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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 4 June 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' 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.

Main results

This is the first living update of our review. We included 20 studies (1 RCT, 3 controlled NRSIs, 16 non-controlled NRSIs) with 5443 participants, of whom 5211 received convalescent plasma, and identified a further 98 ongoing studies evaluating convalescent plasma or hyperimmune immunoglobulin, of which 50 are randomised. We did not identify any completed studies evaluating hyperimmune immunoglobulin.

Overall risk of bias of included studies was high, due to study design, type of participants, and other previous or concurrent treatments.

Effectiveness of convalescent plasma for people with COVID-19

We included results from four controlled studies (1 RCT (stopped early) with 103 participants, of whom 52 received convalescent plasma; and 3 controlled NRSIs with 236 participants, of whom 55 received convalescent plasma) to assess effectiveness of convalescent plasma. Control groups received standard care at time of treatment without convalescent plasma.

All-cause mortality at hospital discharge (1 controlled NRSI, 21 participants)

We are very uncertain whether convalescent plasma has any effect on all-cause mortality at hospital discharge (risk ratio (RR) 0.89, 95% confidence interval (CI) 0.61 to 1.31; very low-certainty evidence).

Time to death (1 RCT, 103 participants; 1 controlled NRSI, 195 participants)

We are very uncertain whether convalescent plasma prolongs time to death (RCT: hazard ratio (HR) 0.74, 95% CI 0.30 to 1.82; controlled NRSI: HR 0.46, 95% CI 0.22 to 0.96; very low-certainty evidence).

Improvement of clinical symptoms, assessed by need for respiratory support (1 RCT, 103 participants; 1 controlled NRSI, 195 participants)

We are very uncertain whether convalescent plasma has any effect on improvement of clinical symptoms at seven days (RCT: RR 0.98, 95% CI 0.30 to 3.19), 14 days (RCT: RR 1.85, 95% CI 0.91 to 3.77; controlled NRSI: RR 1.08, 95% CI 0.91 to 1.29), and 28 days (RCT: RR 1.20, 95% CI 0.80 to 1.81; very low-certainty evidence).

Quality of life

No studies reported this outcome.

Safety of convalescent plasma for people with COVID-19

We included results from 1 RCT, 3 controlled NRSIs and 10 non-controlled NRSIs assessing safety of convalescent plasma. Reporting of adverse events and serious adverse events was variable. The controlled studies reported on adverse events and serious adverse events only in participants receiving convalescent plasma. The duration of follow-up varied. Some, but not all, studies included death as a serious adverse event.

Grade 3 or 4 adverse events (13 studies, 201 participants)

The studies did not report the grade of adverse events. Thirteen studies (201 participants) reported on adverse events of possible grade 3 or 4 severity. The majority of these adverse events were 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 (14 studies, 5201 participants)

Fourteen studies (5201 participants) reported on serious adverse events. The majority of participants were from one non-controlled NRSI (5000 participants), which reported only on serious adverse events limited to the first four hours after convalescent plasma transfusion. This study included death as a serious adverse event; they reported 15 deaths, four of which they classified as potentially, probably or definitely related to transfusion. Other serious adverse events reported in all studies were predominantly allergic or respiratory in nature, including anaphylaxis, transfusion-associated dyspnoea, and transfusion-related acute lung injury (TRALI). We are very uncertain whether or not convalescent plasma affects the number of serious adverse events.

Authors' conclusions

We are very uncertain whether convalescent plasma is beneficial for people admitted to hospital with COVID-19. For safety outcomes we also included non-controlled NRSIs. There was limited information regarding adverse events. Of the controlled studies, none reported on this outcome in the control group. There is only very low-certainty evidence for safety of convalescent plasma for COVID-19.

While major efforts to conduct research on COVID-19 are being made, problems with recruiting the anticipated number of participants into these studies are conceivable. The early termination of the first RCT investigating convalescent plasma, and the multitude of studies registered in the past months illustrate this. It is therefore necessary to critically assess the design of these registered studies, and well-designed studies should be prioritised. Other considerations for these studies are the need to report outcomes for all study arms in the same way, and the importance of maintaining comparability in terms of co-interventions administered in all study arms.

There are 98 ongoing studies evaluating convalescent plasma and hyperimmune immunoglobulin, of which 50 are RCTs. This is the first living update of the review, and we will continue to update this review periodically. These updates may show different results to those reported here.

PLAIN LANGUAGE SUMMARY

Plasma from people who have recovered from COVID-19 to treat individuals with COVID-19

Coronavirus disease 2019 (COVID-19) is a highly infectious respiratory illness caused by a newly recognised type of coronavirus. People infected with this virus may not show signs of the disease, others may develop symptoms, including fever, cough, shortness of breath and sore throat. In some people the infection is more severe and can cause breathing difficulties, 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 to the disease 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 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 treatment causes any unwanted effects. We are continually updating this review as more evidence becomes available.

Our methods

On 4 June 2020 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 or ethnicity, with mild, moderate or severe COVID-19.

Key results

We included 20 completed studies with 5443 participants; 5211 participants received convalescent plasma. We found one randomised controlled trial ((RCT) 103 participants; 52 participants received convalescent plasma). RCTs are clinical studies where people are randomly allocated to receive the treatment (intervention group) or to receive a different treatment or no treatment (control group). RCTs produce the best evidence. We found three controlled non-randomised studies of interventions ((controlled NRSIs) 236 participants; 55 participants received convalescent plasma). These controlled NRSIs did not randomly allocate participants but did include a control group of participants who did not receive convalescent plasma. The remaining 16 studies (5201 participants) were not randomised and did not include a control group (non-controlled NRSIs) but provided information about unwanted effects of convalescent plasma.

To assess whether convalescent plasma is an effective treatment for COVID-19, we evaluated results from the RCT and three controlled NRSIs. The control groups received standard care at the time of treatment without convalescent plasma. There was not enough evidence to determine whether or not convalescent plasma affected the risk of death due to any cause at hospital discharge, time to death, or need for breathing support.

To assess whether convalescent plasma causes unwanted effects, we also evaluated the 16 non-controlled NRSIs (5201 participants). We identified some serious unwanted effects, which could be related to convalescent plasma, including death, allergic reactions or respiratory complications. We are very uncertain whether or not convalescent plasma affects the number of serious unwanted events.

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

Certainty of the evidence

Our certainty (confidence) in the evidence was very limited because there was only one randomised study 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 very uncertain whether plasma from people who have recovered from COVID-19 is an effective treatment for people hospitalised with COVID-19. We are very uncertain whether or not convalescent plasma affects the number of serious harms. These findings could be related to the natural progression of the disease, other treatments that the participants received, or to convalescent plasma. Our searches found 98 ongoing studies evaluating convalescent plasma and hyperimmune immunoglobulin, of which 50 are randomised. This is the first living update of our review, and we will continue to update this review with results from completed studies.

SUMMARY OF FINDINGS

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

Convlescent 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	NA	NA	NA	0	NA	
Controlled non-randomised studies of interventions	933 per 1000	**830 per 1000** (569 to 1000)	RR 0.89 (95% CI 0.61 to 1.31)	21 (1 study)	⊕⊖⊖⊖ **Very low** b,c	
Time to death						

Randomised controlled trials (follow-up 28 days)	240 per 1000 dead	**184 per 1000** (79 to 393)	HR 0.74 (95% CI 0.30 to 1.82)	103 (1 study)	⊕⊖⊖⊖ **Very Low** [c,d]	
Controlled non-randomised studies of interventions (follow-up 11 days)	243 per 1000 dead	**120 per 1000** (59 to 235)	HR 0.46, 95% CI 0.22 to 0.96	195 (1 study)	⊕⊖⊖⊖ **Very low** [b,e]	
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)	⊕⊖⊖⊖ **Very Low** [c,d]	
Controlled non-randomised studies of interventions	NA	NA	NA	0	NA	None of the identified studies reported this outcome.
Improvement of clinical symptoms, assessed by need for respiratory support Follow-up: 15 days						
Randomised controlled trials at day 14	176 per 1000	**326 per 1000** (160 to 663)	RR 1.85 (95% CI 0.91 to 3.77)	103 (1 study)	⊕⊖⊖⊖ **Very Low** [c,d]	
Controlled non-randomised studies of interventions	756 per 1000	**817 per 1000** (688 to 975)	RR 1.08 (95% CI 0.91 to 1.29)	195 (1 study)	⊕⊖⊖⊖ **Very low** [b,c]	

Improvement of clinical symptoms, assessed by need for respiratory support Follow-up: 30 days						
Randomised controlled trials at day 28	431 per 1000	**523 per 1000** (344 to 780)	RR 1.20 (95% CI 0.80 to 1.81)	103 (1 study)	⊕⊖⊖⊖ **Very Low** [c,d]	
Controlled non-randomised studies of interventions	NA	NA	NA	0	NA	None of the identified studies reported this outcome.
Quality of Life						
Randomised controlled trials	NA	NA	NA	0	NA	None of the identified studies reported this outcome.
Controlled non-randomised studies of interventions	NA	NA	NA	0	NA	None of the identified studies reported this outcome.
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	NA	NA	NA	201 (13 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 3. Studies did not report the grade of adverse events. The majority of these adverse events were allergic or respiratory events.
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.
Controlled non-randomised studies of interventions	NR	NR in a comparative design	NA	NA	NA	
Non-controlled non-randomised studies of interventions	NA	NA	NA	5201 (14 studies)	⊕⊖⊖⊖ **Very low** g,h	We were unable to summarise numerical data in any meaningful way. An overview of the reported serious adverse events is provided in Table 4 per study. The majority of participants were from one non-controlled non-randomised study of intervention (5000 participants), which reported only on serious adverse events limited to the first four hours after convalescent plasma transfusion. This study included death as a serious adverse event; they reported 15 deaths, four of which they classified as potentially, probably or definitely related to transfusion. Other serious adverse events reported in all studies were predominantly allergic or respiratory in nature, including: anaphylaxis; transfusion-associated dyspnoea; and transfusion-related acute lung injury (TRALI).

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

[a]Control group risk extracted from included studies.
[b]Risk of bias within this study is critical, so we downgraded three points for risk of bias.
[c]We downgraded two points for imprecision because of the very small information size and results including both potential benefit and potential harm.
[d]Risk of bias within this study and for this outcome is unclear, so we downgraded one point for risk of bias.
[e]We downgraded one point for imprecision because of the very small information size.
[f]We assume these adverse events are grade 3-4; not all of the studies reported grading of adverse events.
[g]Risk of bias 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 11.5 million cases and over 535,000 deaths worldwide as of 7 July 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).

With a preliminary hospitalisation rate of 12.3 patients per 100,000 population in the USA, COVID-19 has taken a toll on healthcare capacity, and especially on intensive care unit (ICU) capacity (CDC 2020a). Early reports of the case fatality rate suggest that it 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). 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). 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).

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 2020). 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.

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 2020a).

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 2020a; 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 (Piechotta 2020).

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.

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 RCT was at unclear or high risk of bias and at serious risk of bias for the controlled NRSIs, and none of the studies reported safety data for the control arm. So we also included safety data from prospective and retrospective non-controlled NRSIs, for example, case series (please see Differences between protocol and review), and followed the methodology as specified in the protocol (Piechotta 2020).

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 pre-defined 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
- Time to death

Secondary outcomes

Effectiveness of convalescent plasma for people with COVID-19

- Improvement of clinical symptoms, assessed by need for respiratory support at up to 7 days; 8 to 15 days; 16 to 30 days:
  - oxygen by mask or nasal prongs
  - oxygen by non-invasive ventilation (NIV) or high-flow
  - intubation and mechanical ventilation
  - mechanical ventilation plus high-flow oxygen
  - extracorporeal membrane oxygenation (ECMO)

- 30-day and 90-day mortality
- Time to discharge from hospital
- Admission to the intensive care unit (ICU)
- Length of stay on the ICU
- 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 4 June 2020.

- Databases of medical literature
  - MEDLINE (Ovid, 23 April to 4 June 2020), Appendix 1
  - Embase (Ovid, 23 April to 4 June 2020), Appendix 2
  - PubMed (for epublications ahead of print only; searched 4 June 2020), Appendix 3
  - Center for Disease Control and Prevention COVID-19 Research Article Database (www.cdc.gov/library/researchguides/2019novelcoronavirus/databasesjournals.html; downloaded 4 June 2020), Appendix 4
  - Cochrane COVID-19 Study Register (covid-19.cochrane.org; searched 4 June 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 four review authors (SJV, KLC, VP, 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, or VP) performed all data extractions and assessments. Two other review authors (NS, SJV, KLC, 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 or KLC).

One review author (NS, SJV, KLC, 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, 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
    - ☐ time to death
    - ☐ improvement of clinical symptoms, assessed through need for respiratory support 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
  * 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

Two review authors (VP, NS) independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (please see Differences between protocol and review), with any disagreements resolved by discussion (Higgins 2011). In order to rate the certainty of the evidence, we assessed risk of bias per outcome rather than per study only. We completed a 'Risk of bias' table for each included study using the 'Risk of bias' tool in Review Manager Web. Risk of bias judgements in RCTs are 'high', 'unclear' or 'low'.

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 RCT was at unclear or high risk of bias and at serious risk of bias for the controlled NRSIs, and none of the studies reported safety data for the control arm. 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 or KLC).

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.

Please refer to Appendix 6 for information regarding how we had planned to combine studies with multiple treatment groups.

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 2019b). 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 four principal investigators from included studies (Duan 2020; Li 2020; Liu 2020; Zeng 2020). We received one response (Liu 2020), stating that the authors were not able to provide additional data for this version of

the review. 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.

Please refer to Appendix 6 for information regarding how we had planned to assess heterogeneity.

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

Please refer to Appendix 6 for information regarding how we had planned to synthesise data from RCTs and controlled NRSIs.

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

Subgroup analysis and investigation of heterogeneity

Considering the currently available evidence, any analyses were inappropriate for this version of the review. We therefore plan to perform subgroup analyses of the following characteristics in an update of this review.

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

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

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 (low risk of bias versus 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
- Time to death
- Clinical improvement (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 used GRADEpro GDT software to create a 'Summary of findings' table, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2019a). We assessed the certainty of the evidence for non-controlled NRSIs as reported in the GRADE guidance 3, starting from low-certainty evidence (Balshem 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 2019b). 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 1856 new records, in addition to the 1267 potentially relevant records from the first version (altogether 3123 references). After removing duplicates, we screened 1678 new records for this update (altogether 2717 records) based on their titles and abstracts, and we excluded 2535 records that did

not meet the prespecified inclusion criteria. We evaluated the remaining 182 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

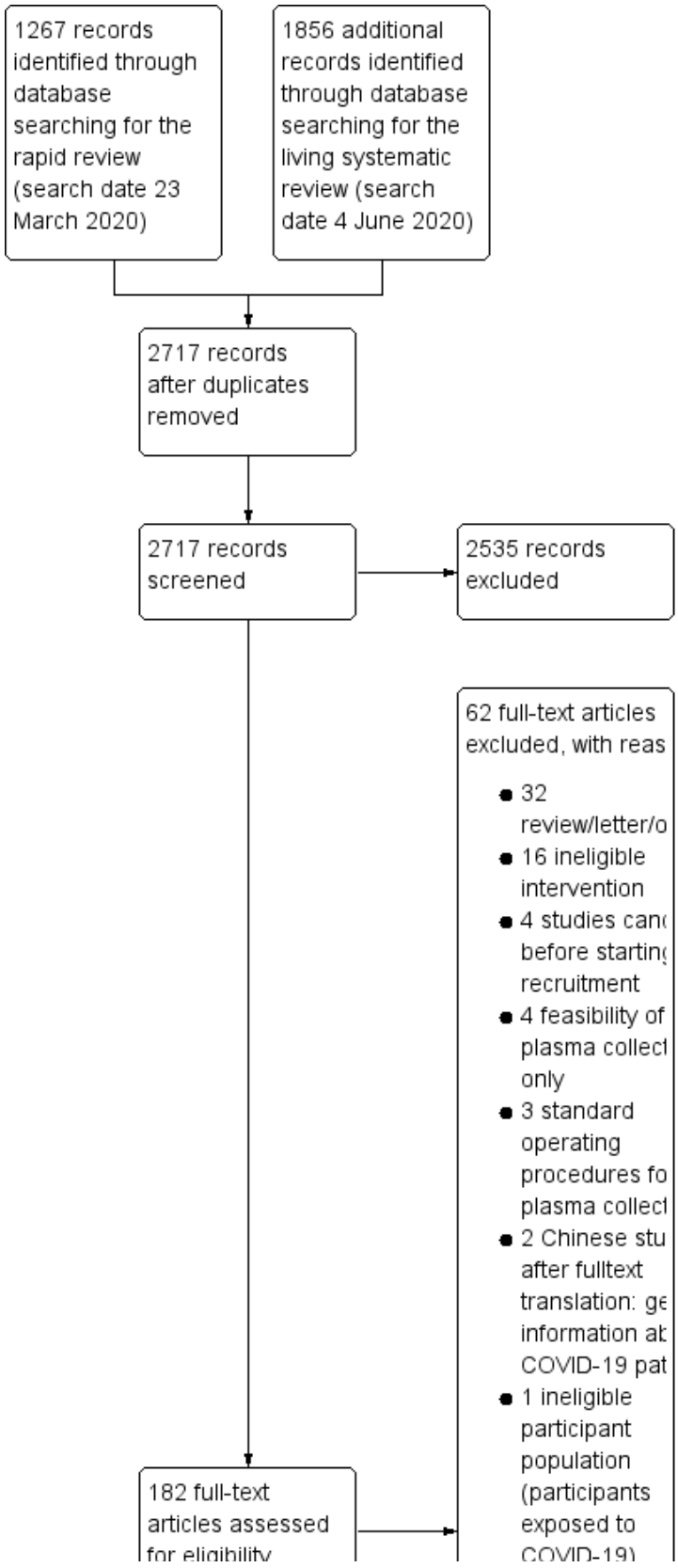


Figure 1. (Continued)

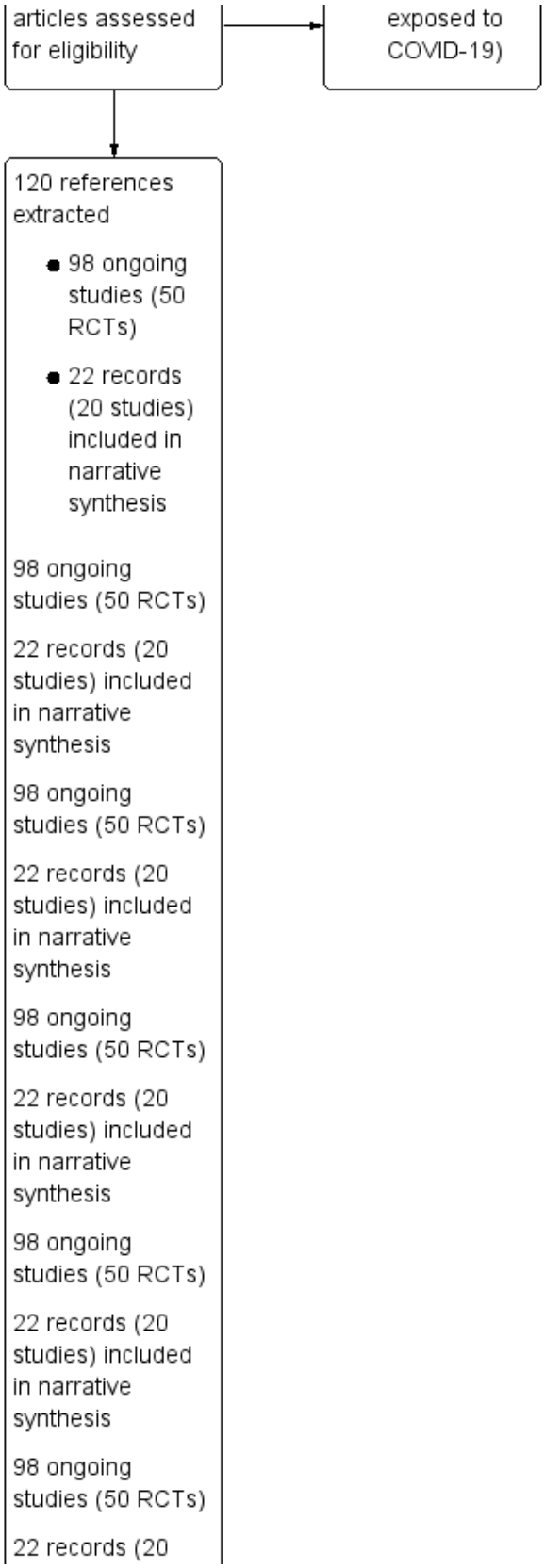
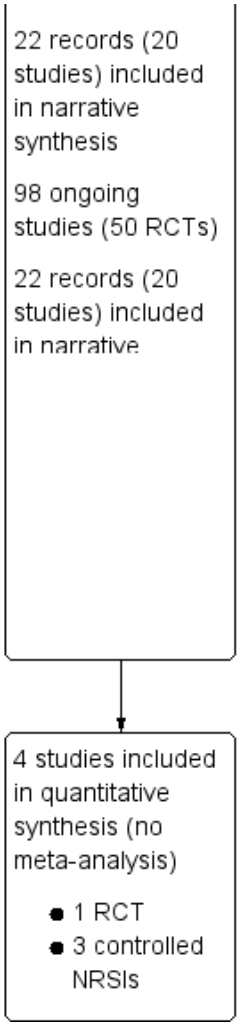


Figure 1. (Continued)



We identified 118 potentially eligible studies within 120 citations: 20 completed studies (22 records) (Ahn 2020; Anderson 2020; Bao 2020b; Duan 2020; Jin 2020; Joyner 2020; Kong 2020; Li 2020; Liu 2020; Pei 2020; Perotti 2020; Salazar 2020; Shen 2020; Tan 2020; Yang 2020; Ye 2020; Zeng 2020; Zhang 2020a; Zhang 2020b; Çınar 2020), and 98 ongoing studies (see 'Ongoing studies' below).

Included studies

We included 20 studies describing 5443 participants in this review, of whom 5211 received convalescent plasma (Ahn 2020; Anderson 2020; Bao 2020b; Çınar 2020; Duan 2020; Jin 2020; Joyner 2020; Kong 2020; Li 2020; Liu 2020; Pei 2020; Perotti 2020; Salazar 2020; Shen 2020; Tan 2020; Yang 2020; Ye 2020; Zeng 2020; Zhang 2020a; Zhang 2020b).

Design and sample size

Efficacy outcomes

We evaluated efficacy and safety outcomes from controlled studies: one RCT (Li 2020; 103 participants of whom 52 received convalescent plasma) and three controlled NRSIs (Duan 2020; Liu 2020; Zeng 2020; 236 participants of whom 55 received convalescent plasma).

Safety outcomes

For safety outcomes, we also evaluated non-controlled NRSIs. However, six non-controlled NRSIs (case reports or case series) did not report whether they evaluated adverse events and are therefore not considered in further analyses (Anderson 2020; Bao 2020b; Kong 2020; Shen 2020; Yang 2020; Çınar 2020). We extracted safety data from 14 studies with 5201 participants who received convalescent plasma (Ahn 2020; Duan 2020; Jin 2020; Joyner 2020; Li 2020; Liu 2020; Pei 2020; Perotti 2020; Salazar 2020; Tan 2020; Ye 2020; Zeng 2020; Zhang 2020a; Zhang 2020b). Of the 10 non-controlled NRSIs, one is an ongoing expanded access study (Joyner 2020; NCT04338360), reporting data for 5000 participants. Because it only reports on the first 5000 participants and meanwhile (as of 09 July 2020; US Covid Plasma 2020) enrolled 48,125 participants of which 31,497 received convalescent plasma, we also kept this record as an ongoing study. Perotti 2020 was prospectively registered and analysed 46 participants. The remaining non-controlled NRSIs were not prospectively registered and reported data for one to 25 participants (Ahn 2020; Jin 2020; Pei 2020; Salazar 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b).

Setting

The one RCT and two controlled NRSIs originated from China (Duan 2020; Li 2020; Zeng 2020), and one controlled NRSIs originated from the USA (Liu 2020). Of the 10 additionally included non-controlled NRSIs that we analysed for safety outcomes, six originated from China (Jin 2020; Pei 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), two originated from the USA (Joyner 2020; Salazar 2020), one from South Korea (Ahn 2020), and one from Italy (Perotti 2020).

