	<p>No safety data for control group available</p>	<p>Only transfusion-related adverse events reported</p>	<p>Observation period unclear, non-occurrence of transfusion-related adverse events only reported in discussion section</p>	<p>The study is too problematic to provide any useful evidence, however better evidence is still insufficient.</p>	
<p>Rasheed 2020</p>	<p>Serious</p>	<p>Serious</p>	<p>Low</p>	<p>Low</p>	<p>Critical</p>	<p>Critical</p>	<p>Critical</p>	<p>Critical</p>

(Continued)

	Only adjusted for age and gender. Other confounders not considered.	Study registered after recruitment was completed. Unclear whether inclusion criteria were defined based on available participants or whether inclusion criteria had been defined before recruitment.	Intervention and control group well-defined. All participants received hydroxychloroquine with azithromycin. Participants in the intervention group received additional convalescent plasma Quote: "Forty nine critically-ill COVID-19 patients were included in the current study. All of the patients were with pneumonia and residing in RCU; As a result of ABO compatibility and limited plasma, 21 of the patients were randomly chosen to take CP, while other age- and sex-matched 28 patients were under the conventional therapy as control group"	All participants received the intended intervention.	No safety data for control group available	Only transfusion-related adverse events reported	no safety data for control group reported	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.
Salazar 2020a	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
	Outcome not reported	Outcome not reported	Outcome not reported	Outcome not reported	Outcome not reported	Outcome not reported	Outcome not reported	Outcome not reported
Xia 2020	Serious	Critical	Moderate	Low	Critical	Critical	Critical	Critical
	Not adjusted, cohort of all patients admitted to Wuhan Huoshenshan Hospital (China) from 4 February 2020 to 30 March 2020	Unclear how participants were allocated to receive convalescent plasma or not.	Quote: "All patients received standard treatments, including anti-virus therapy, traditional Chinese medicine, and respiratory support" Intervention group received additional 200 mL to 1200 mL convalescent plasma.	All assessed participants received intended intervention	No safety data for control group available	Only adverse events after plasma transfusion reported	Retrospective study; selection of all reported results are likely biased; only transfusion-related adverse events reported; no safety data	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

for control group available

(Continued)

Zeng 2020	Serious	Moderate	Critical	Low	Critical	Critical	Critical	Critical
	Not adjusted for confounding factors	Allocation to intervention and control group based on donor-availability Quote: "A total of 21 contemporaneous critically ill patients with COVID-19 were enrolled in the current study (Table 1), and all of them required intensive care unit admission. Six of the patients received convalescent plasma treatment based on the limited availability of convalescent plasma and ABO compatibility. Five of 6 patients in the convalescent plasma treatment group and 11 of 15 in the non-convalescent plasma treatment (control) group were male."	Retrospective study design. Despite missingness of donors, unclear how control group was selected. Treatment details of control group are provided, but knowledge of participants' outcomes at the time of assignment to the control group could have had a major impact on the selection.	All participants received intended intervention. Co-interventions (e.g. antiviral therapy, traditional Chinese medicine, etc.) seem to be balanced across treatment groups.	No safety data for control group available	Only adverse events after plasma transfusion reported	Retrospective study; selection of all reported results are likely biased; only transfusion-related adverse events reported; no safety data for control group available	The study is too problematic to provide any useful evidence, however better evidence is still insufficient.

Appendix 9. Cochrane Childhood Cancer assessment tool for observational studies 'Risk of bias' assessment for: convalescent plasma for people with COVID-19 (safety)

We assessed methodological quality and risk of bias using the 'Risk of bias' assessment criteria for observational studies tool provided by Cochrane Childhood Cancer (see [Table 1](#); [Mulder 2019](#)).