Participants

The RCT by Li 2020 and the controlled NRSIs study by Liu 2020 included participants with clinical symptoms meeting the definitions of severe or life-threatening disease. Duan 2020 transfused convalescent plasma in severely ill individuals. The controlled NRSIs study by Zeng 2020 evaluated critically ill individuals, admitted to ICU.

The majority of the additional studies evaluated for safety outcomes transfused convalescent plasma in critically ill individuals (Ahn 2020; Jin 2020; Joyner 2020; Pei 2020; Perotti 2020; Salazar 2020; Ye 2020; Zhang 2020a; Zhang 2020b). Two of these studies included at least one or more participants with moderate disease severity (Jin 2020; Pei 2020), and one of these studies included one participant with mild disease severity (Ye 2020). One study described one hospitalised participant with moderate disease severity (Tan 2020).

Interventions

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

In all of the controlled studies evaluated for efficacy and safety outcomes, the dose and volume of convalescent plasma transfused varied. 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.

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.

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 (enzyme-linked immunosorbent assay) with a target anti-spike titre of at least 1:320 dilution.

Zeng 2020 was a matched cohort study that transfused six participants one to two doses of convalescent plasma (median 300 mL each dose, range 200mL 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.

In the 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. Five studies reported antibody titres (Jin 2020; Pei 2020; Perotti 2020; Salazar 2020; Zhang 2020b). Two studies reported neutralising antibody titres (Jin 2020; Perotti 2020).

Of the above studies, only eight reported some information on plasma donors (Ahn 2020; Jin 2020; Li 2020; Pei 2020; Perotti 2020; Salazar 2020; Ye 2020; Zhang 2020b). Six studies reported the gender of donors - of these, five included both male and female donors (Li 2020; Pei 2020; Perotti 2020; Salazar 2020; Zhang 2020b), but most of these studies excluded prior pregnancy or tested for HLA and/or HNA antibodies except for Zhang 2020b. However, Pei 2020 included one female donor with a previous history of pregnancy.

Some studies provided information on previously reported symptoms and disease severity of convalescent plasma donors (Ahn 2020; Duan 2020; Salazar 2020; Zhang 2020b). Ahn 2020 reported that the two included donors had been admitted to hospital with fever, cough and pneumonia. Duan 2020 reported that donors had been admitted to hospital, but no other information on severity of illness was available. Salazar 2020 reported that all donors were symptomatic. Zhang 2020b reported that all six donors had fever and cough during the course of disease and were admitted to the hospital.

In the seven studies that reported assessment of donor recovery, all donors were symptom-free and completely recovered from coronavirus disease 2019 (COVID-19) prior to donating plasma (Ahn 2020; Duan 2020; Li 2020; Pei 2020; Salazar 2020; Ye 2020; Zhang 2020b). Seven studies specified that donors had a negative SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test prior to convalescent plasma donation (Duan 2020; Jin 2020; Li 2020; Perotti 2020; Salazar 2020; Ye 2020; Zhang 2020b). 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; Perotti 2020; Zhang 2020b), one study reported that the test was performed on sputum (Duan 2020), whereas three did not report information on the origin of the donor sample (Jin 2020; Salazar 2020; Ye 2020). Ye 2020 and Zhang 2020b reported that an RT-PCR test had also been performed on the convalescent plasma product, in addition to RT-PCR testing of the donor.

Outcomes

We evaluated efficacy and safety outcomes in one RCT and three controlled NRSIs. 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 Duan 2020, primary outcomes were 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 Zeng 2020, the primary outcome was survival and secondary outcomes were clearance of viral PCR and radiological improvement.

We evaluated safety outcomes in all studies that reported these outcomes. Twelve studies reported assessment of adverse events of possibly grade 3 or grade 4 severity (Ahn 2020; Duan 2020; Jin 2020; Li 2020; Liu 2020; Pei 2020; Perotti 2020; Salazar 2020; Tan 2020; Ye 2020; Zeng 2020; Zhang 2020b). Zhang 2020a reported that no adverse event had been observed for one of their participants. It was unclear whether the other participants experienced any adverse events.

Fourteen studies (5201 participants) assessed and reported serious adverse events (Ahn 2020; Duan 2020; Jin 2020; Joyner 2020; Li 2020; Liu 2020; Pei 2020; Perotti 2020; Salazar 2020; Tan 2020; Ye 2020; Zeng 2020; Zhang 2020a; Zhang 2020b).

Please refer to the Characteristics of included studies for more detailed information.

Ongoing studies

Of the 98 ongoing studies, six are expanded access studies from the USA (NCT04338360; NCT04358211; NCT04360486; NCT04363034; NCT04372368; NCT04374370). For the NCT04338360 study, safety data of 5000 participants have been reported (Joyner 2020). However, as Joyner 2020 only reports on the first 5000 participants, and 48,125 participants (of whom 31,497 received convalescent plasma), have been enrolled in the study as of 9 July 2020 (US Covid Plasma 2020), we decided to treat this record as an ongoing study.

50 are RCTs (ChiCTR2000030010; ChiCTR2000030179; ChiCTR2000030627; ChiCTR2000030702; ChiCTR2000030929; EUCTR2020-001310-38; IRCT20200310046736N1; IRCT20200404046948N1; IRCT20200409047007N1; IRCT20200413047056N1; NCT04332835; NCT04333251; NCT04342182; 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).

Of these, 28 are expected to be completed in 2020 (ChiCTR2000030010; ChiCTR2000030179; ChiCTR2000030627; ChiCTR2000030702; ChiCTR2000030929; IRCT20200310046736N1; IRCT20200404046948N1; IRCT20200409047007N1; IRCT20200413047056N1; NCT04332835; NCT04342182; NCT04345523; NCT04345991; NCT04346446; NCT04348656; NCT04356534; NCT04376788; NCT04380935; NCT04381858; NCT04383535; NCT04385186; NCT04385199; NCT04388410; NCT04392414; NCT04393727; NCT04397757; NCT04403477; NCT04405310), and plan to evaluate between 15 and 1200 participants. Of these studies, five RCTs were scheduled to be completed by the time of writing (ChiCTR2000030010; ChiCTR2000030179; ChiCTR2000030627; NCT04345991; NCT04376788), but results are not published yet and study investigators did not reply to our requests.

Four further, large RCTs are planned to be completed in 2021: NCT04344535 and NCT04362176, each randomising 500 participants, NCT04345289, evaluating 1500 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.

Excluded studies

We excluded 62 references that did not match our inclusion criteria.

- Thirty-two were a review of the literature, an editorial, letter or an opinion (Alzoughool 2020; Barone 2020; Bloch 2020; Cao 2020b; Casadevall 2020a; Casadevall 2020b; Chen 2020a; Datta 2020; Dzik 2020; Fleming 2020; Hammarström 2020; Jawhara 2020; Kesici 2020; Khanna 2020; Knudson 2020; Kominers 2020; Kumar 2020; Lanza 2020; Pawar 2020; Roback 2020; Rubin 2020; Seghatchian 2020; Sheridan 2020; Syal 2020; Tanne 2020; Lancet Haematology 2020; Tiberghien 2020; Wong 2020; Yoo 2020; Zeng 2020a; Zhao 2020b; Zhu 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 2020; Lin 2020; NCT04261426; NCT04344379; NCT04350580; NCT04368013; Robbiani 2020; Shi 2020; Xie 2020; de Assis 2020).
- Four studies were cancelled by the investigator before recruiting participants into the study (ChiCTR2000030312; ChiCTR2000030381; ChiCTR2000030442; NCT04325672).
- Four studies pertained to feasibility of collection of convalescent plasma only (Budhai 2020; NCT04344015; NCT04344977; NCT04360278).
- 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

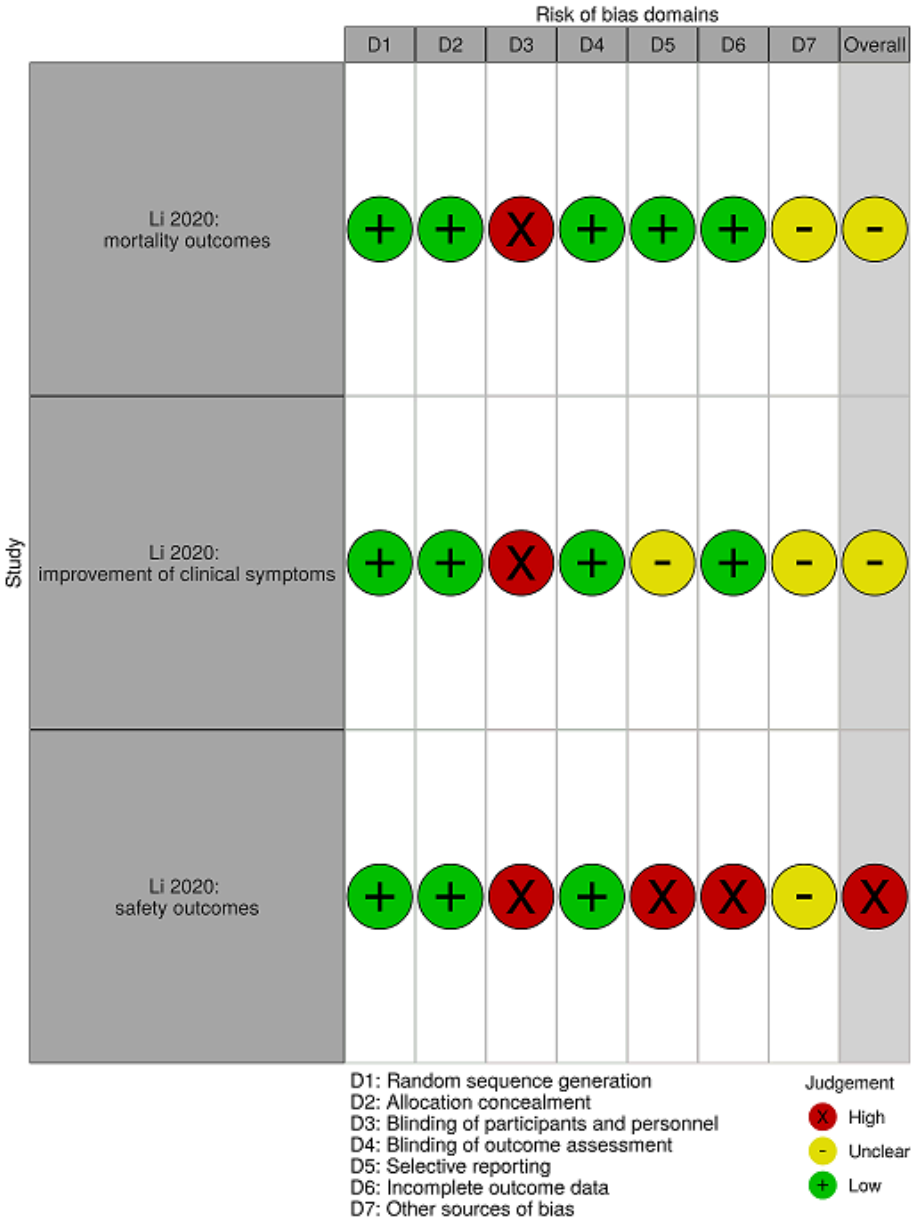
Risk of bias in randomised controlled trials

We assessed methodological quality and risk of bias for one study (Li 2020), using the 'Risk of bias' tool recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Overall judgement

Overall, we rated the risk of bias to be unclear for mortality outcomes, and outcomes assessing improvement of clinical symptoms (efficacy outcomes), and to be high for safety outcomes. The full judgement for the study per category is presented in Figure 2 and the support for judgement in Appendix 7.

Figure 2. Risk of bias summary for randomised controlled trial



Allocation (selection bias)

We judged the risk of attrition bias to be low, as random sequence generation and allocation concealment was described in detail.

Blinding (performance bias and detection bias)

We judged the risk of performance bias to be high, because the trial was not masked for participants and personnel.

We judged the risk of detection bias to be low, because the study authors reported that the outcome assessors were blinded to the study group allocation.

Selective reporting (reporting bias)

We judged the risk of reporting bias to be low for mortality outcomes because the study authors reported that they determined mortality outcomes at the protocol stage.

We judged the risk of reporting bias to be unclear for outcomes addressing improvement of clinical symptoms, because the comparisons at days 7, 14, and 28 were added as a post hoc analysis.

We judged the risk of reporting bias to be high for safety outcomes, because the study authors only reported transfusion-related adverse events.

Incomplete outcome data (attrition bias)

We judged the risk of attrition bias to be low for mortality outcomes and outcomes addressing improvement of clinical symptoms, because the study authors reported results for the intention-to-treat population.

We judged the risk of attrition bias to be high for safety outcomes, because the study authors reported safety data for the intervention group only.

Other potential sources of bias

The trial was terminated early because no participants could be enrolled to the trial after the containment of the epidemic in Wuhan, China. We are unclear about the potential bias of this pre-termination.

In addition, we noticed that effect estimates, which are indicated as odds ratios (ORs) in the primary study, are in fact risk ratios (RRs). We are unclear about the potential bias of this incorrect use.

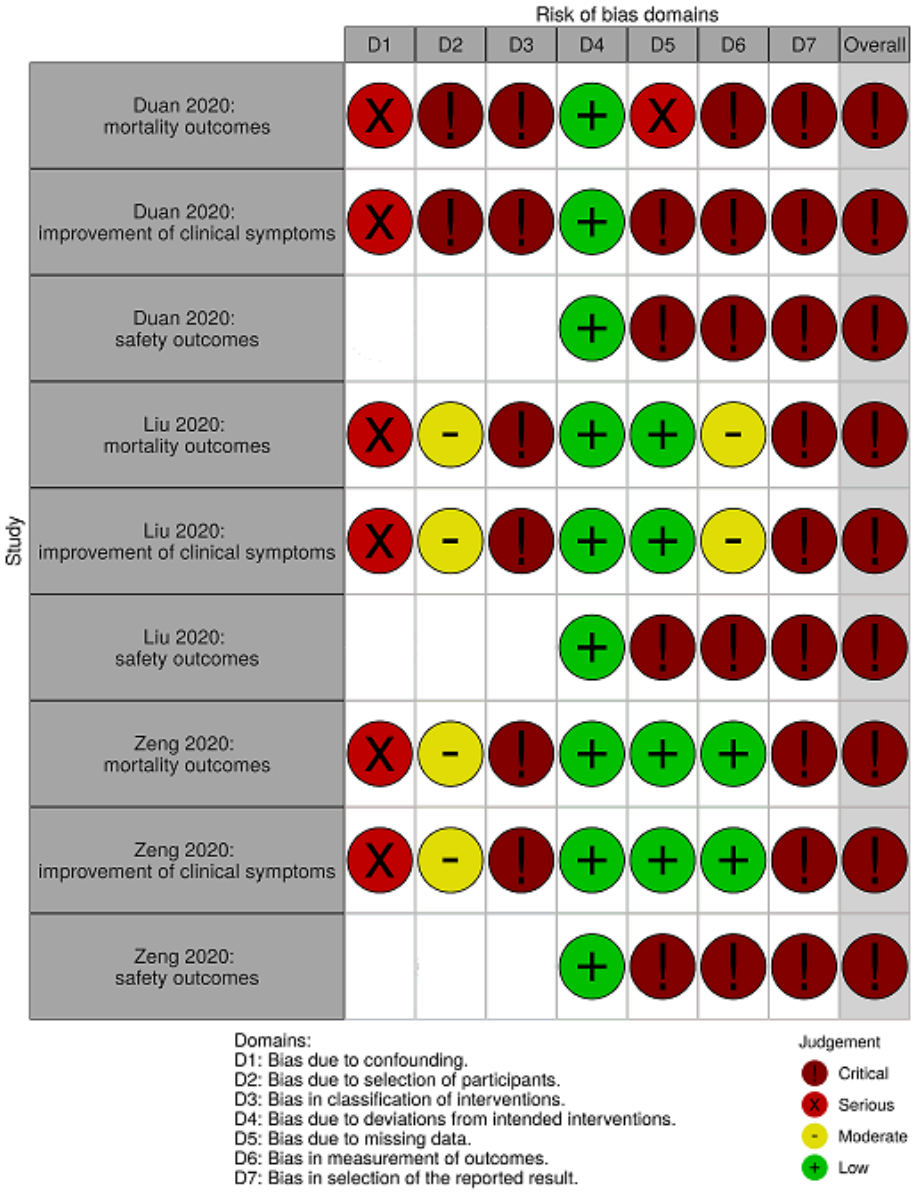
Risk of bias in controlled non-randomised studies of interventions

We assessed methodological quality and risk of bias for three studies (Duan 2020; Liu 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 within and across studies to be critical for all assessed outcomes. Studies are too problematic to provide any useful evidence, however better evidence is not yet available. We present the full judgement per trial and category, including the support for judgement, in Appendix 8; and the 'Risk of bias' summary in Figure 3.

Figure 3. 'Risk of bias' summary for controlled non-randomised studies of interventions



Bias due to confounding

We judged the risk of bias due to confounding to be serious for all 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 co-morbidities, 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. Zeng 2020 did not adjust for any confounding factors.

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.

Bias in selection of participants into the study

We judged the risk of bias in selection of participants into the study to be critical for Duan 2020 for mortality outcomes and outcomes addressing improvement of clinical symptoms. The study 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.

We judged the risk of bias in selection of participants into the study to be moderate for Liu 2020 and Zeng 2020 for mortality outcomes and outcomes addressing improvement of

clinical symptoms. In Liu 2020, 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.

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.

Bias in classification of interventions

We judged the risk of bias in classification of interventions to be critical for all studies for mortality outcomes and outcomes addressing improvement of clinical symptoms, because they assigned participants to the control group retrospectively, and 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.

Bias due to deviations from intended interventions

We judged the risk of bias due to deviations from intended intervention to be low for all studies and all outcomes, 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 serious for Duan 2020 for mortality outcomes, because they reported mortality for participants in the intervention group until day 3 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 low for Liu 2020 and Zeng 2020 for mortality outcomes, because results were reasonably complete.

We judged the risk of bias due to missing data to be critical for Duan 2020 for outcomes addressing improvement of clinical symptoms, because they did not report how long they followed the control group and they did not assess clinical status in terms of respiratory support. We judged the risk of bias due to missing data to be low for Liu 2020 and Zeng 2020 for outcomes addressing improvement of clinical symptoms, because all participants who were still alive had been discharged by the end of follow-up.

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 critical for Duan 2020 for mortality outcomes and outcomes addressing improvement of clinical symptoms, because it was unclear whether the follow-up was comparable between groups.

We judged the risk of bias in measurement of outcomes to be moderate for Liu 2020 for mortality outcomes and outcomes addressing improvement of clinical symptoms, because median follow-ups were comparable between groups. However, outcome assessors were not blinded to the intervention and the study was performed retrospectively.

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 all participants were followed until death or discharge.

We judged the risk of bias in measurement of outcomes to be critical for all studies for safety outcomes, because safety data were not reported 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 critical for all studies and all outcomes, because all studies 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 10 non-controlled NRSIs (Ahn 2020; Jin 2020; Joyner 2020; Pei 2020; Perotti 2020; Salazar 2020; Tan 2020; Ye 2020; Zhang 2020a; Zhang 2020b), using the 'Risk of bias' assessment criteria tool for observational studies provided by Cochrane Childhood Cancer (see Table 1; Mulder 2019). 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.

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 4 and the support for judgement in Appendix 9.

Figure 4. 'Risk of bias' summary for non-controlled non-randomised studies of interventions (assessing safety data only)

Allocation (selection bias)

Except for one study (Joyner 2020), all studies were at high risk of selection bias. We considered study groups not to be representative, as all studies included low numbers of participants (1 to 46 participants) with no control groups.

We judged risk of selection bias to be low for Joyner 2020 because of the prospective study design, the large population size, and the fact that the first 5000 enrolled participants were considered in this interim analysis.

Blinding (performance bias and detection bias)

All studies were unblinded and therefore at high risk of performance and detection bias.

Incomplete outcome data (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 five studies (Ahn 2020; Perotti 2020; Salazar 2020; Ye 2020; Zhang 2020b), because they assessed and reported adverse events and symptoms for all participants.

We judged the risk of attrition bias to be unclear for the other five studies (Jin 2020; Joyner 2020; Pei 2020; Tan 2020; Zhang 2020a), because it was unclear whether they had assessed adverse events for all participants or whether they had selectively reported outcomes. Jin 2020 assessed the outcome for all participants, however the observation period was unclear. Joyner 2020 reported preliminary results only and only reported serious adverse events over a four-hour observation period. Pei 2020 reported one serious adverse event occurring in one participant, however did not report whether they had assessed or observed other adverse events. Tan 2020 reported that their participant experienced moderate fever after the transfusion, however did not report whether other adverse events occurred. Zhang 2020a described that they had observed no adverse events for one of their participants after plasma transfusion, but did not provide any information regarding the occurrence of adverse events for the other participants. They stated in the conclusions that they had not observed any serious adverse events.

Selective reporting (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 four studies (Ahn 2020; Perotti 2020; Salazar 2020; Ye 2020), because both the study population and intervention were well described.

Jin 2020, Joyner 2020, and Zhang 2020a described the study population, but reported only limited information on the intervention. Zhang 2020b provided clear information on the intervention, but scarcely described the participant. We therefore judged the risk of reporting bias to be unclear for these four studies.

We judged the risk of bias to be high for two studies (Pei 2020; Tan 2020), which only reported limited information on the study population and the intervention. However, Pei 2020 was a preprint only, and claimed that the participant characteristics would be provided in the supplementary material once published.

Well-defined outcomes

We judged the risk of reporting bias to be low for four studies (Perotti 2020; Salazar 2020; Ye 2020; Zhang 2020b), because the observation period and results were reported for all participants.

We judged the risk of reporting bias to be unclear for Joyner 2020 because only serious adverse events were reported and results are preliminary.

We judged the risk of reporting bias to be high for the other five studies (Ahn 2020; Jin 2020; Pei 2020; Tan 2020; Zhang 2020a), because it was unclear whether adverse events had been equally assessed for all participants or whether outcomes were selectively reported. Pei 2020 reported one serious adverse event occurring in one participant, however did not report whether they had assessed or observed other adverse events. Tan 2020 reported that their participant experienced moderate fever after the transfusion, however did not report whether other adverse events occurred. Zhang 2020a described they had not observed any adverse events for one of their participants after plasma transfusion, but did not provide any information regarding the occurrence of adverse events for the other participants. They stated in the conclusions that they had not observed any serious adverse events.

Other potential sources of bias

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

Confounding

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

Poorly-defined risk estimates

None of the 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

All-cause mortality at hospital discharge

Randomised controlled trials

Li 2020 reported 28-day mortality. As not all participants had been discharged at the end of follow-up (28 days), we could not analyse all-cause mortality at hospital discharge.

Controlled non-randomised studies of interventions

All three controlled NRSIs (236 participants) reported mortality data for the intervention and control group (Duan 2020; Liu 2020; Zeng 2020). However, we were able to evaluate all-cause mortality at hospital discharge for Zeng 2020 only (21 participants), as not all participants had been discharged at the end of follow-up in Liu 2020 and hospital discharge was unclear for Duan 2020 (end of follow-up three days after transfusion).

Zeng 2020 reported that five out of six participants in the intervention group died, and that 14 out of 15 participants in the control group died. One participant from each group was discharged (RR* 0.89, 95% CI 0.61 to 1.31; very low-certainty evidence). The evidence is very uncertain whether there is a difference between patients receiving convalescent plasma or not.

*We calculated the effect estimate with the reported outcome data. We did not adjust for any confounding factors.

Time to death

Randomised controlled trials

Li 2020 (103 participants) suggests that compared to the control group, convalescent plasma may prolong time from randomisation to death but the evidence is very uncertain (HR* 0.74, 95% CI 0.30 to 1.82; very low-certainty evidence).

*The study authors calculated effect estimates. HRs were calculated using unadjusted Cox proportional hazards models.

Subgroup analysis: severity of disease

The study authors reported subgroup analyses for participants with severe disease and participants with life-threatening disease. 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 prolongs time to death (HR* 0.86, 95% CI 0.34 to 2.41).

*The study authors calculated effect estimates. HRs were calculated using Cox proportional hazards models adjusted for disease severity.

Controlled non-randomised studies of interventions

Liu 2020 (195 participants) reported time to death after a median follow-up time of 11 days for the convalescent plasma group and nine days for the control group. Convalescent plasma may prolong time to death, but the evidence is very uncertain (HR* 0.46, 95% CI 0.22 to 0.96; very low-certainty evidence).

*We calculated the effect estimate with the reported outcome data using the Parmar and Tierney approach (Tierney 2007), as described in the Measures of treatment effect. We did not adjust for any confounding factors, however the study population was a 1:4 matched-sample and adjusted for duration of symptoms prior to admission, therapeutic anticoagulant, broad-spectrum antibiotics, and antivirals.

Subgroup analysis: severity of disease

We identified a significant subgroup difference (test for interaction P = 0.05) for non-intubated participants, favouring the convalescent plasma transfusion arm (HR* 0.19, 95% CI 0.05 to 0.72) and no evidence of a difference for participants who were intubated (HR* 1.24, 95% CI 0.33 to 4.67).

*The study authors calculated effect estimates (Liu 2020). HRs were calculated for a 1:4 matched-sample and adjusted for duration of symptoms prior to admission, therapeutic anticoagulant, broad-spectrum antibiotics, and antivirals

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

Randomised controlled trials

Li 2020 reported this outcome for 103 participants. However, the definition of the outcome differed from the one we used. The study authors 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 extracorporeal membrane oxygenation (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 3). The study authors added a post hoc analysis to compare the rates of improvement at these days.

The evidence is very 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; very low-certainty evidence). Convalescent plasma transfusion may increase improvement of clinical symptoms, as assessed by need for respiratory support at 14 days (RR* 1.85, 95% CI 0.91 to 3.77; very low-certainty evidence), and 28 days (RR* 1.20, 0.80 to 1.81; very low-certainty evidence), but the evidence is very uncertain.

*We calculated the effect estimate with the reported outcome data (see Analysis 1.1; Analysis 1.2; Analysis 1.3). We did not adjust for any confounding factors.

Li 2020 expressed effect estimates as odds ratios (ORs), therefore we recalculated relative effects as RRs. We noticed, that our calculation arrived at the same numerical values, and therefore highlight that effect estimates that are indicated as ORs by Li 2020 are in fact RRs.

Subgroup analysis: severity of disease

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 1.4; Analysis 1.5; Analysis 1.6, respectively).

Controlled non-randomised studies of interventions

All controlled NRSIs reported this outcome (please see Table 3), however reporting differed across studies.

Liu 2020 assessed improvement of clinical symptoms, as assessed by need for respiratory support at day 14, including 39 participants in the intervention group and 156 participants in the control group. Zeng 2020 reported that one out of six participants in the intervention group and one out of 15 participants in the control group had improved and were discharged at the latest point of follow-up (time point unclear). It was unclear whether they still needed any respiratory support after discharge. Five out of six participants in the intervention group and 14 out of 15 in the control group had died.

Duan 2020 reported improvement of clinical symptoms, as assessed by need for respiratory support only for the intervention group. They reported a decreased need for respiratory support in four out of 10 participants within three days of convalescent plasma transfusion. One other participant was reported to require only intermittent oxygenation after previously receiving continuous low-flow oxygenation via nasal cannula. The study also reported on two individuals who required no respiratory support preceding convalescent plasma therapy. No information on improvement of clinical symptoms for other time points was available.

30-day and 90-day mortality

Randomised controlled trials

Li 2020 reported no significant difference in 28-day mortality between both groups (RR* 0.65, 95% CI 0.29 to 1.46). The study authors did not evaluate 90-day mortality.

*We calculated the effect estimate with the reported outcome data (see Analysis 1.7). We did not adjust for any confounding factors.

Li 2020 expressed effect estimates as ORs, therefore we recalculated relative effects as RRs. We noticed, that our calculation arrived at the same numerical values, and therefore highlight that effect estimates, which are indicated as ORs by Li 2020, are in fact RRs.

Controlled non-randomised studies of interventions

None of the controlled NRSIs reported 28-day mortality.

Time to discharge from hospital

Randomised controlled trials

Li 2020 provided clear criteria for hospital discharge and assessed this outcome by day 28:

- body temperature returned to normal for longer than three days
- respiratory symptoms improved without the need for oxygen support
- two consecutive, negative PCR test results from nasopharyngeal swabs at least 24 hours apart

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. The results show that compared to standard therapy alone, convalescent plasma therapy may slightly reduce time to discharge (HR* 1.61, 95% CI 0.88 to 2.93).

*The study authors calculated effect estimates. HRs were calculated using unadjusted Cox proportional hazards models.

Controlled non-randomised studies of interventions

Time to discharge from hospital was not reported for any of the controlled NRSIs. Duan 2020, Liu 2020 and Zeng 2020 reported how many participants had been discharged at longest follow-up available (0 to 31 days), without any evidence of a difference between the participants in the convalescent plasma transfusion group and the control group (Duan 2020: RR* 7.00, 95% CI 0.41 to 120.16; Liu 2020: RR* 1.08, 95% CI 0.86 to 1.35; Zeng 2020: RR* 2.50, 95% CI 0.18 to 33.83).

*We calculated the effect estimate with the reported outcome data (see Analysis 2.1). We did not adjust for any confounding factors.

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.

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 for participants receiving convalescent plasma only, all studies are listed together.

Number of participants with grade 3 and grade 4 adverse events

Thirteen studies (201 participants) reported assessment of adverse events of possibly grade 3 or grade 4 severity (Ahn 2020; Duan 2020; Jin 2020; Li 2020; Liu 2020; Pei 2020; Perotti 2020; Salazar 2020; Tan 2020; Ye 2020; Zeng 2020; Zhang 2020a; Zhang 2020b). However, Zhang 2020a only reported that they had observed no adverse events for one of their participants; it was unclear whether the other three participants did or did not experience any adverse events. Twelve studies therefore reported the presence or absence of adverse events for all participants receiving convalescent plasma.

Four studies reported the occurrence of adverse events that were possibly grade 3 or 4 severity but they did not report the degree of severity (see Table 4).

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).

Tan 2020, a case study, reported that the participant experienced moderate fever (38.9 °C) after convalescent plasma transfusion.

One of the three participants in Pei 2020 had severe anaphylactic shock after receiving 30 mL of plasma from a female donor with a history of pregnancy.

Nine studies (reporting on 99 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 receiving 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 very low certainty and none of the studies reported this outcome for any control group.

Number of participants with serious adverse events

Fourteen studies (5201 participants) assessed serious adverse events (Ahn 2020; Duan 2020; Jin 2020; Joyner 2020; Li 2020; Liu 2020; Pei 2020; Perotti 2020; Salazar 2020; Tan 2020; Ye 2020; Zeng 2020; Zhang 2020a; Zhang 2020b).

Four studies reported on the occurrence of serious adverse events (Joyner 2020; Li 2020; Pei 2020; Perotti 2020), see Table 5.

Joyner 2020 reported data for 5000 participants from an ongoing US FDA (Food and Drug Administration) Expanded Access Programme. The study authors evaluated the incidence of serious adverse events in the first four hours after convalescent plasma transfusion only. Fifteen participants (0.3%) died; the study authors classified four of these deaths as potentially, probably, or definitely related to the convalescent plasma transfusion (0.1%). Eleven TRALIs (0.2%), seven TACOs (0.1%), and three severe allergic reactions (0.1%) occurred, all of them related to the plasma transfusion.

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. 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).

One participant in Pei 2020 (3 participants) experienced a serious adverse event. As described above, this individual had severe anaphylactic shock after receiving convalescent plasma from a female donor with a history of pregnancy.

No serious adverse events occurred in 10 studies (100 participants).

Reporting of serious adverse events was variable across these studies. In the controlled studies, there was reporting on serious adverse events in participants receiving convalescent plasma only with no reporting in the control group. 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.

We are very uncertain whether or not convalescent plasma affects the number of serious adverse events. The evidence is very low certainty.

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 first living update of our review.

We identified one randomised controlled trial (RCT) (which was stopped early), three controlled non-randomised studies of interventions (NRSIs), and 16 non-controlled NRSIs (for safety outcomes only). These studies evaluated 5443 participants, of whom 5211 received convalescent plasma. We identified a further 98 ongoing studies evaluating convalescent plasma or hyperimmune immunoglobulin, of which 50 are randomised.

Risk of bias

The risk of bias of the included RCT was unclear for efficacy outcomes and high for safety outcomes. All 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. As six non-controlled NRSIs did not report safety data, we included 10 non-controlled NRSIs for safety outcomes. The overall risk of bias of the 10 assessed non-controlled NRSIs was also high.

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 included results from controlled studies to assess effectiveness of convalescent plasma. We rated all outcomes as very low certainty, and we were unable to pool data across studies. We present results per study.

All-cause mortality at hospital discharge

We could not analyse results from the RCT as not all participants had been discharged at the end of follow-up (28 days). We included one controlled NRSI (reporting on 21 participants) to assess this outcome. We are very uncertain whether convalescent plasma has any effect on all-cause mortality at hospital discharge.

Time to death

We included one RCT (103 participants) and one controlled NRSI (195 participants) to assess this outcome. Convalescent plasma may prolong time from randomisation or start of treatment to death compared to the control group, but the evidence is very uncertain.

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

We included one RCT (reporting on 103 participants) and one controlled NRSI (reporting on 195 participants) to assess this outcome. We are very uncertain whether convalescent plasma has any effect on the improvement of clinical symptoms at seven days, 14 days, and 28 days (very low-certainty evidence). Two other controlled NRSIs (reporting on 20 and 21 participants, respectively) reported clinical improvement for the intervention group only, and the observation period was unclear.

Quality of life

None of the included studies reported this outcome.

Safety of convalescent plasma for people with COVID-19

We included results from RCTs, controlled NRSIs, and non-controlled NRSIs to assess the safety of convalescent plasma. Only 14 out of the 20 studies reported safety outcomes; six non-controlled NRSIs did not report safety outcomes. Reporting of adverse events and serious adverse events was variable across these studies. In the RCT and controlled NRSIs, there was reporting on adverse events and serious adverse events only in participants receiving 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

The grade of adverse events after convalescent plasma transfusion was not reported. Thirteen studies (201 participants) reported on adverse events (of possible grade 3 or 4 severity). The majority of these adverse events comprised 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

Fourteen studies (5201 participants) reported on serious adverse events. The majority of participants were from one non-controlled NRSI (5000 participants), which reported only on serious adverse events limited to the first four hours after convalescent plasma transfusion. This study included death as a serious adverse event. They reported 15 deaths, four of which they classified as potentially, probably or definitely related to transfusion. Other serious adverse events reported in all studies also predominantly comprised allergic or respiratory adverse events, which include anaphylaxis, transfusion-associated dyspnoea and TRALI. We are very uncertain whether or not convalescent plasma affects the number of serious adverse events.

Overall completeness and applicability of evidence

We identified one RCT (that was stopped early), three controlled NRSIs, and 16 non-controlled NRSIs, evaluating convalescent plasma in adults, most with severe COVID-19. These studies included 5443 participants (ranging from 1 to 5000 participants), of whom 5211 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 controlled studies only (4 studies, 339 participants). In the three controlled NRSIs, selection of the control groups is only briefly reported and relevant confounding factors were not considered in the analyses (e.g. age, gender, severity of disease, co-morbidities).

None of the controlled studies reported adverse events for the control arm. One large, non-controlled NRSI (5000 participants) provided serious adverse events data, which occurred within the first four hours after convalescent plasma transfusion. The evidence for grade 3 and 4 adverse events is very uncertain, as adverse events were inconsistently reported across study designs.

We identified 98 ongoing studies, six are expanded access studies from the USA, and 50 are RCTs. Of these studies, five RCTs were planned to be completed already (ChiCTR2000030010; ChiCTR2000030179; ChiCTR2000030627; NCT04345991; NCT04376788), but results are not published yet and study investigators did not reply to our requests for additional information. An additional 23 RCTs are planned to be completed in 2020. The publication of the results of these studies will necessitate an update of this review. The conclusions of the updated review could 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 one unblinded RCT, which was stopped early because there were no more eligible participants due to containment of the epidemic in Wuhan, China (Li 2020). It is unclear to what extent this pre-termination may bias the results of the study. The certainty of the evidence in the reported outcomes was further reduced because of the very small information size and results including both potential benefit and potential harm for convalescent plasma therapy.

We identified three controlled NRSIs (Duan 2020; Liu 2020; Zeng 2020), which were all at critical risk of bias. None of these studies provided results for the same outcome, however, even if they had, we would not have meta-analysed the results because of this critical risk of bias. The certainty of the evidence in the reported outcomes was further reduced because of the very small information size and results mostly including both potential benefit and potential harm for convalescent plasma therapy.

Because all 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 is of very low certainty and without a control group, the outcome could not be considered in context.

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 one RCT, three controlled NRSIs, and 16 non-controlled NRSIs. 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, the only RCT was stopped early due to the containment of the epidemic in Wuhan, China, leading to the enrolment of fewer participants than planned and consequently a lower power to detect an effect. We anticipate 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 registries, as can be seen from the additional 28 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.

Although we have very limited confidence in the available evidence, we are not aware of any 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 safety and effectiveness of convalescent plasma for people with COVID-19.

A recent 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 severe acute respiratory syndrome (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 can, in that sense, not 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 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 event, or serious adverse event. 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 safety and effectiveness of convalescent plasma and hyperimmune immunoglobulin for treatment of people hospitalised with COVID-19 is of 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 whether or not convalescent plasma affected the risk of 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. 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 first version of the living systematic review investigating the use of convalescent plasma or hyperimmune immunoglobulin for people with COVID-19, we included data from one small randomised controlled trial (RCT). The recruitment rate of this RCT was lower than expected, leading to the enrolment of far fewer participants than planned and consequently a lower power to detect an effect. The study authors noted this as one of the limitations of their study. We anticipate the currently decreasing number of people with COVID-19 in some countries being eligible for inclusion, 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 notion that there are potentially too few 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, there remains the possibility of a second wave in the near future, 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 potentially lower quality of these publications.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahn 2020

Study characteristics	
Methods	• Trial design: case series • Type of publication: journal publication • Setting: ICU • Recruitment dates: 22 February 2020-29 March 2020 • Country: South Korea • Language: English • Number of centres: 1 • Trial registration number: NR • Date of trial registration: NR
Participants	• Age: 67 and 71 • Gender: 1 male, 1 female • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 2 • Severity of disease: critical • Co-morbidities: case 2 - medical history of hypertension • Inclusion criteria: NR • Exclusion criteria: NR • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): 400 mg of hydroxychloroquine once daily and lopinavir/ritonavir 400 mg/100 mg twice daily, empirical antibiotics, 4 L/min oxygen flow via nasal cannula, high-flow oxygen therapy
Interventions	• Intervention(s): CP therapy • Details of CP: * Type of plasma: apheresis plasma, collected with Spectra Optia apheresis system (CMNC software; Spectra Optia IDL Tubing set; Terumo BCT, Lakewood, CO, USA) * Volume: 500 mL total * Number of doses: 2 * Type of antibody test(s) and antibody-titre(s): anti-SARS-CoV-2 IgG antibody in plasma was measured by ELISA (Novel Coronavirus COVID-19 IgG ELISA kit; Epitope Diagnostics, San Diego, CA, USA) and OD ratio for IgG * Pathogen inactivated: NR * RT-PCR tested: NR • Details of donors: * Gender: male * HLA and HNA antibody-negative: NR * Severity of disease: pneumonia * Timing from recovery from disease: 18-21 days * RT-PCR tested: yes in 1 participant • Treatment details, including time of plasma therapy (e.g. early stage of disease): administered 7 (case 2) and 22 (case 1) days after admission • Comparator: not applicable • Concomitant therapy: 400 mg of hydroxychloroquine once daily and lopinavir/ritonavir 400 mg/100 mg twice daily, empirical antibiotics, intubation and mechanical ventilator care, IV methylprednisolone (0.5/1 mg/kg/day daily). Unclear whether these treatments were stopped before plasma transfusion or continuously given • Duration of follow-up: up to 26 days • Treatment cross-overs: not applicable • Compliance with assigned treatment: good (all compliant)
Outcomes	• Primary study outcome(s): NR

Ahn 2020 *(Continued)*

- Primary review outcomes
  - All-cause mortality at hospital discharge: reported
  - 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): 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
  - 30-day and 90-day mortality: not applicable
  - Admission to the ICU: reported
  - Length of stay on the ICU: reported
  - Time to discharge from hospital: reported
  - QoL: NR
- Additional study outcomes: SARS-CoV-2 RNA by rRT-PCR, IL-6 and CRP, white blood cell count, lymphocyte count, arterial blood gas analysis (PaO2/FiO2), chest X-ray, overall improvement of clinical symptoms

Notes

- Sponsor/funding: funding was provided by: Ministry of Health and Welfare (HI14C1324), Korea HIV/AIDS Cohort Study (2019-ER5101-00)
- COIs: the authors have no potential conflicts of interest to disclose
- Other: "this study was approved by the IRB of Severance Hospital (IRB No. 4-2020-0076) and with participants' written informed consent. The images are published under agreement of the patients."

Anderson 2020

Study characteristics

Methods

- Trial design: case report
- Type of publication: case reports in Women's Health
- Setting: teaching hospital
- Recruitment dates: NR
- Country: USA
- Language: English
- Number of centres: 1
- Inclusion/exclusion criteria: NR
- Trial registration no.: NR
- Date of trial registration: NR

Participants

- Age: 35 years
- Gender: female
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 1
- Severity of disease: critical
- Co-morbidities: type 2 diabetes mellitus, asthma, and class III obesity, 22 weeks pregnant
- Inclusion criteria: NR
- Exclusion criteria: NR
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): 6 L nasal cannula, high-flow non-invasive positive-pressure ventilation

Interventions

- Intervention(s): CP therapy

Anderson 2020 *(Continued)*

- Details of CP:
  - Type of plasma: NR
  - Volume: NR
  - Number of doses: 1
  - 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): on admission day
- Comparator: not applicable
- Concomitant therapy: 6 L nasal cannula, high-flow non-invasive positive-pressure ventilation. Rocephin 2 g IV daily and azithromycin, 500 mg IV for concern for possible superimposed bacterial pneumonia. Unclear whether these treatments were stopped before plasma transfusion or continuously given. Hydroxychloroquine 400 g twice daily was initiated on the day of admission, followed by 400 mg daily for 3 days. Patient received a therapeutic dose of low molecular weight heparin for the duration of admission. Patient was intubated and placed on mechanical ventilation. Intermittent pressure support with IV ephedrine was provided as needed for hypotension. Prone ventilation was attempted on hospital day 4 and discontinued. A short course of IV glucocorticoids with hydrocortisone 50 mg IV which was started as a 3-times-daily dose and tapered over the course of 5 days was initiated. Steps to establish management of hyperglycaemia were also initiated. Patient was started on remdesivir on hospital day 5 with a 200 mg IV dose. Remdesivir therapy continued with 100 mg IV doses every 24 h for an additional 9 days. Supplemental oxygen via nasal cannula was initiated following extubation.
- Duration of follow-up: 14 days
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: good

Outcomes

- Primary study outcome(s): NR
- Primary review outcomes
  - All-cause mortality at hospital discharge: reported
  - 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):
    - ☐ periods of intermittent hypertension and hypotension on day 2
    - ☐ cardiac arrhythmia (torsades de pointes) on day 4
  - 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
  - 30-day and 90-day mortality: not applicable
  - Admission to the ICU: reported
  - Length of stay on the ICU: reported
  - Time to discharge from hospital: reported
  - QoL: NR
- Additional study outcomes: blood pressure, AST and ALT, renal dysfunction, vital signs, cardiac arrhythmia

Notes

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

Anderson 2020 *(Continued)*

- Other: patient consent: obtained. This case report was peer reviewed.

Bao 2020b

Study characteristics	
Methods	• Trial design: case report • Type of publication: epub, ahead of print • Setting: hospital • Recruitment dates: 16 February-19 March 2020 • Country: China • Language: English • Number of centres: 1 • Trial registration number: NR • Date of registration: NR
Participants	• Age: 38 • Gender: male • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 1 • Severity of disease: severe • Co-morbidities: nil • Inclusion criteria: NR • 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
	  * Volume: 150ml to 200 mL each dose
	  * Number of doses: 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-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 9 and 24 days after admission
	• For studies including a control group: comparator (type): not applicable
	• Concomitant therapy: antibiotics, haemostatic drugs were administered, low-temperature noradrenaline dilution solution and low-temperature thrombin solution, antifungals, antivirals, tracheostomy, ventilation, craniotomy, mannitol
	• Duration of follow-up: up to 32 days
	• Treatment cross-overs: not applicable
	• Compliance with assigned treatment: not applicable

Outcomes	• Primary study outcome(s): NR

Bao 2020b *(Continued)*

- Primary review outcomes
  - All-cause mortality at hospital discharge: reported
  - 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): 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
  - 30-day and 90-day mortality: not applicable
  - Admission to the ICU: reported
  - Length of stay on the ICU: NR
  - Time to discharge from hospital: NR
  - QoL: NR
- Additional study outcomes: NR

Notes

- Sponsor/funding: no funding received
- COIs: all study authors declare no competing interests
- 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
- Co-morbiditities: cardiovascular and/or cerebrovascular diseases and essential hypertension
- Inclusion criteria: 1 of the conditions 2-4 plus condition 1: 1) age ≥ 18 years; 2) respiratory distress, respiratory rate ≥ 30 breaths/min; 3) oxygen saturation level < 93% in resting state; and 4) PaO2/FiO2 ≤ 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 through need for respiratory support 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
- Additional study outcomes: lymphocyte count, CRP, ALT, AST, total bilirubin, SaO_2, clinical symptoms improvement, clinical outcome, defined as: death, stable, improved, discharged, neutralising antibody 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)."

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
- Date of trial registration: 19 May 2020

Participants

- 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

Jin 2020 *(Continued)*

- Co-morbidities:
  - 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

- Intervention(s): CP therapy
- Details of CP:
  - 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:
  - 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

- Primary study outcome(s): NR
- Primary review outcomes
  - 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 through need for respiratory support 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
- 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 (CCTR number: ChiCTR2000033056, registered 19 May 2020). URL: www.chictr.org.cn/edit.aspx?pid=53859&htm=4

Joyner 2020

Study characteristics

Methods

- Trial design: expanded access
- Type of publication: preprint publication
- Setting: hospital, 66% ICU
- Recruitment dates: 13 April-11 May 2020
- Country: USA
- Language: English
- Number of centres: 12
- Trial registration number: NCT04338360
- Date of trial registration: 08 April 2020

Participants

- Age: median age 62 years (18-97 years)
- Gender: 3153 men, 1824 women and 23 people in other gender/sex categories
- Ethnicity: Asian (6%), American Indian or Alaskan Native (< 1%), black (18%), white (49%), Native Hawaiian or Pacific Islander (< 1%) and multi-racial (< 1%)
- Number of participants (recruited/allocated/evaluated): recruited: 14,288 patients; allocated: 8932 patients; evaluated: the first 5000 patients

Joyner 2020 *(Continued)*

- Severity of disease: hospitalised adults with severe or life-threatening COVID-19
  - At the time of enrolment, 4051 (81%) patients had severe or life-threatening COVID-19
    - ☐ 72% had respiratory failure
    - ☐ 63% reported dyspnoea
    - ☐ 62% had a blood oxygen saturation ≤ 93%
    - ☐ 43% had lung infiltrates > 50% within 24-28 h of enrolment
    - ☐ 38% had a respiratory frequency ≥ 30 breaths/min-1
    - ☐ 34% had partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
    - ☐ 18% had multiple organ dysfunction or failure
    - ☐ 15% had septic shock
  - 949 (19%) were judged to have a high risk of progressing to severe or life-threatening COVID-19
  - Prior to CP transfusion, 3316 patients (66%) were admitted to the ICU
- Co-morbidities: NR
- Inclusion criteria:
  - Age ≥ 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 ≥ 30/min, blood oxygen saturation ≤ 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: 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 COVID-19 CP
  - Volume: 200-500 mL; according to institutional transfusion guidelines
  - 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:
  - 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): NR
- Comparator: none
- Concomitant therapy: NR
- Duration of follow-up: 4-h follow-up for SAEs, 7-day follow-up for mortality
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: NR

Outcomes

- Primary study outcome(s): key safety metrics after transfusion of ABO-compatible human COVID-19 CP
- Primary review outcomes
  - All-cause mortality at hospital discharge: 7-day mortality rate
  - Time to death: NR

Joyner 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): serious transfusion-related AEs reported
  - Number of participants with SAEs: reported; 4h observation period
  - 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: 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 RO1 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

Kong 2020

Study characteristics	
Methods	• Trial design: case report • Type of publication: journal publication • Setting: hospital • Recruitment dates: February 2020 • Country: China • Language: English • Number of centres: 1 • Inclusion/exclusion criteria: NR • Trial registration Nr.: NR • Date of trial registration: NR
Participants	• Age: 100 years • Gender: male • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 1 • Severity of disease: mild • Co-morbidities: 30-year record of hypertension, abdominal aortic aneurysm, cerebral infarction, prostate hyperplasia, and complete loss of cognitive function for the preceding 3 years • Inclusion criteria: NR • Exclusion criteria: NR

Kong 2020 *(Continued)*

	• Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): high-flow oxygen therapy, nutritional support and symptomatic treatment

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  * Type of plasma: NR
	  * Volume: 200 mL once, 100 mL once
	  * Number of doses: 2
	  * 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): administered on 7th and 11th day of hospitalisation
	• Comparator: not applicable
	• Concomitant therapy: high-flow oxygen therapy, nutritional support, symptomatic treatment and antiviral treatment with traditional Chinese medicine. Unclear whether these treatments were stopped before plasma transfusion or continuously given
	• Duration of follow-up: 13 days
	• Treatment cross-overs: not applicable
	• Compliance with assigned treatment: good

Outcomes	• Primary study outcome(s): NR
	• Primary review outcomes
	  * All-cause mortality at hospital discharge: reported
	  * 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): 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
	  * 30-day and 90-day mortality: not applicable
	  * Admission on the ICU: reported
	  * Length of stay on the ICU: not applicable
	  * Time to discharge from hospital: reported
	  * QoL: NR
	  * Additional study outcomes: absolute lymphocyte counts, CRP, IL-6, viral load, vital signs

Notes	• Sponsor/funding: this work was supported by the CAMS Innovation Fund for Medical Sciences (CIFMS) (Grant Nos. 2020-I2M-CoV19-006 and 2016-I2M-3-024) and Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (Grant Nos. 2018PT32016). • COIs: the study authors have no potential conflicts of interest to disclose • Other: not applicable

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
	• Co-morbidities: 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
	• 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

Li 2020 *(Continued)*

- 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
- 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
  - 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
- 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 (± 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 • Co-morbidities: 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) • 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 ≥ 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

Liu 2020 *(Continued)*

	• 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 through need for respiratory support 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
	• Additional study outcomes: none

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.