'Risk of bias' assessment of [Bradfute 2020](#)

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Adverse events	High	Prospectively registered single-arm study, recruitment of 30 participants planned; but only 13 recruited/ 12 included
Outcome detectors blinded to intervention (detection bias)	Adverse events	Low	Assessment of outcome probably not biased through awareness of intervention
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Low	Assessed and reported for all participants
Well-defined study group (reporting bias)	Adverse events	Low	Population and intervention are well described
Well-defined outcome (reporting bias)	Adverse events	Unclear	Reported for all participants, but observation period unclear
Well-defined risk estimates (analyses)	Adverse events	Not applicable	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Adverse events	High	Not adjusted for confounding factors

'Risk of bias' assessment of [Donato 2020](#)

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Adverse events	Unclear	Prospectively registered single-arm study, 47 participants only
Outcome detectors blinded to intervention (detection bias)	Adverse events	Low	Assessment of outcome probably not biased through awareness of intervention
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Low	Assessed and reported for all participants
Well-defined study group (reporting bias)	Adverse events	Low	Population and intervention are well described
Well-defined outcome (reporting bias)	Adverse events	Unclear	Reported for all participants, but observation period unclear
Well-defined risk estimates (analyses)	Adverse events	Not applicable	No analyses performed

(Continued)

Important prognostic factors or follow-up taken adequately into account (confounding)	Adverse events	High	Not adjusted for confounding factors
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'Risk of bias' assessment of Dulipsingh 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Adverse events	Unclear	Prospectively registered single-arm study, 47 participants only
Outcome detectors blinded to intervention (detection bias)	Adverse events	Low	Assessment of outcome probably not biased through awareness of intervention
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Unclear	Event reported for one participant, unclear whether all participants assessed or similarly assessed
Well-defined study group (reporting bias)	Adverse events	Low	Population and intervention are well described
Well-defined outcome (reporting bias)	Adverse events	Unclear	Event reported for one participant, other participants probably did not experience any event. Observation period unclear
Well-defined risk estimates (analyses)	Adverse events	Not applicable	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Adverse events	High	Not adjusted for confounding factors

'Risk of bias' assessment of Jin 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Adverse events	High	6 of 146 COVID-19 patients in Guizhou Jiangjunshan Hospital who received convalescent plasma therapy included in report, retrospectively registered
Outcome detectors blinded to intervention (detection bias)	Adverse events	Low	Assessment of outcome probably not biased through awareness of intervention
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Unclear	Assessed for all participants over study period, follow-up unclear
Well-defined study group (reporting bias)	Adverse events	Unclear	Study population well described, but intervention scarcely described

(Continued)

Well-defined outcome (reporting bias)	Adverse events	Unclear	Reported for all participants, but observation period unclear
Well-defined risk estimates (analyses)	Adverse events	Not applicable	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Adverse events	High	Not adjusted for confounding, results only reported for 6 of 146 participants receiving convalescent plasma

'Risk of bias' assessment of Joyner 2020a

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Adverse events	Low	Large population size, prospective study, interim analysis of safety data for 20,000 participants (out of 35,322 participants)
Outcome detectors blinded to intervention (detection bias)	Adverse events	Low	Assessment of outcome probably not biased through awareness of intervention
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Low	Interim results; serious adverse events assessed over 7 days after transfusion
Well-defined study group (reporting bias)	Adverse events	Low	Study population and intervention well described
Well-defined outcome (reporting bias)	Adverse events	Low	Interim results for 20,000 participants; assessed and reported for all participants
Well-defined risk estimates (analyses)	Adverse events	Low	Quote: "cumulative incidence of each of a series of SAEs [serious adverse events] was summarised using a point estimate and 95% score confidence interval (CI)"
Important prognostic factors or follow-up taken adequately into account (confounding)	Adverse events	Low	Not adjusted, but confounding unlikely

'Risk of bias' assessment of Madariaga 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Adverse events	Unclear	Prospectively registered, 10 participants only
Outcome detectors blinded to intervention (detection bias)	Adverse events	Low	Assessment of outcome probably not biased through awareness of intervention

(Continued)

Complete outcome assessment/follow-up (attrition bias)	Adverse events	Low	Safety assessed and reported for all participants
Well-defined study group (reporting bias)	Adverse events	Low	Study population and intervention well described
Well-defined outcome (reporting bias)	Adverse events	Unclear	Observation period not described
Well-defined risk estimates (analyses)	Adverse events	Not applicable	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Adverse events	High	Not adjusted for confounding factors