Pei 2020

Study characteristics	
Methods	• Trial design: case series • Type of publication: preprint, supplementary material missing • Setting: NR • Recruitment dates: NR • Country: China • Language: English • Number of centres: 1 • Trial registration number: NR • Date of registration: NR
Participants	(Preprint only, participant characteristics will be described in the supplementary material; not accessible yet) • Age: NR • Gender: NR

Pei 2020 *(Continued)*

- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 3
- Severity of disease: moderate to critical
- Co-morbidities: NR
- Inclusion criteria: severely and critically ill COVID-19 patients, and patients suffering advanced stages of the disease. Duration of the disease is within 3 weeks, novel coronavirus virus nucleic acid test is positive with viraemia. Severely and critically ill COVID-19 patients assessed by clinicians. Patients with long-term (> 4 weeks) positive novel coronavirus nucleic acid test
- Exclusion criteria: congenital IgA deficiency. A history of allergy including plasma infusion, human plasma protein products, sodium citrate. Plasma inactivated by methylene blue virus is strictly prohibited in patients with methylene blue allergy. Other history of severe allergies and contraindications. At the end of critical illness with irreversible multiple organ failure. Other conditions that are not suitable for infusion assessed by clinicians
- 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: apheresis plasma. Fully automatic apheresis machine or a fully automatic blood cell separator (refer to technical operation procedures of blood station). Volume: 200-400 mL (the exact volume should be assessed by clinicians). The interval between plasma collection should be > 2 weeks. Storage: it is made available under a CC-BY-NC 4.0 International license. Follow the principle of sterility, repackaging the plasma 100-200 mL each. Store at 2-6 °C for 48 h. For long-term storage, it should be rapidly frozen to −20 °C. Packaging: labelling requirements - refer to technical operation procedures of blood station
  * Volume: according to the clinical status and the participant's weight. Usually the infusion dose is 200-500 mL (4-5 mL/kg)
  * Number of doses: according to the clinical status and the participant's weight. Usually the infusion dose is 200-500 mL (4-5 mL/kg)
  * Antibody test and antibody-titre: ELISA, colloidal gold label technology, chemiluminescence; > 1:160
  * Pathogen inactivated or not: NR
  * RT-PCR tested: negative novel coronavirus nucleic acid test
- Details of donors
  * Gender: both
  * HLA and HNA antibody-negative: excluded: with a history of pregnancy or transfusion whose HNA antibody and HLA antibody are positive
  * Severity of disease: NR
  * Timing from recovery from disease: > 3 weeks after the onset of symptoms of COVID-19 and complete resolution of symptoms at least 14 days prior to donation
  * RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): administered between 12 and 27 days after admission
- For studies including a control group: comparator (type): not applicable
- Concomitant therapy: NR
- Duration of follow-up: up to 36 days
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: moderate (2/3 compliant, 1 participant received 30 mL of CP and experienced an AE)

Outcomes

- Primary study outcome: NR
- Primary review outcomes
  * All-cause mortality at hospital discharge: reported
  * Time to death: not applicable

Pei 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): 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: NR
  - 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
- Additional study outcomes: SARS-CoV-2 nucleic acid test

Notes	• Sponsor/funding: no funding received • COIs: all study authors declare no competing interests • Other: "the participants gave their written informed consent and approved by the hospital ethics committee. All relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript. Yes. All necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived. Yes. I understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance). Yes. I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable. Yes"

Perotti 2020

Study characteristics	
Methods	• 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	• 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 • Co-morbidities: 19 (41%) had ≥ 2 comorbidities, including diabetes, hypertension, cancer

Perotti 2020 *(Continued)*

- Inclusion criteria:
  - 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:
  - 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	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• Details of CP
	  * 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) titers 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 tissue culture microtiter 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 ≥ 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

Perotti 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): 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
  - 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
- 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

Salazar 2020

Study characteristics

Methods

- Trial design: single-arm intervention
- Type of publication: journal preproof
- Setting: hospital
- Recruitment dates: 28 March–14 April 2020
- Country: USA
- Language: English
- Number of centres: 1
- Trial registration number: NR
- Date of trial registration: NR

Participants

- Age: 19-77 years (median 51, IQR 42.5 to 60)
- Gender: 11 male, 14 female
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 25
- Severity of disease: severe or life-threatening
- Co-morbidities: diabetes (10 patients), hypertension (9 patients), hyperlipidaemia (5 patients), and gastrointestinal reflux disease (4 patients)
- 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 ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or pulmonary infiltrates > 50% within 24 to 48 hours.
  - 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: NR
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation)

Salazar 2020 *(Continued)*

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  * Type of plasma: obtained by apheresis using the Trima Accel automated blood collection system (Terumo BCT)
	  * Volume: 300 mL
	  * Number of doses: 1-2 (1 patient had 2 doses 6 days apart)
	  * Type of antibody test(s) and antibody-titre(s): to assess antibody titers, we used 2 ELISAs, 1 based on recombinant purified ectodomain (ECD) of the spike protein and the second using recombinant RBD of the spike protein. The titers of the CP used for transfusion ranged from 0-1350 for the RBD and ECD domains.
	  * Pathogen inactivated: NR
	  * RT-PCR tested: NR
	• Details of donors:
	  * Gender: male and female
	  * HLA and HNA antibody-negative: yes
	  * Severity of disease: all symptomatic, 1 hospitalised
	  * Timing from recovery from disease: > 14 days
	  * RT-PCR tested: yes
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): median time from symptom onset to transfusion was 10 days (IQR, 7.5 to 12.5), and from hospitalisation to transfusion was 2 days (IQR, 2 to 4)
	• Comparator: not applicable
	• Concomitant therapy: tocilizumab and steroids, hydroxychloroquine, azithromycin, ribavirin, lopinavir/ritonavir, remdesivir, 12 participants on mechanical ventilation, 10 on low-flow oxygen, 3 on high-flow oxygen, 1 on ECMO
	• Duration of follow-up: up to 27 days
	• Treatment cross-overs: not applicable
	• Compliance with assigned treatment: good (all compliant)

Outcomes	• Primary study outcome(s): safety
	• 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 (none)
	  * Number of participants with SAEs: reported (1 patient developed a morbilliform rash 1 day post-transfusion that lasted for several days)
	  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported (of 25 participants, 9 showed improvement by day 7, and by day 14 post-transfusion, 19 participants showed improvement, as assessed by discharge or at least a 1-point improvement on a modified clinical scale)
	  * 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
	• Additional study outcomes: improvement in the modified 6-point WHO ordinal scale at day 14 post-transfusion, blood results (white blood count, liver function tests, ferritin, CRP, LDH)

Notes	• Sponsor/funding: this study was supported by the National Institutes of Health grants AI146771-01 and AI139369-01, and the Fondren Foundation, Houston Methodist Hospital and Research Institute (to JMM). This research has been funded in whole or part with federal funds under a contract from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Contract Number

Salazar 2020 *(Continued)*

	75N93019C00050 (to JL and GCI). A portion of this work was funded through Cooperative Agreement W911NF-12-1-0390 by the Army Research Office (to JDG). • COIs: the study authors have no potential conflicts of interest to disclose • Other: all necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.

Shen 2020

Study characteristics	
Methods	• Trial design: case series • Type of publication: preliminary communication in JAMA • Setting: hospital, infectious disease department • Recruitment dates: 20 January 2020-25 March 2020 • Country: China • Language: English • Number of centres: 1 • Trial registration number: NR • Date of registration: NR
Participants	• Age: 36-65 years • Gender: 3 male, 2 female • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 5 • Severity of disease: critical • Comorbidities: hypertension, mitral insufficiency (1 participant), none in 4 participants • Inclusion criteria: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; PAO2/FIO2 < 300; and mechanical ventilation • Exclusion criteria: NR • Additional diagnoses: bacterial pneumonia; fungal pneumonia; severe ARDS; myocardial damage, MODS • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): antiviral therapy (including lopinavir/ritonavir; interferon alfa-1b; favipiravir, arbidol; darunavir), corticosteroids (methylprednisolone), mechanical ventilation
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * Type of plasma: CP prepared from 5 donors aged 18-60 years by apheresis * Volume: 400 mL total of ABO-compatible CP on the same day it was obtained from the donor * Number of doses: 2 (each dose 200-250 mL) on the same day * Antibody test and antibody-titre: SARS-CoV-2–specific antibody (IgG) binding titre > 1:1000 (end point dilution titre, by ELISA) and a neutralisation titre > 40 (end point dilution titre); horseradish peroxidase–conjugated goat anti–human IgG (for IgG antibody titre detection) and IgM (for IgM antibody titre detection) (Sangon Biotech) * Pathogen inactivated or not: NR * RT-PCR tested: NR

Shen 2020 *(Continued)*

- Details of donors:
  - Gender: NR
  - HLA and HNA antibody-negative: NR
  - Severity of disease: all donors had been previously diagnosed with laboratory-confirmed COVID-19 and subsequently tested negative for SARS-CoV-2 and other respiratory viruses, as well as for hepatitis B virus, hepatitis C virus, HIV, and syphilis at the time of blood donation
  - Timing from recovery from disease: the donors had been well (asymptomatic) for at least 10 days
  - RT-PCR tested: a serum SARS-CoV-2– specific ELISA antibody titre > 1:1000 and a neutralising antibody titre > 40
- Treatment details, including time of plasma therapy (e.g. early stage of disease): administered between 10 and 22 days after admission
- For studies including a control group: comparator (type): not applicable
- Concomitant therapy: antiviral therapy (including lopinavir/ritonavir; interferon alfa-1b; favipiravir, arbidol; darunavir), corticosteroids (methylprednisolone)
- Duration of follow-up: up to 63 days from hospital admission
- Treatment cross-overs: none
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome: initial clinical experience with CP transfusion administered to critically ill patients with COVID-19
- Primary review outcomes
  - All-cause mortality at hospital discharge: reported
  - 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): 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: 3 discharged from hospital, 2 remained in hospital (stable)
  - 30-day and 90-day mortality: NR (all alive)
  - Admission on the ICU: all were admitted to ICU
  - Length of stay on the ICU: 11, 14, 18 days for 3 participants, remained in ICU for 2 participants
  - Time to discharge from hospital: 51-55 days (3 participants), 2 remained in hospital (stable)
- Additional study outcomes: changes of body temperature, Sequential Organ Failure Assessment (SOFA) score (range 0-24, with higher scores indicating more severe illness), PAO2/FIO2, viral load (qRT-PCR), serum antibody titre (ELISA), routine blood biochemical index (CRP, procalcitonin, IL6), ARDS, and ventilatory and ECMO supports before and after CP transfusion, CT chest findings

Notes

- Sponsor/funding: "this work was supported by the National Science and Technology Major Project (2018ZX10711001, 2017ZX10103011, 2017ZX10204401), Sanming Project of Medicine in Shenzhen (SZSM201412003, SZSM201512005), China Postdoctoral Science Foundation (2019T120147, 2018M641508), Shenzhen Science and Technology Research and Development Project (202002073000001), National Natural Science Foundation of China (81902058), Shenzhen Science and Technology Research and Development Project (202002073000002), and The Key Technology R&D Program of Tianjin (17YFZCSY01090)."
- COIs: no conflicts to disclose
- Other:" the study was approved by the ethics committees from Shenzhen Third People's Hospital, and each participant gave written informed consent."

Tan 2020

Study characteristics

Tan 2020 *(Continued)*

Methods	• Trial design: case report • Type of publication: preprinted article from medRxiv and bioRxiv (not peer-reviewed) • Setting: a designated hospital in Wuhan, China • Recruitment dates: 25 January-19 March 2020 • Country: China • Language: English • Number of centres: 1 • Trial registration number: NR (not applicable) • Date of trial registration: NR
Participants	• Age: 40-50 • Gender: male • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 1 (note: 1 other patient case described, but did not receive CP and general characteristics of 130 patients admitted with COVID-19 were described and compared to participant) • Severity of disease: moderate • Comorbidities: NR • Inclusion criteria: NR • Exclusion criteria: NR • Additional diagnoses: none • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): antiviral therapy, Chinese traditional medicine, supportive care, antipyrexials
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * Type of plasma: plasma was collected from recovered patients with COVID-19 * Volume: 400 mL * Number of doses: NR * Type of antibody test(s) and antibody-titre(s): NR * 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: NR ☐ RT-PCR tested: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): day 48 of hospital admission * For studies including a control group: comparator (type): other patients admitted to the same hospital, 1 specific patient used as comparator (middle-aged woman with moderate-severity illness) * Concomitant therapy: antiviral therapy (type: NR), Chinese traditional medicine (type: NR) * Duration of follow-up: 55 days * Treatment cross-overs: none * Compliance with assigned treatment: good (all compliant)
Outcomes	• Primary study outcome: NR • Primary review outcomes * All-cause mortality at hospital discharge: reported * Time to death: not applicable

Tan 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: patient developed fever 4 h into transfusion
  - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days:
  - 30-day and 90-day mortality: NR (alive)
  - Admission on the ICU: not admitted to ICU
  - Length of stay on the ICU: not admitted to ICU
  - Time to discharge from hospital: discharge date NR
  - QoL: NR
- Additional study outcomes: viral load, fever, cough, lung infection, biochemical markers (IL6 levels, procalcitonin levels), full blood examination, lymphocyte subsets, coagulation profile

Notes

- Sponsor/funding: "this work was supported in part by award numbers 81872028 and 81672693 (H.M.) from the National Natural Science Foundation of China, cstc2017jcyjBX0071 (H.M.) from the Foundation and Frontier Research Project of Chongqing and T04010019 (H.M.) from the Chongqing Youth Top Talent Project"
- COIs: none to disclose
- Other: "all relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript. Yes, all necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived. Yes I understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).YesI have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable. Yes"

Yang 2020

Study characteristics

Methods

- Trial design: case report
- Type of publication: preprint
- Setting: hospitalised patient
- Recruitment dates: 9 February-17 March 2020
- Country: China
- Language: English
- Number of centres: 1
- Trial registration number: NR
- Date of trial registration: NR

Participants

- Age: 62 years
- Gender: female
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 1
- Severity of disease: critical
- Co-morbidities: NR
- Inclusion criteria: NR
- Exclusion criteria: NR

Yang 2020 *(Continued)*

	• Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): non-invasive positive pressure ventilation, high-flow oxygen therapy, Solu Medrol, Voriconazole, Sulfamethoxazole, Magnesium Isoglycyrrhizinate (MgIG), and Enoxaparin

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  * Type of plasma: NR
	  * Volume: 400 mL x 2, 200m L x 5
	  * Number of doses: 5
	  * 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): administered in a critically ill patient (on 14, 16, 24, 27 February, 2 March) 2020
	• Comparator: not applicable
	• Concomitant therapy: non-invasive positive pressure ventilation, high-flow oxygen therapy, Solu Medrol, Voriconazole, Sulfamethoxazole, Magnesium Isoglycyrrhizinate (MgIG), and Enoxaparin. Unclear whether these treatments were stopped before plasma transfusion or continuously given
	• Duration of follow-up: up to 37 days (admitted 9 February-17 March)
	• Treatment cross-overs: not applicable
	• Compliance with assigned treatment: good

Outcomes	• Primary study outcome(s): NR
	• Primary review outcomes
	  * All-cause mortality at hospital discharge: reported
	  * 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): 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 (off high flow on March 5)
	  * 30-day and 90-day mortality: not applicable
	  * Admission on the ICU: reported
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: reported
	  * QoL: NR
	• Additional study outcomes: full blood examination, CT chest findings, inflammatory markers (IL1, IL2R, IL6, TNFalpha, IL8, IL10)

Notes	• Sponsor/funding: COVID-19 Rapid Response Call from Huazhong University of Science and Technology; National Natural Science Foundation of China • COIs: the study authors have no potential conflicts of interest to disclose • Other: nil

Ye 2020

Study characteristics	
Methods	• Trial design: case series • Type of publication: preprint • Setting and dates: inpatient • Recruitment period: 31 January 2020-22 March 2020 • Country: China • Language: English • Number of centres: 1 • Trial registration number: NR • Date of trial registration: NR
Participants	• Age: 28-75 years (participants 1-6: 69, 75, 56, 63, 28, 57) • Gender: 3 male, 3 female (participants 1-6: M, F, M, F, F, M) • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 6 • Severity of disease: critical (note: participant 5 was not critically ill), late course of disease, laboratory values mostly normal • Comorbidities: bronchitis and Sjogren's in participants 3 and 4, none in other participants • Inclusion criteria: (1) laboratory-confirmed cases; (2) patients with abnormalities in chest CT (participant 5 was an exception); (3) patients with deteriorated symptoms after standard treatment; (4) patients with persistent positive result of throat swab; (5) critically ill patients • Exclusion criteria: (1) patients allergic to plasma contents; (2) patients positive for HBV, HCV and HIV; (3) patients with uncontrolled bacterial mixed infection; (4) patients with malignant tumours; (5) patients who developed MODS • Additional diagnoses: none • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): oxygen therapy (nasal) in 4 participants, antiviral therapy (arbidol in all participants), antibiotics (levofloxacin in 1 participant)

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * Type of plasma: ABO-compatible CP
	  * Volume: 200 mL
	  * Number of doses: ≥ 1 (ranges 1-3; participants 1-6: 3, 2, 3, 1, 1, 1)
	  * Antibody-test and antibody-titre: anti-SARS-CoV-2 IgM and IgG
	  * Pathogen inactivated or not: NR
	  * RT-PCR tested: free of residual SARS-CoV-2 by real time PCR
	• Details of donors:
	  * Gender: NR
	  * HLA and HNA antibody-negative: NR
	  * Severity of disease: NR
	  * Timing from recovery from disease: an afebrile status for at least 3 days; at least 3 weeks following disease onset
	  * RT-PCR tested: negative for SARS-CoV-2 nucleic acid for consecutive two RT-PCR tests

Ye 2020 *(Continued)*

- Treatment details, including time of plasma therapy (e.g. early stage of disease): critically ill participants in later stages of infection
  a. admission to study centre on 7 February, first transfusion on 10 March, repeated transfusions on 13 and 16 March
  b. admission to study centre on 12 February, first transfusion on 5 March, repeated transfusion on 9 March
  c. admission to study centre on 12 February, first transfusion on 5 March, repeated transfusion on 6 and 9 March
  d. admission to study centre on 11 February, first transfusion on 10 March
  e. admission to study centre on 5 March, first transfusion on 13 March
  f. admission to study centre on 12 March, first transfusion on 18 March
- For studies including a control group: comparator (type): none
- Concomitant therapy: oxygen therapy, antiviral therapy (arbidol in all participants), antibiotics (levofloxacin in 1 participant)
- Duration of follow-up: up to discharge (5 participants; 1 further monitored after negative swab tests (follow-up unclear))
- Treatment cross-overs: none
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome:
  * Improvement in symptoms and chest CT in the following days after indicated intervention
- Primary review outcomes
  * All-cause mortality at hospital discharge: reported
  * 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: reported, none occurred (3-day follow-up)
  * Number of participants with SAEs: reported, none occurred (3-day follow-up)
  * Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: specific time of recovery NR
  * 30-day and 90-day mortality: reported (all alive and time point not reached)
  * Admission on the ICU: none admitted to ICU
  * Length of stay on the ICU: reported, none admitted to ICU
  * Time to discharge from hospital: reported in 5 participants, range 10-34 days, 1 further monitored after negative swab tests (follow-up unclear)
  * QoL: NR
- Additional study outcomes: Blood and swab samples were obtained to measure serum anti-SARS-CoV-2 IgM and IgG titres and throat SARS-CoV-2 nucleic acid, respectively

Notes

- Sponsor/funding: "this study was partially sponsored by grants National Natural Science Foundation of China (#81802301 to Mingxiang Ye, #81772500 to Tangfeng Lv), and Jiangsu Provincial Key Research and Development Program (BE2018713 to Xinyi Xia)."
- COIs: study authors declare no competing interests
- Other: "this study was reviewed and approved by the Medical Ethical Committee of Wuhan Huoshenshan Hospital. Written informed consent was obtained from each participant. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication."

Zeng 2020

Study characteristics

Zeng 2020 *(Continued)*

Methods	• 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	• 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) • Co-morbidities: 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	• Intervention(s): CP therapy
	• Details of CP:
	  * Type of plasma: NR
	  * Volume: median 300 mL (range 200-600mL)
	  * 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:
	  * 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	• Primary study outcome(s): survival
	• Primary review outcomes
	  * All-cause mortality at hospital discharge: reported (5 of 6 patients died)
	  * Time to death: reported

Zeng 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 through need for respiratory support 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
- 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.

Zhang 2020a

Study characteristics	
Methods	• Trial design: case series • Type of publication: novel report in Chest journal • Setting: hospitals in China • Recruitment period: 30 January-17 March 2020 • Country: China • Language: English • Number of centres: 4 • Trial registration number: NR (case series) • Date of trial registration: NR

Participants	• Age: 31-73 years
	  * participant 1: 69; participant 2: 55; participant 3: 73; participant 4: 31
	• Gender: 2 male, 2 female
	  * participant 1: F; participant 2: M; participant 3: M; participant 4: F
	• Ethnicity: not stated
	• Number of participants (recruited/allocated/evaluated): 4
	• Severity of disease: critical
	• Comorbidities: hypertension (participants 1 and 3), COPD (participant 2), chronic kidney impairment (participant 3), pregnancy (participant 4)
	• Inclusion criteria: NR
	• Exclusion criteria: NR

Zhang 2020a *(Continued)*

- Additional diagnoses:
  - participant 1: bacterial pneumonia, fungal pneumonia, pneumorrhagia, ARDS, septic shock
  - participant 2: ARDS
  - participant 3: ARDS, renal failure, fungal pneumonia, multiple organ failure, septic shock, pneumorrhagia, cystorrhagia, GI bleeding, pneumothorax
  - participant 4: ARDS, septic shock, multiple organ failure, cardiac failure, newborn death due to asphyxia, bacterial infection
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation)
  - participant 1: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha), antibacterial therapy, antifungal therapy, supportive care, IVIG, albumin, zadaxin, mechanical ventilation
  - participant 2: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha 2a), noninvasive mechanical ventilation/high-flow nasal cannula, corticosteroids (methylprednisolone)
  - participant 3: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha 2b, oseltamivir, ribavirin), mechanical ventilation, renal replacement therapy, antifungal therapy (caspofungin, voriconazole), venovenous ECMO
  - participant 4: antiviral therapy (lopinavir-ritonavir, ribavirin), mechanical ventilation, renal replacement therapy, antibacterial therapy (imipenem, vancomycin), caesarean section, venovenous ECMO

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * Type of plasma: prepared from recovered patients, no other information provided
	  * Volume: 200-2400 mL
	  ☐ participant 1: 900 mL
	  ☐ participant 2: 200 mL
	  ☐ participant 3: 2400 mL
	  ☐ participant 4: 300 mL
	  * Number of doses: 1-8 doses
	  ☐ participant 1: 3 doses (200 mL, 400 mL, 300 mL each)
	  ☐ participant 2: 1 dose
	  ☐ participant 3: 8 doses (each dose not stated)
	  ☐ participant 4: 1 dose
	  * Antibody test and antibody-titre: NR
	  * 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: NR
	  * RT-PCR tested: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): days 11-41 admission

Zhang 2020a *(Continued)*

- participant 1: days 19, 29, 30 admission
- participant 2: day 11 admission
- participant 3: day 15, 23, 27, 30, 32, 34, 38, 41 admission
- participant 4: day 19 admission

- For studies including a control group: comparator (type): none (not applicable)
- Concomitant therapy:
  - participant 1: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha), antibacterial therapy, antifungal therapy, supportive care, IVIG, albumin, zadaxin, mechanical ventilation
  - participant 2: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha 2a), noninvasive mechanical ventilation/high-flow nasal cannula, corticosteroids (methylprednisolone)
  - participant 3: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha 2b, oseltamivir, ribavirin), mechanical ventilation, renal replacement therapy, antifungal therapy (caspofungin, voriconazole), venovenous ECMO
  - participant 4: antiviral therapy (lopinavir-ritonavir, ribavirin), mechanical ventilation, renal replacement therapy, antibacterial therapy (imipenem, vancomycin), caesarean section, venovenous ECMO
- Duration of follow-up: up to 51 days
- Treatment cross-overs: none
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome: NR
- Primary review outcomes
  - All-cause mortality at hospital discharge: reported
  - 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): none
  - Number of participants with SAEs: none
  - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes (extubation date reported), 15 days post-first plasma infusion (participant 1) and 22 days post-first plasma infusion (participant 4), participant 2 already off respiratory support prior to plasma infusion, participant 3 remained in ICU up to the time of report writing
  - 30-day and 90-day mortality: NR (all alive)
  - Admission on the ICU: all in ICU at baseline
  - Length of stay on the ICU: NR
  - Time to discharge from hospital: 3 participants, 1 remained in ICU up to the time of report writing
  - QoL- NR
- Additional study outcomes: viral load, antibody (ELISA), chest imaging results

Notes

- Sponsor/funding: NR
- COIs: none disclosed
- Other: NR

Zhang 2020b

Study characteristics

Methods

- Trial design: case report
- Type of publication: open-access article
- Setting: inpatient/ICU
- Recruitment period: NR
- Country: China

Zhang 2020b *(Continued)*

- Language: English
- Number of centres: 1
- Trial registration number: NR (case report)
- Date of trial registration: NR

Participants	• Age: 64 years • Gender: female • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 1 • Severity of disease: severe • Comorbidities: hypertension, diabetes • Inclusion criteria: NR • Exclusion criteria: NR • Additional diagnoses: NR • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): mechanical ventilation
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * Type of plasma: IgM reactive plasma; free of hepatitis B and C virus, HIV, syphilis, and residual SARS-CoV-2 * Volume: 200 mL * Number of doses: unclear * Type of antibody test and antibody-titre: IgG titrated by semiquantitative ELISA: 1:1: 6.59; 1:10: 5.33; 1:20: 4.87; 1:40: 3.87; 1:80: 3.24; 1:160: 2.20; 1:320: 2.17/> 1:160 * Pathogen inactivated or not: NR * RT-PCR tested: NR • Details of donors: * Gender: 4 male, 2 female, * HLA and HNA antibody-negative: NR * Severity of disease: laboratory-confirmed SARS-CoV-2 infection * Timing from recovery from disease: NR * RT-PCR tested: recovery certificated by 2 consecutively negative SARS-CoV-2 PCR assay • Treatment details, including time of plasma therapy (e.g. early stage of disease): 1 week after admission to ICU • For studies including a control group: comparator (type): not applicable • Concomitant therapy: NR • Duration of follow-up: 11 days after transfusion; then transferred to general ward • Treatment cross-overs: none • Compliance with assigned treatment: good (compliant), transferred to general ward
Outcomes	• Primary study outcome: antibody levels in CP • Primary review outcomes * All-cause mortality at hospital discharge: reported * Time to death: not applicable

Zhang 2020b *(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 through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported for day 11
  - 30-day and 90-day mortality: NR (all alive)
  - Admission on the ICU: reported
  - Length of stay on the ICU: reported
  - Time to discharge from hospital: remains on general ward
- Additional study outcomes: lymphocyte count, renal and liver function, prothrombin time, CPK, LDH and myocardial enzymes

Notes	• Sponsor/funding: "this study was supported by Medical Science and Technology Development Foundation, Nanjing Department of Health (ZKX18050). Dr. Xiang Xue is supported by the National Institutes of Health (K01DK114390) and a Research Scholar Grant from the American Cancer Society (RSG-18-050-01-NEC)." • COIs: declared to have no conflicts of interest • Other: case series focusing on CP donors

Çınar 2020

Study characteristics	
Methods	• Trial design: case report • Type of publication: journal publication • Setting: hospital • Recruitment dates: NR • Country: Turkey • Language: English • Number of centres: 1 • Trial registration number: NR • Date of registration: NR
Participants	• Age: 55 • Gender: male • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 1 • Severity of disease: moderate to critical • Co-morbidities: myelodysplasia, disseminated systemic tuberculosis infection and kidney disease • Inclusion criteria: NR • Exclusion criteria: NR • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): an antiviral drug (favipiravir), meropenem, tocilizumab, 4-drug regimen for tuberculosis, low-flow oxygen
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy

Çınar 2020 *(Continued)*

- Details of CP:
  - Type of plasma: collected using Trima Accel®Automated Blood Collection Systemfrom a donor who had previously recovered from COVID-19 disease and met universal donation criteria.
  - Volume: 200 mL each dose
  - Number of doses: 2
  - Antibody test and antibody-titre: anti-SARS-CoV-2 IgG semi-quantitative titre of the donor's plasma studied by the EUROIMMUN ELISAkit (order no EI 2606-9601 G. Produced by EUROIMMUN AG, Seekamp31, 23560 Lübeck, Germany) was positive (Titer 6.6; < 0.8 negative, ≥ 0.8 to < 1.1 borderline, ≥ 1.1 positive)
  - 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: NR
  - RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): administered between 1 and 3 days after admission
- For studies including a control group: comparator (type): not applicable
- Concomitant therapy: an antiviral drug (favipiravir), meropenem, tocilizumab, 4-drug regimen for tuberculosis, low-flow oxygen
- Duration of follow-up: up to 11 days
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: not applicable

Outcomes

- Primary study outcome(s): NR
- Primary review outcomes
  - All-cause mortality at hospital discharge: reported
  - 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): 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
  - 30-day and 90-day mortality: not applicable
  - Admission on the ICU: reported
  - Length of stay on the ICU: reported
  - Time to discharge from hospital: reported
  - QoL: NR
- Additional study outcomes: NR

Notes

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

AE: adverse event; **ALT**: alanine aminotransferase; **ARDS:** acute respiratory distress syndrome; **AST**: aspartate transaminase; **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; **ECMO:** extracorporeal membrane oxygenation; **ELISA:** enzyme-linked immunosorbent assay; **FiO2:** fractional inspired oxygen; **GI:** gastrointestinal; **HBV/HCV:** hepatitis B/C; **HLA**: human leukocyte antigen; **HNA**: human neutrophil antigen; **ICU:** intensive care unit; **IgA (B/G/M):** immunoglobulin A (B/G/M); **IL-6:** interleukin-6; **IQR:** interquartile range; **IRB:** Institutional Review Board; **IV:** intravenous; **IVIG:** intravenous immunoglobulin; **LDH:** lactate dehydrogenase;

MODS: multiple organ dysfunction syndrome; **NR:** not reported; **OD:** optical density; **OSA:** obstructive sleep apnoea; **PaO2:** arterial blood oxygen partial pressure; **PCR:** polymerase chain reaction; **QoL:** quality of life; **RBD:** receptor binding domain; **RCT:** randomised controlled trial; **RNA:** ribonucleic acid; **RT-PCR:** reverse transcription polymerase chain reaction; **SAE:** serious adverse event; **SARS:** severe acute respiratory syndrome; **SARS-CoV-2**: severe acute respiratory syndrome coronavirus 2; **TACO:** transfusion-associated circulatory overload; **TAD:** transfusion-associated dyspnoea; **TRALI:** transfusion-related acute lung injury

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alzoughool 2020	Review
Barone 2020	Review
Bloch 2020	Review
Brasil Ministerio 2020	Standard operating procedure
Budhai 2020	Feasibility of plasma collection only
Cao 2020a	Ineligible intervention
Cao 2020b	Review
Casadevall 2020a	Review
Casadevall 2020b	Editorial
Chen 2020a	Review
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
Datta 2020	Review
de Assis 2020	Ineligible indication
Dzik 2020	Review
Díez 2020	Ineligible intervention
Fleming 2020	Letter
Franchini 2020	Standard operating procedure
Hammarström 2020	Review
Hu 2020	Ineligible intervention
ISRCTN86534580	Ineligible intervention

Study	Reason for exclusion
Jawhara 2020	Review
Jiang 2020	Ineligible intervention
Kesici 2020	Letter
Khanna 2020	Review
Knudson 2020	Letter
Kominers 2020	Review
Kumar 2020	Review
Lancet Haematology 2020	Editorial
Lanza 2020	Letter
Lin 2020	Ineligible intervention
Ministerio de Salud 2020	Standard operating procedure
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
Pawar 2020	Review
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
Roback 2020	Review
Robbiani 2020	Ineligible intervention
Rubin 2020	Review

Study	Reason for exclusion
Seghatchian 2020	Review
Sheridan 2020	Review
Shi 2020	Ineligible intervention
Syal 2020	Review
Tanne 2020	Review
Tiberghien 2020	Review
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
Wong 2020	Review
Xie 2020	Ineligible intervention
Yoo 2020	Review
Zeng 2020a	Letter
Zhao 2020b	Review
Zhu 2020	Letter

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR2000029850

Study name	Study on convalescent plasma treatment for severe patients with novel coronavirus pneumonia (COVID-19)
Methods	• 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	• Inclusion criteria
	  * 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
	• Exclusion criteria
	  * Hypersensitive to immunoglobulin
	  * IgA deficiency

ChiCTR2000029850 *(Continued)*

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• 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): standardised comprehensive treatment
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

Outcomes	• Primary study outcome: fatality rate
	• Primary review outcomes
	  * All-cause mortality at hospital discharge: yes (fatality rate)
	  * 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
	  * 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
	  * Viral titres in respiratory samples
	  * Incubation period
	  * PaO2/FiO2
	  * Cytokines/chemokines

Starting date	15 February 2020
Contact information	Liang Yu 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 Xiaowei Xu 79 Qingchun Road, Shangcheng District, Hangzhou, Zhejiang, China, 310003, xxw69@126.com
Notes	• 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	• 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	• Inclusion criteria * 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 ≤ 93%; 3) PaO2/FiO2 ≤ 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 * 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	• CP therapy or hyperimmune immunoglobulin therapy: Anti-SARS-CoV-2 virus inactivated plasma • Details of CP: * 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	• 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 * 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	Liu Ying Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital) , 1 Yintan Road, Dongxihu District, Wuhan, Hubei, China , 430023, whsjytyy_gcp@163.com Zhang Dingyu 1 Yintan Road, Dongxihu District, Wuhan, Hubei, China, 430023, 1813886398@qq.com
Notes	• 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	• 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	• Inclusion criteria
	  * 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 ≥ 18 years old
	  * Patient or his/her legal guardian will participate voluntarily and sign the informed consent
	• Exclusion criteria
	  * 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	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP
	  * 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	• Primary study outcome: SARS-CoV-2 DNA, antibody levels
	• Primary outcomes
	  * All-cause mortality at hospital discharge: NR
	  * Time to death: NR
	• 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: NR
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR
	• Additional study outcomes
	  * 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 day1, 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	Liping Wang Affiliated Hospital of Xuzhou Medical University, 9 Kunpeng Road, Gulou District, Xuzhou, Jiangsu, 163wangliping@163.com China Xuebing Yan

ChiCTR2000030039 *(Continued)*

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

ChiCTR2000030179

Study name	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19)
Methods	• 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	• Inclusion criteria * 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 * 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	• CP therapy or hyperimmune immunoglobulin therapy: routine treatment + plasma treatment • 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: no • Treatment cross-overs: no
Outcomes	• Primary study outcomes: cure rate, mortality • Primary review outcomes * 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	Liu Wei The First Affiliated Hospital of Nanchang University, 17 Yongwai Main Street, Nanchang, Jiangxi, China, 330006, cdyfyliuwei@163.com Le Aiping 17 Yongwai Main Street, Nanchang, Jiangxi, China, 330006, leaiping@126.com
Notes	• Recruitment status: recruiting • Prospective completion date: 24 April 2020 • Sponsor/funding: The First Affiliated Hospital of Nanchang University, raised independently

ChiCTR2000030627

Study name	Study for using the healed novel coronavirus pneumonia (COVID-19) patients plasma in the treatment of severe critical cases
Methods	• Trial design: RCT • Sample size: 15 in each arm (30) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1

Participants	• Inclusion criteria
	  * 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
	  * 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	• 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	Plasma of the convalescent in the treatment of novel coronavirus pneumonia (COVID-19) common patient: a prospective clinical trial
Methods	• Trial design: open-label, RCT • Sample size: 25 in each arm (50) • Setting: inpatient

ChiCTR2000030702 *(Continued)*

- Country: China
- Language: translated to English
- Number of Centres: 4

Participants	• Inclusion criteria * 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 * 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 ≤ 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 disseminated intravascular coagulation ((DIC)), etc * Severe congestive heart failure, or other relative contraindications for plasma transfusion determined by study authors
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: conventional treatment and CP therapy • 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: conventional treatment • Concomitant therapy: symptomatic treatment, antiviral treatment, and antibacterial treatment

ChiCTR2000030702 *(Continued)*

	• Treatment cross-overs: NR

Outcomes	• Primary study outcome: time to clinical recovery after randomisation
	• 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 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
	  * 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

Starting date	15 February 2020
Contact information	Liu Zhong Institute of Blood Transfusion, Chinese Academy of Medical Sciences, 26 Huacai Road, Chenghua District, Chengdu, Sichuan, China, 610000, Liuz@ibt.pumc.edu.cn Cao Bin 2 Yinghua Street East, Chaoyang District, Beijing, China, 100029, caobin_ben@163.com
Notes	• 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

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)
Methods	• 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

ChiCTR2000030929 *(Continued)*

Participants	• Inclusion criteria * 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 ☐ detect nucleic acid of novel coronavirus positive by real-time fluorescent RT-PCR ☐ have highly homologous to known novel coronavirus by sequencing ☐ detect sero-specific lgM- and lgG-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: ☐ respiratory distress, respiratory rate ≥ 30 times/minute ☐ in the resting state, oxygen saturation is ≤ 93% ☐ for lung radiology, the lesion has obtained > 50% obvious improvement within 24-48 h ☐ PaO2)/FiO2 ≤ 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 * Clinical classification of patients with severe novel coronavirus infection is to meet any of the following: ☐ respiratory failure occurs and requires mechanical ventilation; ☐ shock occurs; ☐ 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	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * 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	• 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: * 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	• 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	• 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	• Inclusion criteria
	  * 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 10^9/L, platelet < 50 x 10^9/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	• Recruitment status: recruiting • Prospective completion date: 17 July 2020 • Sponsor/funding: Eastern Theater General Hospital, 305 Zhongshan Road East, Xuanwu District, Nanjing, Jiangsu, China

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	• Trial design: open-label, RCT • Sample size: 120 • Setting: inpatient • Country: Germany • Language: English • Number of centres: 5
Participants	• Inclusion criteria * Patients with SARS-CoV-2 infection * Age ≥ 18 years and ≤ 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: ☐ respiratory rate ≥ 30 breaths/minute under ambient air ☐ requirement of any type of ventilation support ☐ needs ICU treatment * Written informed consent by patient or legally authorised representative

EUCTR2020-001310-38 *(Continued)*

- Exclusion criteria
  * 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 ≥ 3 and/or pre-existing reduction of left ventricular ejection fraction to ≤ 30%
  * Cardiovascular failure requiring ≥ 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	Interventions • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * type of plasma: fresh frozen plasma 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 • 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

EUCTR2020-001310-38 *(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: 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-Bluspendedienst Baden-Württemberg - Hessen gGmbH, Germany

IRCT20151228025732N53

Study name	Evaluation of the therapeutic effects of convalescent plasma (CP) of recovered people from COVID-19 in improving clinical and laboratory symptoms of hospitalised patients
Methods	• Trial design: non-randomised, parallel group • Sample size: 12 (6 control 6 intervention) • Setting: inpatient • Country: Iran • Language: English • Number of centres: 1
Participants	• Inclusion criteria * Patients admitted to the ICU who receive mechanical invasive or non-invasive ventilation, Pa02/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)

IRCT20151228025732N53 *(Continued)*

	• Exclusion criteria
	  * 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	• CP therapy or hyperimmune globulin therapy: CP
	• Details of CP:
	  * type of plasma: CP, prepared from recovered patients
	  * volume: 2 units
	  * number of doses: 2
	  * antibody-titre: > 1:320
	  * pathogen inactivated or not: NR
	• 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 +98 23 3345 1336 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
Participants	• Inclusion criteria * 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 * 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	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * 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	• 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 * All-cause mortality at hospital discharge: NR * Time to death: NR

IRCT20200310046736N1 *(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: NR
  - QoL: NR
- Additional outcomes
  - Negative result for COVID-19 RT-PCR test
  - Normal CT scan
  - Recovery and normal levels of biomarkers associated with COVID-19

Starting date	24 March 2020
Contact information	Parastoo Moradi Choghakabodi, Iran (Islamic Republic of); parastoomoradi40@yahoo.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 24 July 2020 • Sponsor/funding: Ahvaz University of Medical Sciences, 61357-15794 Ahvaz, Iran

IRCT20200325046860N1

Study name	Evaluation of convalescent plasma therapy in the treatment of patients with COVID-19 disease
Methods	• Trial design: non-randomised, parallel group • Sample size: 200 • Setting: moderate to severe disease • Country: Iran • Language: English • Number of centres: 4

Participants	• Inclusion criteria
	  * Blood oxygen saturation < 90%
	  * Abnormal lung CT scan
	  * Significant shortness of breath
	  * Fever
	  * Not improving in the next 48 h
	  * No possibility of discharge in the next 48 h
	  * Consent
	• Exclusion criteria
	  * Patient should not be connected to a ventilator
	  * Patient has not given consent

Interventions	• CP therapy or hyperimmune globulin therapy: CP

IRCT20200325046860N1 *(Continued)*

	• Details of CP:
	  * 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
	  * 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 treatment
	• Concomitant therapy: conventional treatment
	• Treatment cross-overs: none

Outcomes	• Primary study outcome: improving respiratory function of patients
	• 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): 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 (no follow-up period stated)
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: yes
	  * QoL: NR
	• Additional study outcomes: NR

Starting date	15 March 2020
Contact information	Hassan Abolghasemi +98 21 8126 3166 h.abolghasemi.ha@gmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: 20 August 2020 (expected recruitment end date) • Sponsor/funding: Darmanara Co, Iran Blood Transfusion Organization

IRCT20200404046948N1

Study name	Randomized, parallel-controlled and multi-center clinical study evaluating the efficacy and safety of convalescent plasma, in the treatment of patients with severe SARS-CoV-2 infection (COVID-19)
Methods	• Trial design: open-label, RCT • Sample size: 60 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 4

IRCT20200404046948N1 *(Continued)*

Participants	Participants
	• Inclusion criteria
	  * 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 ≥ 30/min, blood oxygen saturation ≤ 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
	  * 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	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * 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
	• 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

IRCT20200404046948N1 *(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
  - 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	The effect of plasma administration of COVID-19 survivors in patients with acute respiratory distress syndrome due to COVID-19
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
	• Exclusion criteria
	  * Uncontrolled hypertension
	  * Advanced heart failure
	  * Systolic blood pressure < 90 mm Hg
	  * COPD
	  * Patient is intubated
	  * Chronic renal failure with GFR < 30

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP

IRCT20200409047007N1 *(Continued)*

	• Details of CP:
	  * 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	• Primary study outcome: mortality rate in first month from the time of entry into the study
	• Primary review outcomes
	  * All-cause mortality at hospital discharge: yes
	  ☐ mortality rate in first month from the time of entry into the study
	  * Time to death: NR, first month 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: 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	• 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	• Trial design: randomised, clinical trial • Sample size: 15 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 1

IRCT20200413047056N1 *(Continued)*

Participants	• Inclusion criteria
	  * 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:
	  ☐ respiratory rate ≥ 30/min; or
	  ☐ rest SpO2 ≤ 90%; or
	  ☐ PaO2/FiO2 ≤ 300 mmHg; or
	  ☐ respiratory failure and needs mechanical ventilation; or
	  ☐ multiple organ failure and needs ICU monitoring
	• Exclusion criteria
	  * NR

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * 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	• 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
	  * 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-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

IRCT20200413047056N1 *(Continued)*

Starting date	18 April 2020
Contact information	Malihe Zangoue, Birjand University of Medical Sciences, Birjadn, Iran; mzangoue@yahoo.com
Notes	• Recruitment status: recruiting • Prospective completion date: 15 August 2020 • Sponsor/funding: Birjand University of Medical Sciences, Birjand, Iran

NCT04264858

Study name	Treatment of acute severe 2019-nCoV pneumonia with immunoglobulin from cured patients
Methods	• Trial design: non-randomised, parallel-assigned, open trial • Sample size: 10 • Setting: inpatient • Country: China • Language: English • Number of centres: 1
Participants	• Inclusion criteria * Volunteers who have understood and signed the informed consent * Age ≥ 18 years, gender unlimited * Patients diagnosed with acute severe COVID-19 pneumonia ☐ laboratory (RT-PCR)-confirmed infection with COVID-19 ☐ lung involvement confirmed with pulmonary CT scan ☐ 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 * 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	• CP therapy or hyperimmune immunoglobulin therapy: immunoglobulin of cured patients • Details of CP: * 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	• 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).