'Risk of bias' assessment of Olivares-Gazca 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Adverse events	Unclear	prospectively registered, 10 participants only
Outcome detectors blinded to intervention (detection bias)	Adverse events	Low	Assessment of outcome probably not biased through awareness of intervention
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Low	Safety probably assessed for all participants
Well-defined study group (reporting bias)	Adverse events	Low	Study population and intervention well described
Well-defined outcome (reporting bias)	Adverse events	Unclear	Described that no adverse events had been observed, follow-up unclear
Well-defined risk estimates (analyses)	Adverse events	Not applicable	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Adverse events	High	Not adjusted for confounding factors

'Risk of bias' assessment of Perotti 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Adverse events	Unclear	Prospectively registered, 46 participants only
Outcome detectors blinded to intervention (detection bias)	Adverse events	Low	Assessment of outcome probably not biased through awareness of intervention

(Continued)

Complete outcome assessment/follow-up (attrition bias)	Adverse events	Low	Assessed and reported for all participants, 7-day follow-up
Well-defined study group (reporting bias)	Adverse events	Low	Study population and intervention well described
Well-defined outcome (reporting bias)	Adverse events	Low	Assessed and reported for all participants, 7-day follow-up
Well-defined risk estimates (analyses)	Adverse events	Not applicable	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Adverse events	High	Not adjusted for confounding factors

WHAT'S NEW

Date	Event	Description
30 August 2020	New search has been performed	Two RCTs, eight controlled NRSIs and nine non-controlled NRSIs included
30 August 2020	New citation required and conclusions have changed	Additional safety data included (more than 20,000 participants)

HISTORY

Review first published: Issue 5, 2020

Date	Event	Description
3 June 2020	New citation required and conclusions have changed	We included results from one RCT and three controlled NRSIs and added further safety data from non-controlled NRSIs.
31 May 2020	New search has been performed	We included eight new studies.

CONTRIBUTIONS OF AUTHORS

VP: methodological expertise, and conception and writing of the review

KLC: clinical expertise, and conception and writing of the review

SJV: clinical expertise, and conception and writing of the review

CD: development of the search strategy

IM: development of the search strategy

EMW: clinical expertise and advice

AL: clinical expertise and advice

DJR: clinical expertise and advice

CK: clinical expertise and advice

ZM: clinical expertise and advice

CS-O: clinical expertise and advice

LJE: clinical and methodological expertise, and conception and writing of the review

NS: methodological expertise and advice, and conception and writing of the review

DECLARATIONS OF INTEREST

VP: none known

KLC: HSANZ Leukaemia Foundation PhD scholarship to support studies at Monash University. This is not related to the work in this review.

SJV: none known

CD: none known

IM: none known

EMW: I have received funding support from Australian Medical Research Future Fund for a trial of convalescent plasma. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

AL: none known

DJR: investigator on the REMAP-CAP and RECOVERY trial. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

CK: none known

ZM: I have received funding support from Australian Medical Research Future Fund for a trial of convalescent plasma. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

CS-O: is a member of the BEST Collaborative Clinical Study Group and Associate Editor for *Transfusion Medicine* Journal. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

LJE: co-lead of the COVID-19 immunoglobulin domain of the REMAP-CAP trial and investigator on the RECOVERY trial. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

NS: none known

SOURCES OF SUPPORT

Internal sources

- Sanquin Blood Supply, Netherlands
 - Center for Clinical Transfusion Research
- University Hospital of Cologne, Germany
 - Cochrane Cancer, Department I of Internal Medicine
- Monash University, Australia
 - Transfusion Research Unit, Department of Epidemiology and Preventive Medicine
- NHS Blood and Transplant, UK
 - NHS Blood and Transplant
- Leukaemia Foundation and HSANZ, Australia
 - Haematology Society of Australia and New Zealand (HSANZ)

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of studies

As the evidence we found from RCTs was at moderate or high risk of bias and at serious or critical risk of bias for the controlled NRSIs, and as none of these studies reported safety data for the control arm, we also included safety data from prospectively and retrospectively registered non-comparative study designs (e.g. case series) and followed the methodology as specified in the protocol ([Piechotta 2020a](#)). We decided to include registered non-controlled NRSIs only to minimise selection bias. Because of the missing comparator, efficacy data of non-controlled studies cannot be placed in context and therefore do not provide any useful evidence. In contrast to the protocol, we therefore decided to only include safety data of non-controlled studies.