NCT04264858 *(Continued)*

- 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: 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	• 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	• Trial design: prospective single-arm intervention study • Sample size: 15 • Setting: inpatient • Country: China • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Participants were diagnosed as COVID-19
	  * Participants received anti-SARS-CoV-2 inactivated CP
	  * Written informed consent
	• Exclusion criteria
	  * Participants lacked detailed medical history

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): not applicable
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

Outcomes	• 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
	  * All-cause mortality at hospital discharge: yes
	  * 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: 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
	  * 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)
	  ☐ 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	• 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	• Trial design: single-arm intervention study • Sample size: 30 • Setting: inpatient • Country: Iran • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * COVID-19 patients
	  * Consent to attend the study
	  * Age 30-70 years
	  * Not intubated
	  * PaO2/FiO2 is > 200 or SpO2 is > 85%
	• Exclusion criteria
	  * 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	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• 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): not applicable
	• Concomitant therapy: NR
	• Treatment cross-overs: NR

Outcomes	• 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,C 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	• 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	• 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	• 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	• 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	• Inclusion criteria
	  * 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	• 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 vs best supportive care in hospitalized patients with interstitial pneumonia due to COVID-19
Methods	• Trial design: open-label, phase I, parallel-RCT • Sample size: 115 • Setting: hospital • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * ≥ 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
	  * ≤ 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
	  * ≥ 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	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• Details of CP:
	  * 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)*

	• Concomitant therapy: oxygen therapy • Treatment cross-overs: not applicable

Outcomes	• Primary study outcome: reduction in oxygen and ventilation support (time frame: through study completion, an average of 4 weeks)
	• 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-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	• 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	• 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 ≥ 18 years
	  * Confirmed SARS-CoV-2 infection by RT-PCR
	  * Serious or life-threatening infection defined as:
	  ☐ serious: dyspnoea; respiratory rate ≥ 30 cycles/min; blood oxygen saturation ≤ 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/µL)
	  * 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	• 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	• Trial design: expanded access • Sample size: NR • Setting: hospital • Country: USA • Language: English • Number of centres: 12

Participants	• Inclusion criteria
	  * Age ≥ 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 ≥ 30/min, blood oxygen saturation ≤ 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	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• Details of CP:
	  * 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	• 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	• Recruitment status: expanded access available • Prospective completion date: NR • Sponsor/funding: Mayo Clinic

NCT04340050

Study name	Pilot study for use of convalescent plasma collected from patients recovered from COVID-19 disease for transfusion as an empiric treatment during the 2020 pandemic at the University of Chicago Medical Center
Methods	• Trial design: single-arm, phase I, intervention study • Sample size: 10 • Setting: hospital • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * ≥ 18 years
	  * Laboratory-confirmed COVID-19
	  * Severe or immediately life-threatening COVID-19. (Severe defined as dyspnoea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, PaO2/FiO2 < 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 patients 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
	  * Written informed consent, willingness to comply with all protocol requirements, agreement to storage of specimens for future testing from patient or power of attorney or a healthcare proxy

NCT04340050 *(Continued)*

	• Exclusion criteria
	  * 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

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP therapy
	• Details of CP:
	  * type of plasma
	  * volume: 300 mL
	  * number of doses: 1
	  * antibody-titre
	  * pathogen inactivated or not: NR
	• Treatment details, including time of plasma therapy (e.g. early stage of disease): must be < 21 days from the start of illness
	• For studies including a control group: comparator (type): not applicable
	• Concomitant therapy: NR
	• Treatment cross-overs: not applicable

Outcomes	• Primary study outcome: feasibility of performing study pathway, type of respiratory support
	• Primary review outcomes
	  * All-cause mortality at hospital discharge: yes
	  * 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
	  * Feasibility of performing study pathway consisting of consenting convalescent donors, harvesting CP, application for FDA emergency investigational new drug use for administering CP to the patients
	  * Type of respiratory support defined as room air, high-flow oxygen, intubation
	  * Cardiac arrest
	  * Time to transfer to ICU
	  * ICU mortality

Starting date	10 April 2020
Contact information	Maria Lucia Madariaga, MD; 773-270-2004; mlmadariaga@bsd.uchicago.edu
Notes	• Recruitment status: active, not recruiting • Prospective completion date: 31 December 2021 • Sponsor/funding: NR

NCT04342182

Study name	Convalescent plasma therapy from recovered COVID-19 patients as therapy for hospitalized patients with COVID-19 (CONCOVID Study) (ConCoVid-19)
Methods	• Trial design: open-label, RCT • Sample size: 426 • Setting: hospitalised patients • Country: Netherlands • Language: English • Number of centres: 2

Participants	• Inclusion criteria
	  * Patients with PCR-confirmed COVID disease
	  * Written informed consent by patient or legal patient representative
	  * Age > 18
	• Exclusion criteria
	  * Patient in which a 'no ICU admission' or 'no invasive ventilation' restriction was implemented at the time of screening for the study
	• 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
	• Donor exclusion criteria
	  * Donors excluded 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

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: Infusion of plasma retrieved from donors with a history of PCR-proven symptomatic COVID
	  * volume: 300 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): NR
	• For studies including a control group: comparator (type): standard of care (supportive care, oxygen, antibiotics)
	• Concomitant therapy: standard of care
	• Treatment cross-overs: none

Outcomes	• Primary study outcome: overall mortality until discharge from the hospital or a maximum of 60 days after admission whichever comes first
	• Primary review outcomes
	  * All-cause mortality at hospital discharge: yes (overall mortality until discharge from the hospital or a maximum of 60 days after admission whichever comes first)
	  * Time to death: yes

NCT04342182 *(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 30 days post-discharge)
	  * Admission on the ICU: yes
	  * Length of stay on the ICU: yes
	  * Time to discharge from hospital: yes
	  * QoL: NR
	• Additional outcomes
	  * Impact of plasma therapy on the decrease in SARS-CoV-2 shedding from airways (time frame: until hospital discharge, estimated average 2 weeks)

Starting date	8 April 2020
Contact information	Bart Rijnders, MD, PhD+31107033510; b.rijnders@erasmusmc.nl
Notes	• Recruitment status: recruiting (1 site only, 2nd site not yet recruiting) • Prospective completion date: 1 July 2020 • Sponsor/funding: Erasmus Medical Center

NCT04343261

Study name	Convalescent plasma in the treatment of COVID 19
Methods	• Trial design: single-arm intervention study • Sample size: 15 • Setting: hospital • Country: USA • Language: English • Number of centres: 1

Participants	• 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

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP

NCT04343261 *(Continued)*

	• Details of CP:
	  * type of plasma: NR
	  * volume: 2 units (mL 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): severe or life-threatening
	• For studies including a control group: comparator (type): none (single-arm)
	• Concomitant therapy: NR
	• Treatment cross-overs: not applicable

Outcomes	• Primary study outcome: mortality within 28 days, viral load, serum antibody titers
	• Primary review outcomes
	  * All-cause mortality at hospital discharge: yes (within 28 days)
	  * Time to death: yes (within 28 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): 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 (within 28 days only)
	  * Admission on the ICU: NR
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR
	  * QoL: NR
	• Additional outcomes:
	  * Reduction of viral load
	  * Change in serum antibody titres

Starting date	10 April 2020
Contact information	Contact: Latha Dulipsingh, MD860-714-4402; Latha.Dulipsingh@trinityhealthofne.org
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 1 April 2021 • Sponsor/funding: Saint Francis Care

NCT04343755

Study name	Phase IIa study exploring the safety and efficacy of convalescent plasma from recovered COVID-19 donors collected by plasmapheresis as treatment for hospitalized subjects with COVID-19 infection
Methods	• Trial design: single-arm intervention study • Sample size: 55 • Setting: hospital • Country: USA • Language: English • Number of centres: 1

NCT04343755 *(Continued)*

Participants	• 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
	• 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
	• Donor eligibility criteria:
	  * Age 18-60
	  * History of a positive nasopharyngeal swab for COVID-19
	  * At least 14 days from resolution of COVID-19-associated symptoms
	  * 2 negative nasopharyngeal swabs done at least 24 h apart for COVID-19 RNA
	  * COVID-19 neutralising antibody > 1:64
	  * 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) 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)

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * type of plasma: NR
	  * 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): none (single-arm)
	• Concomitant therapy: NR
	• Treatment cross-overs: none (single-arm)

Outcomes	• Primary study outcome:
	  * For patients hospitalized for COVID-19 but not intubated: mechanical ventilation rate at 7 days from starting treatment in hospitalized COVID-19 patients
	  * For patients 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: yes (up to 60 days)
	  * Time to death: yes (up to 60 days)

NCT04343755 *(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 (need and duration of mechanical ventilation)
  - 30-day and 90-day mortality: yes (up to 60 days)
  - Admission on the ICU: NR
  - Length of stay on the ICU: NR
  - Time to discharge from hospital: yes (up to 60 days)
  - QoL: NR
- Additional outcomes:
  - 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
  - Time to symptoms resolution
  - Rate of virologic clearance by nasopharyngeal swab
  - Impact of donor titres level on efficacy
  - Impact of donor titres level on safety
  - Recipient anti-SARS-CoV2 titre assessment

Starting date	9 April 2020
Contact information	• Mariefel Vendivil; 551-996-5828; Mariefel.Vendivil@HackensackMeridian.org • Marlo Kemp; 551-996-4464; Marlo.Kemp@HackensackMeridian.org
Notes	• Recruitment status: recruiting • Prospective completion date: April 2021 • Sponsor/funding: Hackensack Meridian Health

NCT04344535

Study name	Convalescent plasma to reduce complications associated with COVID-19 infection: a randomized trial comparing the efficacy and safety of high-titre anti-SARS-CoV-2 plasma vs. standard plasma in hospitalized patients with COVID-19 infection
Methods	• Trial design: randomised phase 1/2 • Sample size: 500 • Setting: hospital • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Adults ≥ 18 years
	  * Hospitalised with PCR+ COVID-19 infection
	  * If female must not be pregnant and/or breastfeeding

NCT04344535 *(Continued)*

	• Exclusion criteria
	  * 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
	  * Adults ≥ 18 years
	  * Hospitalised with PCR-positive COVID-19 infection
	  * If female must not be pregnant and/or breastfeeding

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• 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. A double-blinded, randomized, multi-stage, 6-armed placebo-controlled trial in the framework of an adaptive trial platform
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
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 ≤ 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 x 10^9 /L); ALT > 5 x ULN; platelet count < 50,000 per mm3 (= 50 x 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 1:1:1:1:1:1 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

NCT04345289 *(Continued)*

	• 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
	• 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	• Recruitment status: recruiting • Prospective completion date: 15 June 2021 • Sponsor/funding: Thomas Benfield

NCT04345523

Study name	Multi-center, randomized clinical trial of convalescent plasma therapy versus standard of care for the treatment of COVID-19 in hospitalized patients
Methods	• Trial design: multicentre, randomised, clinical trial • Sample size: 278 • Setting: hospital

NCT04345523 *(Continued)*

	• Country: Spain • Language: English • Number of centres: 9
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 ≤ 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	• 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	• Trial design: phase 1, single-arm study • Sample size: 20

NCT04345679 *(Continued)*

	• Setting: hospital • Country: Hungary • Language: English • Number of centres

Participants	• Inclusion criteria
	  * Age: > 18 years
	  * Admitted to hospital due to SARS CoV-2 infection
	  * Written informed consent
	• Exclusion criteria
	  * 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
	  * 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
	  * Age: < 18 or > 60 years
	  * Female patients who are pregnant
	  * HIV1/2 hepatitis B/C or syphilis infection

Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * 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	• Primary study outcome: changing of viral load of SARS-CoV2
	• Primary review outcomes
	  * All-cause mortality at hospital discharge: yes
	  ☐ 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	• Eszter Fodor, medical doctor; +36306640494; eszter.fodor@orthosera.com • Zsombor Lacza, MD, PhD; +36305249554; zsombor.lacza@orthosera.com
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 1 April 2021 • Sponsor/funding: Orthosera Kft

NCT04345991

Study name	Cohort multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in covid-19 patients - CORIMUNO-CORIPLASM: efficacy of convalescent plasma to treat SARS-CoV2 infected patients
Methods	• 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	• Inclusion criteria
	  * 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
	  * Pregnancy
	  * Current documented and uncontrolled bacterial infection
	  * Prior severe (grade 3) allergic reactions to plasma transfusion

Interventions	• 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 ≥ 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)*

	• Number of centres: 2
Participants	• Inclusion criteria * 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: ☐ respiratory distress, respiratory rate ≥ 30 breaths/min ☐ oxygen saturation level < 93% in resting state ☐ PaO2)/FiO2 ≤ 300 mmHg ☐ lung infiltrates > 50% within 24-48 h • Exclusion criteria * 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 * PaO2/FiO2 < 150 * Donors who were recovered with use of steroids during treatment
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * 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	• Primary study outcome: proportion of participants remaining free of mechanical ventilation • Primary review outcomes * All-cause mortality at hospital discharge: yes ☐ 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 Pa02/Fi02 ratio in both groups (time frame: day 2)
	  * Improvement in Pa02/Fi02 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%40hotmail.com?subject=NCT04346446, ILBS-COVID-02, Efficacy of Convalescent Plasma Therapy in Severely Sick COVID-19 Patients
Notes	• Recruitment status: completed • Prospective completion date: 20 June 2020 • Sponsor/funding: Institute of Liver and Biliary Sciences, India

NCT04346589

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 critically ill ventilated patients with coronavirus disease 2019 (COVID-19)
Methods	• Trial design: interventional (single-arm) • Sample size: 10 • Setting: critically ill patients • Country: Italy • Language: English • Number of centres: 5

Participants	• Inclusion criteria
	  * > 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

NCT04346589 *(Continued)*

	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 • Exclusion criteria * Patient being treated with other anti-COVID-19 experimental treatments
Interventions	• CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: * 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	• Primary study outcome: number of mechanical ventilation days • Primary review outcomes * All-cause mortality at hospital discharge: yes (up to 6 months) * 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: yes * Length of stay on the ICU: yes * Time to discharge from hospital: NR * QoL: NR • Additional outcomes * Number of mechanical ventilation days * Shift to CPAP ventilation
Starting date	April 2020
Contact information	Piero Luigi Ruggenenti, MD; 0039 035 267 ext 3814; pruggenenti@asst-pg23.it
Notes	• Recruitment status: not yet recruiting • Prospective completion date: July 2020 • Sponsor/funding: A.O. Ospedale Papa Giovanni XXIII, Aferetica - Italy (BO)

NCT04347681

Study name	A national collaborative multicenter phase II study for potential efficacy of convalescent plasma to treat severe COVID-19 and patients at high risk of developing severe COVID-19
Methods	• Trial design: non-randomised, parallel assignment • Sample size: 40 (all receiving intervention) • Setting: hospital • Country: Saudi Arabia • Language: English • Number of centres: 10
Participants	• Inclusion criteria * ≥ 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: ☐ dyspnoea ☐ respiratory frequency ≥ 30/min ☐ blood oxygen saturation ≤ 93% ☐ PaO2/FiO2 < 300, and/or lung infiltrates > 50% within 24-48 h * 3. Life-threatening disease is defined as: ☐ respiratory failure ☐ septic shock, and/or ☐ multiple organ dysfunction or failure • Exclusion criteria * Negative or non-conclusive test COVID-19 rRT-PCR test for SARS-CoV-2 * Mild symptoms * Hospitalisation not requiring ICU admission
Interventions	• CP therapy or hyperimmune globulin therapy: CP therapy • Details of CP: * 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	• Primary study outcome: ICU length of stay, safety and serious adverse reactions • Primary review outcomes * All-cause mortality at hospital discharge: yes (up to 12 weeks) * Time to death: yes (up to 12 weeks)

NCT04347681 *(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: yes
	  * Length of stay on the ICU: yes
	  * Time to discharge from hospital: NR
	  * QoL: NR
	• 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	• Recruitment status: recruiting in 1 site • Prospective completion date: 11 April 2021 • Sponsor/funding: King Fahad Specialist Hospital Dammam

NCT04348656

Study name	A randomized open-label trial of CONvalenscent plasma for hospitalized adults with acute COVID-19 respiratory illness (CONCOR-1)
Methods	• Trial design: randomised, clinical trial • Sample size: 1200 • Setting: hospital • Country: Canada • Language: English • Number of centres: 27

Participants	• Inclusion criteria
	  * ≥ 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
	  * 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	• CP therapy or hyperimmune immunoglobulin therapy: CP

NCT04348656 *(Continued)*

	• Details of CP:
	  * 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	• Primary study outcome: endpoint of the need for intubation or patient death in hospital
	• 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	• 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	• Trial design: single-arm, interventional • Sample size: 20 • Setting: critically ill patients • Country: Egypt • Language: English

NCT04348877 *(Continued)*

	• Number of centres: 1
Participants	• Inclusion criteria * 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 ≤ 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 • 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 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

NCT04348877 *(Continued)*

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	• Trial design: single-arm, interventional • Sample size: 2000 • Setting: moderate-severe cases • Country: Pakistan • Language: English • Number of centres: 1 reported
Participants	• Inclusion criteria * 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: ☐ moderately severe disease as defined by the following features: shortness of breath; respiratory rate ≥ 30/min; arterial blood oxygen saturation ≤ 92%,; and/or lung infiltrates > 25% within 24-48 h ☐ severe life-threatening disease as defined by the presence of any of the following features: respiratory failure; shock; multiple organ dysfunction • Exclusion criteria * 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	• CP therapy or hyperimmune globulin therapy: CP • Details of CP: * 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 ☐ children: 15 mL/kg over 4-6 h once in patients under 35 kg body weight ☐ 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	• Primary study outcome: change in COVID-19 severity status (for categories: see additional outcomes)

NCT04352751 *(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): 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 ≤ 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	• Recruitment status: not yet recruiting • Prospective completion date: April 2021 • Sponsor/funding: Hilton Pharma

NCT04353206

Study name	A feasibility study assessing the safety of multiple doses of anti-SARS-CoV-2 plasma in mechanically ventilated intubated patients with respiratory failure due to COVID-19
Methods	• Trial design: single-arm, interventional • Sample size: 90 • Setting: ICU • Country: USA • Language: English • Number of centres: 3

NCT04353206 *(Continued)*

Participants	• Inclusion criteria
	  * ≥ 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
	• 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 disseminated intravascular coagulation, 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	• 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	An open label, phase 2 study evaluating the efficacy and safety of high-titre anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19 infection
Methods	• Trial design: non-randomised • Sample size: 106 • Setting: hospital • Country: USA • Language: English • Number of centres: NR

Participants	• Inclusion criteria
	  * 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:
	  ☐ respiratory rate ≥ 24/min
	  ☐ oxygen support > 3 L/min by nasal cannula
	  ☐ new onset or worsening of respiratory symptoms with radiologic confirmation of bilateral ground glass opacities that cannot be attributed to another cause
	  * Patient/HCPOA must agree to storage of blood specimens for future testing
	  * Patient/HCPOA is willing and able to provide electronic informed consent and comply with all protocol requirements. If patient is unable to consent due to incapacity, HCPOA 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 to limit coronavirus associated complications: a randomized double-blind, phase 2 study comparing the efficacy and safety of high-titer anti-SARS-CoV-2 plasma vs. placebo in emergency room patients
Methods	• Trial design: RCT • Sample size: 206 • Setting: patients presenting to ED • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Age ≥ 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
	  * 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	• CP therapy or hyperimmune globulin therapy: CP
	• Details of CP:
	  * 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	• Primary study outcome: time to disease progression
	• Primary review outcomes
	  * 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	• 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	• Trial design: single-arm intervention study • Sample size: 100 • Setting: hospital • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Age 18-80 years
	  * Symptomatic CoVID-19 disease requiring hospitalisation
	  * SARS-CoV-19 PCR positive
	  * Elevated high-sensitivity troponin
	• Exclusion criteria
	  * 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	• CP therapy or hyperimmune globulin therapy: CP
	• Details of CP:
	  * 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	• Primary study outcome: mortality at day 28
	• Primary review outcomes
	  * All-cause mortality at hospital discharge: yes (at day 28)
	  * 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 (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
	  * 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	• 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 by COVID-19
Methods	• Trial design: interventional, single-arm • Sample size: 90 • Setting: critically ill patients • Country: Mexico • Language: English • Number of centres: 4

NCT04356482 *(Continued)*

Participants	• Inclusion criteria
	  * All patients with COVID-19 test positive
	  * Severely ill patient
	  ☐ respiratory difficulty
	  ☐ sat O2 < 93% without O2 but improves with the use of supplemental oxygen
	  ☐ CT scan image: COVID-19-compatible pneumonia
	  ☐ ≥ 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
	  ☐ respiratory difficulty that does not improve with supplemental oxygen, requiring intubation and connecting to ventilatory support of no > 72 h or 3 days
	  ☐ CT image: COVID-19 compatible pneumonia
	  ☐ ≥ 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
	  ☐ survival over 5 days
	  * Pregnant women are accepted
	• Exclusion criteria
	  * Patients with asymptomatic/mild disease for COVID-19
	  * Children < 16 years old
	  * Patients with atypical pneumonia without COVID-19 diagnostic for PCR-RT

Interventions	• CP therapy or hyperimmune globulin therapy: CP therapy
	• Details of CP:
	  * 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	• Primary study outcome: clinical improvement, improvement in tomographic image, test positivity for COVID-19, early and late complications
	• 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: 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)*

	• Additional outcomes
	  * 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	• 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	Use of convalescent plasma therapy for COVID-19 patients with hypoxia: a prospective randomized trial
Methods	• Trial design: randomised, clinical trial • Sample size: 40 • Setting: hospitalised patients • Country: Bahrain • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * COVID-19 diagnosis
	  * Hypoxia, (oxygen saturation of ≤ 92% or PO2 < 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
	  * 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	• CP therapy or hyperimmune immunoglobulin therapy: CP
	• Details of CP:
	  * 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

NCT04356534 *(Continued)*

Outcomes	• Primary study outcome: requirement for invasive ventilation
	• 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%40rcsi-mub.com?subject=NCT04356534, BDF/R&REC/2020-423, Convalescent Plasma Trial in COVID -19 Patients
Notes	• Recruitment status: not yet recruiting • Prospective completion date: 30 June 2020 • Sponsor/funding: Royal College of Surgeons in Ireland - Medical University of Bahrain

NCT04357106

Study name	COPLA Study: treatment of severe forms of coronavirus infection with convalescent plasma
Methods	• Trial design: single-arm, interventional • Sample size: 10 • Setting: ICU • Country: Mexico • Language: English • Number of centres: 1

NCT04357106 *(Continued)*

Participants	• Inclusion criteria
	  * SARS-CoV2 infection with serious evolution and in ICU
	  * With or without ventilatory assistance
	  * Treated or not with hydroxychloroquine 200 mg every 12 h
	  * Either sex
	  * > 18 years
	  * Signed informed consent
	• Exclusion criteria
	  * Treated with the following medications: azithromycin, ritonavir/lopinavir, remdesivir, interferons, ruxolinitib, tocilizumab
	  * Severe kidney failure who require replacement therapy

Interventions	• CP therapy or hyperimmune globulin therapy: CP therapy
	• Details of CP:
	  * type of plasma: apheresis plasma
	  * volume: 200 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): NR
	• For studies including a control group: comparator (type): none
	• Concomitant therapy: with or without ventilation, hydroxychloroquine
	• Treatment cross-overs: none

Outcomes	• Primary study outcome: lung injury (PaO2/FiO2 relation), overall survival
	• Primary review outcomes
	  * All-cause mortality at hospital discharge: yes (up to 30 days)
	  * Time to death: yes (up to 30 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 (up to 7 days)
	  * Number of participants with SAEs: yes (up to 7 days)
	  * 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 (up to 30 days)
	  * Admission on the ICU: yes (in ICU)
	  * Length of stay on the ICU: NR
	  * Time to discharge from hospital: NR
	  * QoL: NR
	• Additional outcomes
	  * Lung injury defined as PaO2/FiO2 relation (time frame: 7 days)

Starting date	13 April 2020
Contact information	Juan Carlos Olivares-Gazca, MD, MPH; 2222438100; jolivares@hsctmexico.com José Manuel Priesca-Marin, MD; 2222438100; mpriesca@hsctmexico.com
Notes	• Recruitment status: recruiting • Prospective completion date: August 2020 • Sponsor/funding: Centro de Hematología y Medicina Interna

NCT04358211

Study name	Expanded access to convalescent plasma to treat and prevent pulmonary complications associated with COVID-19
Methods	• 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
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

NCT04358211 *(Continued)*

	• 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
	• 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	April 3 2020
Contact information	Nakhle Saba, MD nsaba@tulane.edu Tulane Medical CenterAvailable New Orleans, Louisiana, USA, 70112
Notes	• 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	• 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

NCT04358783 *(Continued)*

	• Number of centres: 1 Clinical trial comparing convalescent plasma to BAT for the treatment of severely ill and critically ill patient with COVID-19 Patients with SARS-CoV-2 PCR-confirmed infection with pulmonary infiltrates and hypoxaemia will be screened and invited to participate
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, SO2 < 93%, PaO2/FiO2 < 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 ≤ 65mmHg 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	• 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	• 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 ≥ 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) ≤ 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) ≥ 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	Contact: Max O'Donnell, MD 212-305-5794 mo2130@cumc.columbia.edu Contact: Andrew Eisenberger, MD 212-305-0983 abe6@cumc.columbia.edu Columbia University Irving Medical Center/NYPRecruiting New York, New York, USA, 10032
Notes	• Recruitment status: recruiting • Prospective completion date: April 2021 • Sponsor/Funding: Max R. O'Donnell, Columbia University