Types of interventions

We added standard immunoglobulin as an eligible control treatment.

Types of outcome measures

We renamed the outcome 'time to death' as 'mortality (time to event)'. This did not change the outcome measurement we are interested in.

We revised the secondary outcome 'Improvement of clinical symptoms' according to the revised outcome measure set for COVID-19 clinical research ([COMET 2020](#)). Instead of defining cut-offs ourselves, we refer to the recommended standardised scales. It now reads:

- Improvement of clinical symptoms, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale ([WHO 2020e](#)), WHO Ordinal Scale for Clinical Improvement ([WHO 2020f](#))) at up to 7 days, 8 to 15 days, 16 to 30 days

We added the outcome, 'quality of life' after discussion with a patient representative, and the outcome 'virological response assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days' because this was suggested during the peer review of the last version of this review.

Electronic searches

As publication bias might influence all subsequent analyses and conclusions, we searched all potential relevant trials registries in detail to detect ongoing as well as completed studies, but not yet published studies. Nowadays, it is mandatory to provide results at least in the trials registry. In case results were not published elsewhere, we had planned to extract and analyse these data. However, no outcome data had yet been added to the trials registries. We decided to exclude study registries in the search strategy, because they are already included in the Cochrane COVID-19 Study Register, which is updated Monday to Friday and exclude the WHO COVID-19 Global Research Database. The WHO COVID-19 Global Research Database and LitCov are included in the collection of Center for Disease Control and Prevention COVID-19 Research Article Database. The search part for COVID-19 was updated for the search strategies from IM and CD peer reviewed it.

Data extraction and management

We had planned to extract data using a standardised data extraction form developed in [Covidence](#). However, we could not adapt the standardised form to our needs. Therefore we generated a customised data extraction form in Microsoft Excel ([Microsoft Corporation 2018](#)).

Measures of treatment effect

We had planned to use the Excel tool of the purpose-built method based on the Parmar and Tierney approach ([Parmar 1998](#); [Tierney 2007](#)), to estimate hazard ratios (HRs) with the reported data, if HRs were not available. We were able to read off mortality data from the Kaplan-Meier curve provided by [Gharbharan 2020](#) per day. Because we did not have the rights to edit the Excel tool to add a greater number of time intervals, we could not use the Excel tool. We therefore used a digitising software ([GetData Graph Digitizer](#)) to estimate the HR for [Gharbharan 2020](#).

Summary of findings and assessment of the certainty of the evidence

At protocol stage we had planned to assess the certainty of the evidence for our primary outcomes (all-cause mortality at hospital discharge and time to death), only. However, for the first (rapid) version of this review, we decided to assess the certainty of the evidence also for prioritised secondary outcomes (clinical improvement, grade 3 and 4 adverse events, and serious adverse events) to increase the informative value on effectiveness and safety of convalescent plasma therapy. For the living systematic review we also prioritised patient quality of life as an important patient outcome and added this outcome to the 'Summary of findings' table. We specified in the methods how we graded the certainty of the evidence, especially for non-randomised controlled trials using ROBINS-I for 'Risk of bias' assessment, for calculation of absolute effects for time to event outcomes and for writing informative statements for the findings and certainty of the evidence.

Some passages in this protocol, especially in the methods section, are from the standard template of Cochrane Haematology.

INDEX TERMS**Medical Subject Headings (MeSH)**

Bias; Cause of Death; Coronavirus Infections [mortality] [*therapy]; COVID-19; Immunization, Passive [adverse effects] [methods] [statistics & numerical data]; Non-Randomized Controlled Trials as Topic [statistics & numerical data]; Pandemics; Pneumonia, Viral [mortality] [*therapy]; Randomized Controlled Trials as Topic [statistics & numerical data]; Treatment Outcome

MeSH check words

Humans