NCT04360486

Study name	Expanded access protocol for the treatment of coronavirus disease 2019 (COVID-19) with anti-SARS-CoV-2 convalescent plasma (ASCoV2CP)
Methods	• 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	• Inclusion criteria:
	  * 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
	  * 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	• Intervention(s): anti-SARS-CoV-2 convalescent plasma
	• Details of CP:
	  * Type of plasma: fresh frozen plasma, 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):
	  * generally reserved for patients at severe risk or at risk of progression to life-threatening disease. In adults defined as:
	  ☐ Dyspnoea
	  ☐ Respiratory frequency ≥ 30/min
	  ☐ Blood oxygen saturation ≤ 93%
	  ☐ Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
	  ☐ 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:
	  ☐ Respiratory failure
	  ☐ Septic shock
	  ☐ Multiple organ dysfunction or failure
	• Comparator: N/A
	• Concomitant therapy: NR
	• Treatment cross-overs: N/A

Outcomes	• Primary study outcome(s): efficacy of this treatment will not be evaluated
	• Primary review outcomes reported
	  * 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	• 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	• 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	• Inclusion criteria
	  * 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:
	  * 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	• 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 6177328624koganezova@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	• 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	• Inclusion criteria * All sexes * Age ≥ 18 years * Currently hospitalised or in an ED with anticipated hospitalisation * Symptoms of acute respiratory infection, defined as ≥ 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 * 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	• Intervention(s): e.g.. SARS-CoV-2 convalescent plasma • Details of CP: * 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	• Primary study outcome(s): * COVID Ordinal Outcomes Scale: day 15 (time frame: study day 15) 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	Amanda J Bistran-Hall (615) 875-8531 amanda.j.bistran-hall@vumc.org Principal Investigator: Todd Rice, MD Vanderbilt University Medical Center Vanderbilt University Medical Center

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 ≤ 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	• Primary study outcome(s): NR
	• Primary review outcomes reported
	  * All-cause mortality at hospital discharge: (give details e.g. 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):
	  * 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

Starting date	27 April 2020
Contact information	Danielle Evans (501) 526-7906 DEvans@uams.edu David Avery (501) 214-2101 daavery@uams.edu University of Arkansas
Notes	• Recruitment status: expanded access - available • Prospective completion date: NR • Sponsor/Funding: University of Arkansas

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
Methods	• 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

Participants	• Inclusion criteria:
	  * 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

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	Mila B Ortigoza, MD, PhD Mila.Ortigoza@nyulangone.org Michelle Chang Michelle.Chang3@nyulangone.org • Montefiore Medical Center, Bronx, New York, USA, 10467 • NYU Langone Health New York, New York, USA, 10003
Notes	• Recruitment status: recruiting (NYU Langone Health) * 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	• Trial design: proof of concept study, single-group assignment, open-label • Sample size: 10 • Setting: e.g. inpatient • Country: Italy • Language: Engllish • Number of centres: NR

Participants	• Inclusion criteria
	  * 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	Contact: Enos Bernasconi, M.D. +41 91 811 60 22 enos.bernasconi@eoc.ch Contact: Beatrice Bernasconi +41 91 811 60 21 beatrice.bernasconi@eoc.ch Ente Ospedaliero Cantonale, Bellinzona Principal Investigator: Stefano Fontana, M.D. Servizio Trasfusionale, Lugano
Notes	• 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	• 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 Inclusion criteria:

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-oropharyngeal 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 ≤ 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-oropharyngeal 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 ≤ 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 Unversitario Virgen Macarena, Sevilla, Spain, 41009

NCT04366245 *(Continued)*

Notes	• Recruitment status: recruiting • Prospective completion date: December 2021 • Sponsor/funding: Andalusian Network for Design and Translation of Advanced Therapies

NCT04372368

Study name	Convalescent plasma for the treatment of patients with COVID-19
Methods	• Trial design: expanded access • Sample size: ≥ 150 • Setting: inpatient • Country: USA • Language: English • Number of centres: 6

Participants	Inclusion criteria:
	• 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:
	  * Hospitalised with COVID-19
	  * Respiratory rate > 25/min
	  * Oxygen saturation < 96%
	  * With or without radiographic evidence of pulmonary involvement
	• Severe COVID-19 is defined by ≥ 1 of the following:
	  * dyspnoea
	  * respiratory frequency ≥ 30/min
	  * blood oxygen saturation ≤ 93%
	  * Radiographic evidence of pulmonary disease
	• Life-threatening COVID-19 is defined as ≥ 1 of the following:
	  * respiratory failure requiring mechanical ventilation or non-rebreather oxygenation in the ICU
	  * Prone oxygenation
	  * multiple organ dysfunction or failure
	Exclusion criteria:
	• 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	• 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	• Primary study outcome: survival time without need of a ventilator (time frame: day 30)
	• Primary review outcomes reported
	  * All-cause mortality at hospital discharge: 30-day mortality without need of a ventilator
	  * 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: yes (length of stay (time frame: day 30)
	  * QoL: NR
	• Additional study outcomes
	  * 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)

Starting date	May 2020
Contact information	Contact: Christophe MARTINAUD, PU PH +33 141467241christophe.martinaud@intradef.gouv.fr Contact: Christophe RENARD +33 140514103christophe1.renard@intradef.gouv.fr
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 FOEHRENBACHDirection Centrale du Service de Santé des Armées (DCSSA), Study Director:Catherine VERRETService de Santé des Armées-Direction de la Formation de la Recherche et de l'Innovation, Principal Investigator:Christophe MARTINAUDCentre de Transfusion Sanguine des Armées, Principal Investigator:Jean-Luc BOSSONStatistical and methodological investigator - Laboratoire TIMC UMR 5525 CNRS Equipe Themas

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	• Trial design: phase 2, double-blind, RCT • Sample size: 1344 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1
Participants	Inclusion criteria: • ≥ 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° 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 Exclusion criteria: • 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	• Intervention(s): SARS-CoV-2 CP
	• Details of CP:
	  * 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	• Primary study outcome:
	  * 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
	  * 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	Recruitment status: not yet recruiting Prospective completion date: 21 December 2022 Sponsor/funding: Johns Hopkins University, State of Maryland, Bloomberg Foundation, Principal Investigator: David J Sullivan, MD The Johns Hopkins University

NCT04374370

Study name	Severe acute respiratory syndrome coronavirus 2 of the genus betacoronavirus (SARSCoV2) convalescent plasma (CP) expanded access protocol (EAP)
Methods	• Trial design: intermediate-size population, expanded access • Sample size: NR • Setting: inpatient • Country: USA • Language: English

NCT04374370 *(Continued)*

	• Number of centres: NR
Participants	Inclusion criteria: • 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 Severe disease is defined as: • dyspnoea • respiratory frequency ≥ 30/min • blood oxygen saturation ≤ 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 is defined as: • respiratory failure • septic shock, and/or • multiple organ dysfunction or failure Exclusion criteria: • Known contraindication to transfusion or history of prior reactions to transfusion of blood products

Interventions	• Intervention(s): SARS-CoV2 CP
	• Details of CP:
	  * 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	• Primary study outcome: NR
	• Primary review outcomes reported
	  * 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	Recruitment status: available Prospective completion date: NR Sponsor/funding: AdventHealth Orlando, Available: Orlando, Florida, United States, 32803, Principal Investigator: Eduardo Oliveira, MD AdventHealth

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	• Trial design: phase II, open-label, RCT • Sample size: 100 (50 each group) • Setting: inpatient • Country: India • Language: English • Number of centres: 1

Participants	Inclusion criteria
	
	• Patients admitted with RT-PCR-confirmed COVID-19 illness.
	• Age > 18 years
	• Written informed consent
	• Has any of the 2
	  * PaO2/ FiO2 < 300
	  * Respiratory Rate > 24/min and SaO2 < 93% on room air
	
	Or in case of severe or immediately life-threatening COVID-19, for example:

NCT04374487 *(Continued)*

- Severe disease is defined as:
  - dyspnoea
  - respiratory frequency ≥ 30/min
  - blood oxygen saturation ≤ 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	• Trial design: randomized phase 2/3 • Sample size: 182 • Setting: inpatient • Country: Italy • Language: translated to English • Number of centres: 3
Participants	Inclusion criteria: • Age ≥ 65 • pneumonia at CT scan • PaO2/FiO2 ≥ 300 mmHg • Presence of ≥ 1 comorbidities (consider the list provided in Appendix A) • Signed informed consent Exclusion criteria: • 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	• 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)*

	• Number of centres: 2
Participants	Inclusion criteria: • 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. Exclusion criteria: • 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 hypertriglyceridemia, 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	• Intervention(s): high-titre anti-SARS-CoV-2 (COVID 19) CP • Details of CP: * 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	• Primary study outcome: * Transfer to ICU (time frame: Days 0-60) * 28 day mortality (time frame: Days 0-60) • Primary review outcomes reported * All-cause mortality at hospital discharge: 28-day mortality (time frame: Days 0-60) * 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,

NCT04374565 *(Continued)*

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))
  * 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	• Trial design: randomized, open-label, phase II trial • Sample size: 30 • Setting: inpatient • Country: Chile • Language: translated to English • Number of centres: 1
Participants	Inclusion criteria: • 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

NCT04375098 *(Continued)*

	• ECOG before COVID-19 infection 0-2 Exclusion criteria: • PaFi < 200 or mechanical ventilation indication • 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)

NCT04375098 *(Continued)*

Starting date	4 May 2020
Contact information	Contact: Maria Elvira Balcells, MD +562 23543508 ebalcells@uc.cl
Notes	Recruitment status: recruiting 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	• Trial design: prospective, non-randomized, sequential-assigned, clinical trial • Sample size: 240 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1
Participants	• Inclusion criteria: * 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: * 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: * Prior diagnosis of COVID-19 documented by a laboratory test ☐ Abbott RealTime SARS-CoV-2 real-time RT-PCR test on the Abbott m2000 System (inpatient WVU testing) ☐ 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

NCT04376034 *(Continued)*

- Donor exclusion criteria:
  - 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	• Intervention(s): CP
	• 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

NCT04376034 *(Continued)*

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 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	• 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	Inclusion criteria: 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 Exclusion criteria: 1. Patients with pregnancy and lactation 2. Renal failure and heart failure 3. Contraindication for plasma or blood transfusion
Interventions	• Intervention(s): CP • Details of CP (group I): * 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

NCT04376788 *(Continued)*

- Details of CP (group II):
  - 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):
  - 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
  - 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

NCT04376788 *(Continued)*

	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 • 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

NCT04377568 *(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
  - 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
- 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	• Trial design: single-centre, single-arm, open-label interventional trial • Sample size: 30 participants • Setting: inpatient • Country: USA

NCT04377672 *(Continued)*

	• Language: English • Number of centres: 1
Participants	Inclusion criteria: • 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 ≤ 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 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 premedications, 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: ≥ 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	• Trial design: multicentre, open-label RCT • Sample size: 60 • Setting: inpatients • Country: Indonesia • Language English • Number of centres: 3
Participants	Inclusion criteria: • Patients aged ≥ 18 years • COVID-19 confirmed by RT-PCR • Having severe pneumonia • PAO2 / FIO2 < 300 • Using mechanical ventilation Exclusion criteria: • Contraindication to blood transfusions (fluid overload, history of anaphylaxis of blood products) • Multiple and severe organ failure, haemodynamically unstable • Other uncontrolled infections • Disseminated intravascular coagulation (DIC), which requires a replacement factor/FFP • Haemodialysis patients or CRRT (continuous renal replacement therapy) • Active intracranial bleeding • Significant myocardial ischaemia

NCT04380935 *(Continued)*

	• Receiving tocilizumab treatment

Interventions	• Intervention(s): standard of care and 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): NR
	• Comparator: standard therapy
	• Concomitant therapy: NR
	• Treatment cross-overs: no

Outcomes	• Primary study outcome: all cause mortality at 28-day
	• 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): 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	• Trial design: single-centre, double-blind, RCT • Sample size: 500 • Setting: inpatient • Country: Mexico • Language English

NCT04381858 *(Continued)*

	• Number of centres: 1
Participants	Inclusion criteria: • 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: a. Severe respiratory failure (respiratory rate > 25 to < 35 x min, oxygen saturation ≤ 90% with reservoir mask (FiO2 = 100%) b. Requiring invasive mechanical ventilation Exclusion criteria: • Patients with a viral infection other than COVID-19
Interventions	• Intervention(s): CP or human immunoglobulin • Details of CP: * 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	• Primary study outcome: mean hospitalisation time • 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: 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 * 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	Recruitment status: recruiting Prospective completion date: 30 September 2020

NCT04381858 *(Continued)*

	Sponsor/funding: Centenario Hospital Miguel Hidalgo

NCT04381936

Study name	Randomised evaluation of COVID-19 therapy (RECOVERY)
Methods	• 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	• Inclusion criteria: * 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: * 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	• Intervention(s): randomised factorial assignment * 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: * Type of plasma: ABO-identical if possible * Volume: 275mLs +/- 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	• 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	• Trial design: multicentre randomized, double-blind, placebo-controlled clinical trial • Sample size: 333 • Setting: inpatient • Country: Argentina • Language: English • Number of centres: NR
Participants	Inclusion criteria: • Confirmed diagnosis of COVID-19 through qualitative qRT-PCR (GeneDX Co, Ltd or similar) • Imagining-diagnosed pneumonia (X-ray or CT scan) • MSOFA score (Modified SOFA) of ≥ 2 (modified organic failure assessment) • Informed consent Exclusion criteria: • Pregnant women

NCT04383535 *(Continued)*

	• 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	• Intervention(s): CP and placebo • Details of CP: * 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 10-15mL/kg • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	• 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 * 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: 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 * 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	• Trial design: interventional, single-arm, open-label, clinical trial • Sample size: 100 • Setting: inpatients • Country: Egypt • Language: English • Number of centres: NR
Participants	Inclusion criteria: • Passive immunisation group (Group A) * 20 high-risk exposed people (HCPs) who are nasopharyngeal swab SARSCoV-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) * 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 Exclusion criteria: • Passive immunisation group (Group A) * 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) 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	• 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 ≥ 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 ≥ 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

NCT04384497 *(Continued)*

Contact information	Contact: Joakim Dillner, MD, PhD +46 (0) 72-468 24 60 joakim.dillner@ki.se Contact: Johan Ursing, MD, PhD +46 (0) 70-475 15 30 johan.ursing@sll.se
Notes	Recruitment status: recruiting Prospective completion date: December 2020 Sponsor/funding: Karolinska University Hospital/NR

NCT04384588

Study name	COVID19-convalescent plasma for treating patients with active symptomatic COVID 19 infection (FALP-COVID) (FALP-COVID)
Methods	• Trial design: multicentre, single-arm, open-label, non-randomised clinical trial • Sample size: 100 • Setting: inpatient • Country: Chile • Language: English • Number of centres: 4
Participants	Inclusion criteria for all patients: • Patient must sign an informed consent to participate in this trial • Signed consent to participate in this trial must be given not after 14 days from the first day of symptoms COVID-19 related • Patients with severity criteria must have any of the following: dyspnoea and or respiratory rate ≥ 30/min and or saturation ≤ 93% with fraction of inspired oxygen 21% and/or ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaFi) < 300 and/or lung images showing worsening in 24-48 h • Patients without severity criteria but with ≥ 2 risk factors: * ≥ 50 years * Any of the following comorbidities: diabetes mellitus, hypertension, COPD, chronic kidney failure, non-oncological-related chronic immunosuppression * Total bilirubin > 1.2 mg/dL or blood urea nitrogen > 20 mg/dL or lactate dehydrogenase > 245 U/L * D-dimer > 1 mg/L * Neutrophils ≥ 7.3 x 10^3 and/or lymphocytes < 0,8 x 10^3 µl * CRP > 9.5 mg/dL and ferritin > 300 ug/mL * Interleukin-6 > 7 pg/mL * Antineoplastic treatment such as radiotherapy- cytotoxic chemotherapy- immunotherapy- molecular therapy- oncological surgery during the last 8 weeks Exclusion criteria: • known allergy to plasma • Severe multiple organic failure • Active intra brain haemorrhage • Disseminated intravascular coagulation with blood products requirements • Patient with an adult respiratory distress > 10 days • patients with active cancer and life expectancy < 12 months according with medical criteria
Interventions	• Intervention(s): CP

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	Inclusion criteria: • 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) Exclusion criteria: • 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	• Intervention(s): plasma-hyperimmune add on to the standard 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): NR • Comparator: standard therapy • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	• Primary review outcomes reported * All-cause mortality at hospital discharge: 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): 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 * 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	• 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	Inclusion criteria: • >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 Exclusion criteria: • 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 (fresh frozen plasma, cryoprecipitate and platelets), • History of allergic reaction due to IgA deficiency • Allergic reaction to sodium citrate or riboflavin (vitamin B2) History of immunosuppression

Interventions	• Intervention(s): inactivated CP SARS-Cov-2 + support treatment under medical decision (day 0)
	• Details of CP:
	  * 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	• Primary study outcome: mortality reduction in COVID-19 patients treated with inactivated CP + support treatment
	• Primary review outcomes reported
	  * 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	• 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

NCT04385199 *(Continued)*

Methods	• Trial design: open, parallel, RCT • Sample size: 30 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * age > 18 with ≥ 1 of the following:
	  ☐ dyspnoea respiratory rate ≥ 30 breaths/min
	  ☐ Oxygen saturation ≤ 93% PaO2/FiO2
	  ☐ < 300 bilateral airspace opacities on chest radiograph at 24-48 h
	• Exclusion criteria
	  * Acute myocardial infarction in past 30 days
	  * Acute stroke in past 30 days
	  * VV ECMO VA ECMO

Interventions	• Intervention(s): conventional treatment and CP therapy
	• Details of CP:
	  * 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	• Primary study outcome: improvement in respiratory disease (time frame: days 1, 3, 5, 7, 14, 28 post-transfusion)
	  * For intubated participants improvement in PaO2/FiO2
	  * For non-intubated participants time to intubation post-transfusion
	• 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: 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, gtatem1@hfhs.org
Notes	• 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	• Trial design: RCT, double-blinded, multicentre, placebo-controlled • Sample size: 250 • Setting: inpatient • Country: Mexico • Language: English • Number of centres: at least 6

Participants	• Inclusion criteria
	  * Adults ≥ 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
	  * 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	• Intervention(s): normal saline and CP therapy
	• Details of CP:
	  * 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	• Primary study outcome:
	  * Severity and death (time frame: 28 days)
	  * AEs that require study treatment interruption (time frame: 28 days)
	• Primary review outcomes reported
	  * 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	• 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	• Trial design: single-arm intervention • Sample size: 50 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * Adult ≥ 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 ≥ 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 form 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	• Katharine J. Bar, MD (215) 349-8092 BarK@pennmedicine.upenn.edu • Julie Starr 215-349-8527 jstarr@pennmedicine.upenn.edu
Notes	• 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	• Trial design: single-arm intervention • Sample size: 100 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1
Participants	• Inclusion criteria * 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 ☐ Dyspnoea ☐ Respiratory rate > 30/min ☐ Oxygen saturation < 94% ☐ Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 ☐ Lung infiltrates > 50% within 24-48 h * Life-threatening disease defined as any of the following ☐ Respiratory failure ☐ Septic shock ☐ Multiple organ dysfunction or failure ☐ Informed consent provided by patient or healthcare proxy • Exclusion criteria * Receipt of pooled immunoglobulin in past 30 days * Contraindication to transfusion or history of prior reactions to transfusion blood products
Interventions	• Intervention(s): CP therapy • Details of CP: * 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	• 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 * 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	• Michael Baram, MD215-955-5161 Michael.Baram@jefferson.edu • Anna Marie Chang, MD215-605-5897 AnnaMarie.Chang@jefferson.edu
Notes	• 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	• Trial design: single-arm intervention • Sample size: 15 • Setting: inpatient • Country: Switzerland • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * SARS-CoV-2 infection confirmed by PCR in respiratory secretions (naso-pharyngeal 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
	  * Nil

Interventions	• 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	Plasma from individuals who have recovered from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as treatment for acute COVID-19 disease
Methods	• Trial design: single-arm intervention • Sample size: 10 • Setting: inpatient • Country: Sweden • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * 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
	  * 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 *Streptococcus pneumoniae* or *Haemophilus influenzae* in sputum
	  * Disease duration > 8 days
	  * Estimated GFR <60 (kidney failure ≥ stage III)
	  * Pregnancy (urinary-hCG), breast feeding,
	  * History of severe allergic reactions
	  * Inability to give informed consent
	  * Significantly compromised immunity
	  ☐ 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	• Intervention(s): CP therapy
	• Details of CP:
	  * 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

NCT04390178 *(Continued)*

Outcomes	• Primary study outcome:
	  * Decrease in progression to requiring non-invasive or invasive ventilation (within 28 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): 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	• 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	• Trial design: double-blinded RCT • Sample size: 200 • Setting: close contacts of COVID-19 cases • Country: USA • Language: English • Number of centres: 1
Participants	• Inclusion criteria Group B: SARS-CoV-2 PCR-positive but asymptomatic or mild symptoms at screening

NCT04390503 *(Continued)*

- 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
- 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 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

NCT04390503 *(Continued)*

- 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 (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
- History of allergic reaction to transfusion 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 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

NCT04390503 *(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): 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	• Jessica Justman, MD 212-342-0537 jj2158@cumc.columbia.edu • Jennifer Zech, MSc 212-304-5506 jz2973@cumc.columbia.edu
Notes	• 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	• Trial design: open-label, RCT • Sample size: 231 • Setting: ICU • Country: Colombia • Language: English • Number of centres: 8

Participants	• Inclusion criteria
	  * > 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
	  * 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	• Trial design: single-arm intervention • Sample size: 100 • Setting: inpatient • Country: USA • Language: English • Number of centres: 2
Participants	• Inclusion criteria * 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: ☐ Respiratory frequency ≥ 25/min Oxygen saturation ≤ 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 ☐ 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 * Previous history of life-threatening or severe adverse reactions to transfusion blood products
Interventions	• Intervention(s): CP therapy • Details of CP: * 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	• Primary study outcome: * Survival rate (at 28 days) • Primary review outcomes reported * 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	• William Judd, MBA, MHA (C.) 513 865 5020 William_Judd@TriHealth.com
Notes	• 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	• Trial design: open-label RCT • Sample size: 60 • Setting: inpatient • Country: Russia • Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * 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 µg / mL
	  * A signed informed consent
	• Exclusion criteria
	  * 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 µmol/L
	• Pregnancy or breastfeeding

NCT04392414 *(Continued)*

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  * 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	• Primary study outcome:
	  * 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
	  * All-cause mortality at hospital discharge: 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): 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	• Mikhail A Konoplyannikov, PhD +79154027268 mkonopl@mail.ru • Alexander V Averyanov, MD, PhD, dr.averyanov@gmail.com
Notes	• 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	• Trial design: open-label RCT • Sample size: 126 • Setting: inpatient • Country: Italy

NCT04393727 *(Continued)*

	• Language: English • Number of centres: 1

Participants	• Inclusion criteria
	  * 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
	  * mechanical ventilation (both invasive and non-invasive)
	  * PaO2/FiO2 < 200
	  * known hypersensitivity to immunoglobulin or blood components

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  * 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	• Primary study outcome:
	  * Need of invasive mechanical ventilation defined as PaO2/FiO2 < 150 (at 30 days)
	• Primary review outcomes reported
	  * All-cause mortality at hospital discharge: 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: 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	• Marco Falcone 050996735 marco.falcone@unipi.it
Notes	• 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	• Trial design: open-label RCT • Sample size: 75 • Setting: inpatient • Country: Colombia • Language: English • Number of centres: 1
Participants	• Inclusion criteria * 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: ☐ Radiographic evidence of pulmonary infiltrates by images (chest radiography, computed tomography, etc.) ☐ Clinical evaluation (evidence of rales/crackles on examination) and oxygen saturation ≤ 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 * 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	• Intervention(s): CP therapy and hyperimmune immunoglobulin therapy • Details of intervention CP:

NCT04395170 *(Continued)*

	• Type of plasma: NR
	• Volume: 200-250 mL
	• Number of doses: 2, at days 1 and 3 of treatment
	• Antibody-titre: NR
	• 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 ≥ 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	Use of COVID-19 convalescent plasma in the patients infected with COVID-19 (SARS-CoV-2) - efficacy and safety
Methods	• Trial design: single-arm intervention • Sample size: 20 • 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 rat high risk of progressing to severe disease)
	• Comparator: not applicable

NCT04397523 *(Continued)*

	• Concomitant therapy: NR • Treatment cross-overs: not applicable
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
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

NCT04397757

Study name	An an open-label, controlled, phase 1, safety and exploratory efficacy study of convalescent plasma for severely ill, hospitalized participants with COVID-19 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 ≥ 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

NCT04397757 *(Continued)*

Note - An exception must be requested to the Sponsor if ≥ 72 h since positive test

- * 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

NCT04397757 *(Continued)*

	• 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
Starting date	13 March 2020
Contact information	• Katharine J. Bar, MD (215) 349-8092 BarK@pennmedicine.upenn.edu • Julie Starr 215-349-8527 jstarr@pennmedicine.upenn.edu
Notes	• 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	• Trial design: RCT • Sample size: 60 in 3 arms of 20 each • Setting: inpatient • Country: Bangladesh • Language: English • Number of centres: 3
Participants	• Inclusion criteria * 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 * 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 * Between day 22 and day 35 of recovery * 2 consecutive negative RT-PCR samples * Antibody titre > 1:320 • Donor exclusion criteria NR
Interventions	• Intervention(s): CP therapy • Details of CP: * 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)

NCT04403477 *(Continued)*

	• Concomitant therapy: enoxaparin, antibiotic, fluid, immune modulator (steroid) and or antiviral (favipiravir or ramdesivir or lopinavir + ritonavir) • Treatment cross-overs: no

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
Contact information	Mohammad S Rahman, M Phil, FCPS +88 01971840757 srkhasru@gmail.com Fazle R Chowdhury, FCPS; PhD +88 01916578699 mastershakil@hotmail.com
Notes	• Recruitment status: recruiting • Prospective completion date: 20 July 2020 • Sponsor/funding: Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; Dhaka Medical College

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
Methods	• Trial design: RCT • Sample size: 300

NCT04404634 *(Continued)*

- Setting: inpatient
- Country: USA
- Language: English
- Number of centres: 1

Participants	• Inclusion criteria
	  * 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
	  * 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	• Intervention(s): CP therapy
	• Details of CP:
	  * 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	• Primary study outcome:
	  * 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
	  * 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
Notes	• Recruitment status: not yet recruiting • Prospective completion date: January 2023 • Sponsor/funding: Yale University

NCT04405310

Study name	Plasma from convalescent donors with COVID-19 for the management of patients with SARS-COV-2 phase II and III, a double center randomized double blind trial
Methods	• Trial design: RCT • Sample size: 80 • Setting: inpatient • Country: Mexico • Language: English • Number of centres: 2
Participants	• Inclusion criteria * 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 * 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 * Between 10 and 14 days after SARS-CoV-2 illness • Donor exclusion criteria NR
Interventions	• Intervention(s): CP therapy • Details of CP: * 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

NCT04405310 *(Continued)*

	• Treatment cross-overs: no

Outcomes	• Primary study outcome: all-cause mortality within 15 days
	• Primary review outcomes reported
	  * All-cause mortality at hospital discharge: yes, to 15 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, 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
	  * Viral Load by RT-PCR (time frame: 15 days) changes in viral load
	  * Inflamatory 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	Angela Perez-Calatayud, MD +525542389377 gmemiinv@gmail.com Yanet Ventura, MD +52554848965 yanereb@gmail.com
Notes	**Recruitment status**: recruiting **Prospective completion date:** 20 June 2020 **Sponsor/funding:** Grupo Mexicano para el Estudio de la Medicina Intensiva Hospital General Naval de Alta Especialidad - Escuela Medico Naval National Institute of Pediatrics, Mexico Instituto Nacional de Enfermedades Respiratorias

NCT04407208

Study name	Convalescent plasma therapy in patients with COVID-19
Methods	• Trial design: single-arm intervention • Sample size: 10 • Setting: inpatient • Country: Indonesia • Language: English • Number of centres: 1

NCT04407208 *(Continued)*

Participants	• Inclusion criteria
	  * 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
	  * Pregnant
	  * History of anaphylactic reaction in previous blood product transfusion
	• Donor eligibility criteria
	  * Willingly give informed consent
	• Donor exclusion criteria NR

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  * 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	• Primary study outcome:
	  * 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
	  * 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 outcomes:
	  * 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	**Recruitment status**: recruiting **Prospective completion date:** 1 August 2020 **Sponsor/funding:** Biofarma Rumah Sakit Pusat Angkatan Darat Gatot Soebroto Eijkman Institute for Molecular Biology

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	• Trial design: non-randomised • Sample size: 700 • Setting: inpatient and healthcare providers • Country: USA • Language: English • Number of centres:
Participants	• Inclusion criteria * Documented COVID-19 infection by nasal pharyngeal sampling * COVID-19 disease falling into 1 of the following groups: ☐ Critical disease: respiratory failure requiring mechanical ventilation, pressor support, or multiple organ dysfunction/failure ☐ Severe disease: tachypnoea ≥ 30 per min, O2 sats ≤ 93% at rest, PaO2/FiO2 index ≤ 300 mmHg ☐ 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 ☐ Healthcare providers: healthcare providers at risk to exposure to COVID-19 infection or those with mild to non-severe disease • Exclusion criteria * 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	• Intervention(s): CP therapy • Details of CP: * 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)*

	• Number of centres: 6
Participants	• Inclusion criteria * 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: ☐ Respiratory rate 30/min ☐ Oxygen haemoglobin saturation SAT 93 ☐ CRP > 1.5 (ULN < 0.5) ☐ Ferritin value > 100 ☐ Ratio of PaO2:FiO2 < 300 mmHg ☐ 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: ☐ Respiratory failure ☐ Septic shock ☐ 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 * 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 * All donors will be tested for: ☐ the titre of IgG anti-SARS-CoV-2 antibodies (Pasteur Institute) ☐ the titre of neutralising anti-SARS-CoV-2 antibodies (Pasteur Institute) • Donor exclusion criteria NR
Interventions	• Intervention(s): CP therapy • Details of CP: * 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	• Primary study outcome:
	  * 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
	  * 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: 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
	  * 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.

Starting date	23 April 2020
Contact information	Aikaterini Niarchou +30 6949124743 aniarchou@med.uoa.gr Ioanna Charitaki +30 6976156403 j.charitaki@gmail.com
Notes	**Recruitment status**: recruiting **Prospective completion date:** 30 June 2020 **Sponsor/funding:** National and Kapodistrian University of Athens Hellenic Society of Hematology

NCT04412486

Study name	An open label trial of transfusion of COVID-19 convalescent plasma (CCP) to patients with moderate to severe COVID-19
Methods	• Trial design: single-arm interventional • Sample size: 100 • Setting: inpatient • Country: USA • Language: English • Number of centres: 1

NCT04412486 *(Continued)*

Participants	• Inclusion criteria
	  * Age ≥ 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:
	  ☐ Laboratory-confirmed diagnosis of SARS-CoV-2 infection
	  ☐ Hypoxia (PaO2/FiO2 < 300, pulse oximetry < 93% at rest
	  ☐ Evidence of pulmonary infiltration
	  ☐ Respiratory failure
	  ☐ Sepsis
	  ☐ Multiple organ dysfunction or failure (assessed by SOFA score)
	  * Informed consent provided by the patient or LAR
	• 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

NCT04412486 *(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: 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)
  * 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	**Recruitment status**: recruiting **Prospective completion date:** 31 May 2022 **Sponsor/funding:** Gailen D. Marshall Jr., MD PhD University of Mississippi Medical Center

U1111-1251-9286

Study name	Use of convalescent plasma submitted to pathogen inactivation for the treatment of patients with severe COVID-19
Methods	• Trial design: single-arm intervention; historic control • Sample size: 20 • Setting: inpatient • Country: Brazil • Language: Portuguese • Number of centres: 1

U1111-1251-9286 *(Continued)*

Participants	• Inclusion criteria
	  * 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
	• Exclusion criteria
	  * Allergic reactions prior to plasma transfusion
	• Donor eligibility criteria NR
	• Donor exclusion criteria NR

Interventions	• Intervention(s): CP therapy
	• Details of CP:
	  * 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	• Primary study outcome:
	  * 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
	  * 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:
	  * 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	Pedro Kurtz **Address:** Rua do Resende 156 **City:** Ro de Janeiro / Brazil **Zip Code:** 20231092 **Telephone:** 2122779352

U1111-1251-9286 *(Continued)*	**E-mail:** kurtzpedro@mac.com
Notes	• 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

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; **DVT:** deep vein thrombosis; **ECMO:** extracorporeal membrane oxygenation; **ED:** emergency department; **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; **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; **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

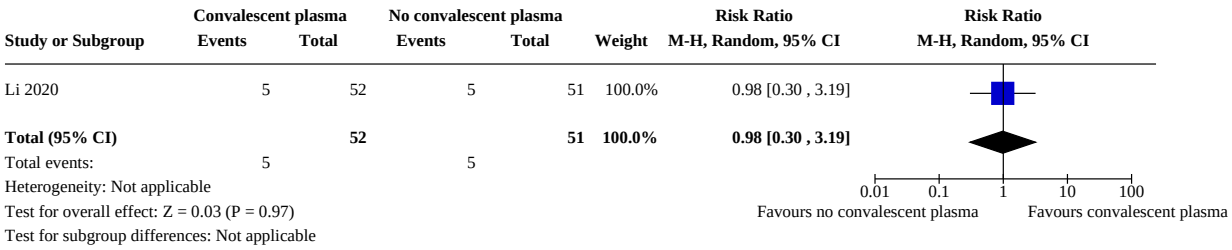
DATA AND ANALYSES

Comparison 1. Results from RCT

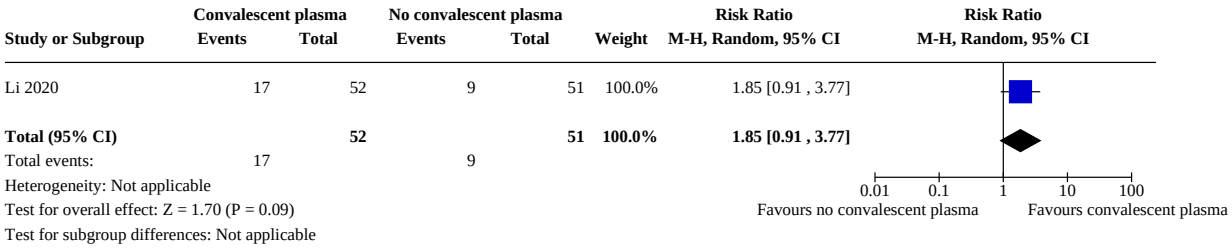
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Improvement of clinical symptoms at up to 7 days (assessed by need for respiratory support)	1	103	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.30, 3.19]
1.2 Improvement of clinical symptoms at 8 to 15 days (assessed by need for respiratory support)	1	103	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.91, 3.77]
1.3 Improvement of clinical symptoms at 16 to 30 days (assessed by need for respiratory support)	1	103	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.80, 1.81]
1.4 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
1.4.1 Severe disease	1	45	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.18, 2.85]
1.4.2 Life-threatening disease	1	58	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.19, 20.86]
1.5 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

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.5.1 Severe disease	1	45	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.05, 4.76]
1.5.2 Life-threatening disease	1	58	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.22, 4.55]
1.6 Improvement of clinical symptoms at 16 to 30 days (assessed by need for respiratory support): sub-group severity of disease	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.6.1 Severe disease	1	45	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.98, 1.83]
1.6.2 Life-threatening disease	1	58	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.33, 2.24]
1.7 30-day mortality	1	101	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.29, 1.46]

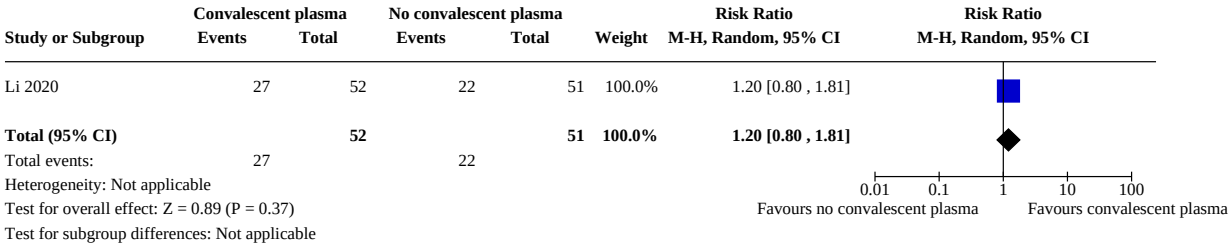
Analysis 1.1. Comparison 1: Results from RCT, Outcome 1: Improvement of clinical symptoms at up to 7 days (assessed by need for respiratory support)



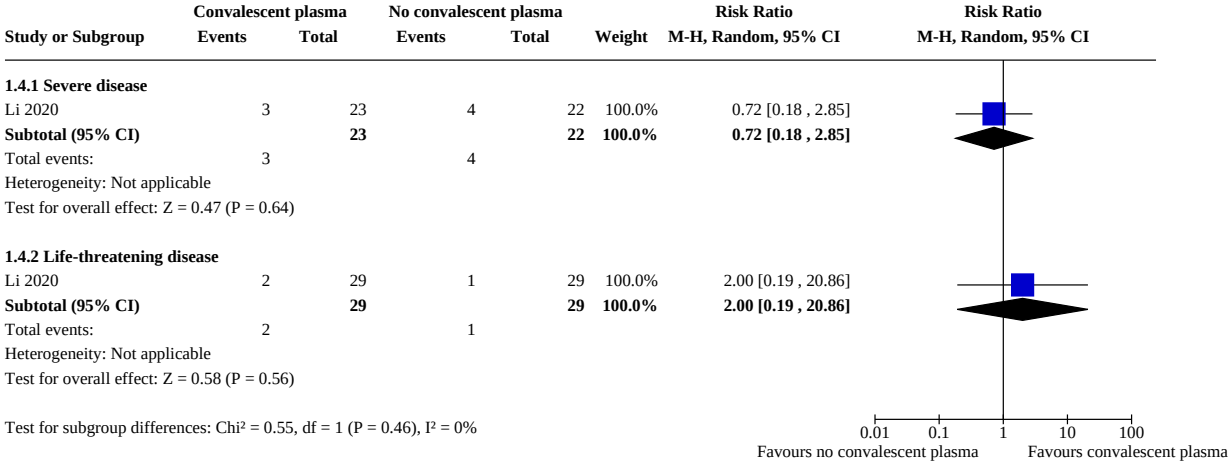
Analysis 1.2. Comparison 1: Results from RCT, Outcome 2: Improvement of clinical symptoms at 8 to 15 days (assessed by need for respiratory support)



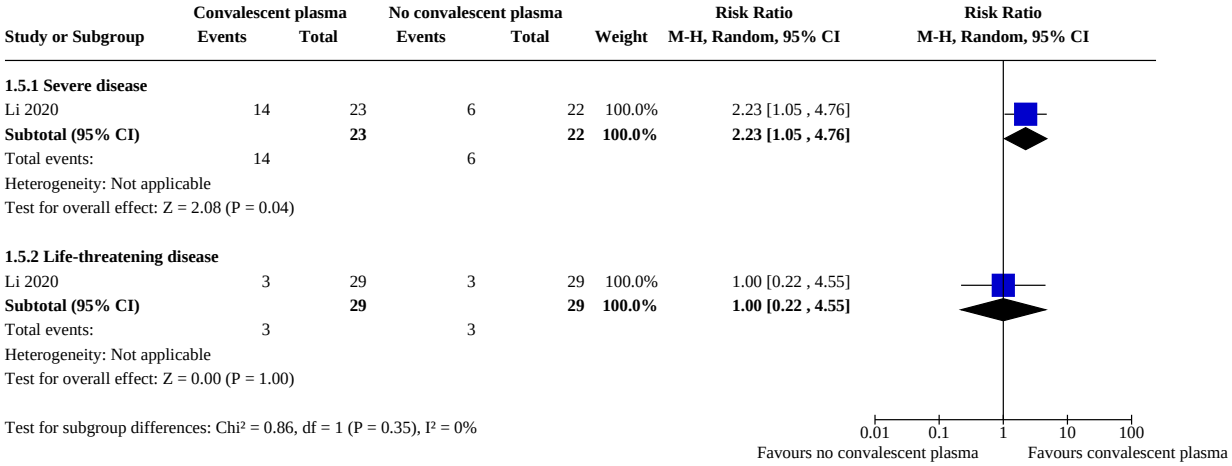
Analysis 1.3. Comparison 1: Results from RCT, Outcome 3: Improvement of clinical symptoms at 16 to 30 days (assessed by need for respiratory support)



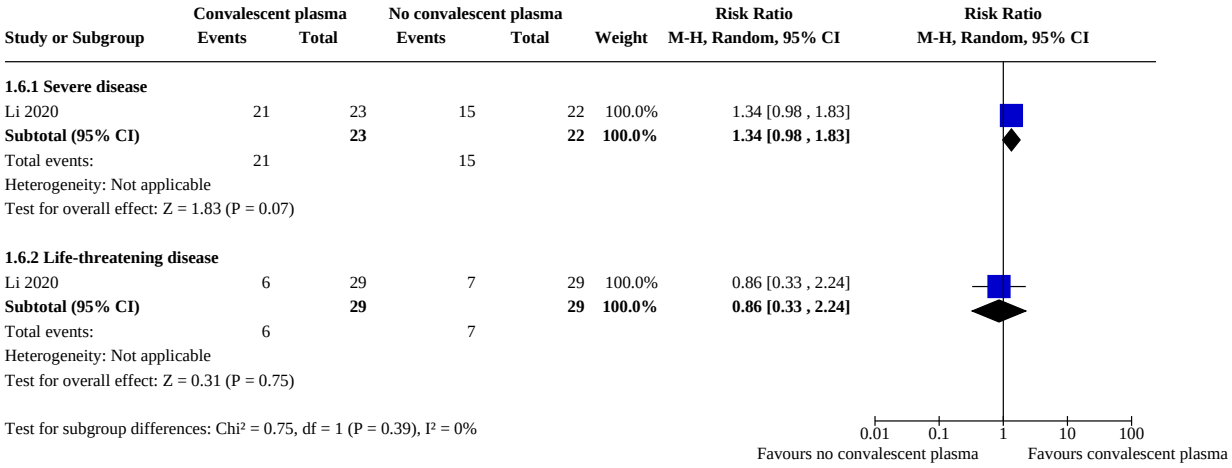
Analysis 1.4. Comparison 1: Results from RCT, Outcome 4: Improvement of clinical symptoms at up to 7 days (assessed by need for respiratory support): subgroup severity of disease



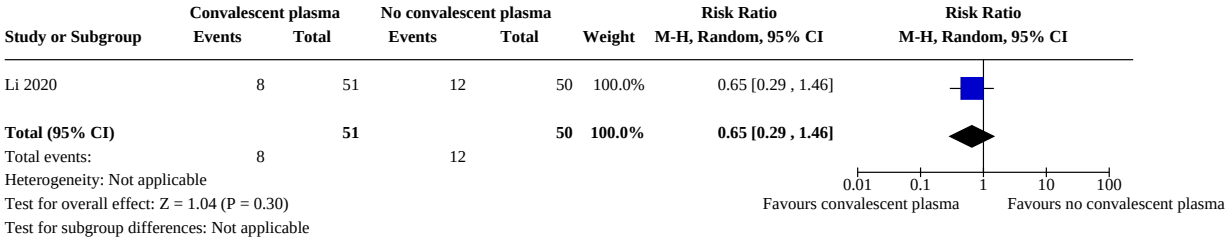
Analysis 1.5. Comparison 1: Results from RCT, Outcome 5: Improvement of clinical symptoms at 8 to 15 days (assessed by need for respiratory support): subgroup severity of disease



Analysis 1.6. Comparison 1: Results from RCT, Outcome 6: Improvement of clinical symptoms at 16 to 30 days (assessed by need for respiratory support): subgroup severity of disease



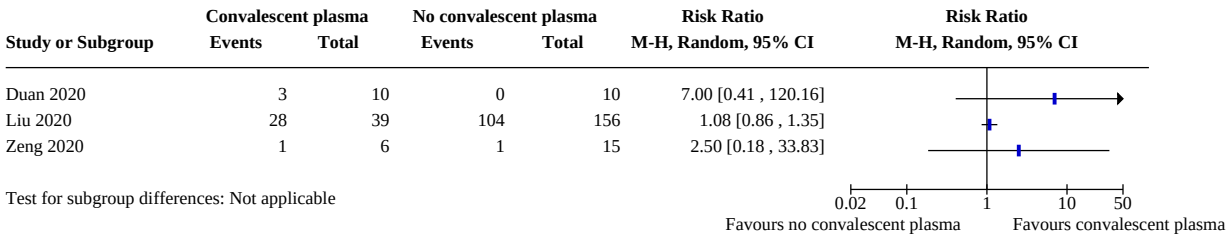
Analysis 1.7. Comparison 1: Results from RCT, Outcome 7: 30-day mortality



Comparison 2. Results from controlled NRSIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Time to discharge from hospital	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 2.1. Comparison 2: Results from controlled NRSIs, Outcome 1: Time to discharge from hospital



ADDITIONAL TABLES

Table 3. 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)												
Li 2020	52	51	• 14 on invasive mechanical ventilation and/or ECMO • 21 high-flow oxygen and/or noninvasive ventilation • 15 supplemental oxygen but no high-flow oxygen or noninvasive ventilation • 2 no supplemental oxygen	• 11 on invasive mechanical ventilation and/or ECMO • 23 high-flow oxygen and/or noninvasive ventilation • 15 supplemental oxygen but no high-flow oxygen or noninvasive ventilation • 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%)
Controlled non-randomised studies of interventions (NRSIs)												
Duan 2020	10	10	• 2 mechanical ventilation and high-flow nasal cannula • 1 mechanical ventilation • 3 high-flow nasal cannula • 2 low-flow nasal cannula • 2 no respiratory support	NR	3/8 participants with clinical improvement • 1 on mechan-	NR	NR	NR	NR	NR	Longest follow-up: 3 days after transfusion (3/8 participants with clinical improvement) • 1 on mechanical ventilation • 4 on high-flow nasal cannula • 2 on low-flow nasal cannula	NR

Table 3. Improvement of clinical symptoms (assessed by need for respiratory support) *(Continued)*

					ical ventilation • 4 on high-flow nasal cannula • 2 on low-flow nasal cannula • 3 no respiratory support					• 3 no respiratory support	
Liu 2020	39	156	• 4 on mechanical ventilation and intubated • 27 on high-flow oxygen • 7 on nasal cannula (18%) • 1 no respiratory support	• 16 on mechanical ventilation and intubated • 108 on high-flow oxygen • 32 no information but either on nasal cannula or no respiratory support	NR	NR	• 32/39 patients with clinical improvement or stable	• 118/156 patients with clinical improvement or stable	NR	NR	Median follow-up time was 11 (1 to 28) days • 5 deaths • 28 discharged (respiratory support unclear) • 6 unclear	Median follow-up time was 9 (0 to 31) days • 38 deaths • 104 discharged (respiratory sup-
					NR	NR	• 7 with worsened	• 38 with wors-	NR	NR		

Table 3. Improvement of clinical symptoms (assessed by need for respiratory support) *(Continued)*

											oxygen status or death (18%) • 32 with improved or stable oxygen status (respiratory support unclear) (82%)	ened oxygen status or death (24.3%) • 118 with improved or stable oxygen status (respiratory support unclear) (75.7%)			port unclear) • 14 unclear	
Zeng 2020	6	15	• 4 on ECMO • 1 on mechanical ventilation • 1 on high-flow	• 12 on ECMO • 1 on mechanical ventilation • 2 on high-flow	NR	NR	NR	NR	NR	NR	Longest follow-up: NR • 5 deaths • 1 discharged (respiratory support unclear)	Longest follow-up: NR • 14 deaths • 1 discharged (respiratory
					• 1 on mechanical ventilation • 5 respiratory	NR	• 1 on mechanical ventilation • 5 respiratory	NR	• 1 died • 5 respiratory support	NR		

Table 3. Improvement of clinical symptoms (assessed by need for respiratory support) *(Continued)*

	pi- ra- tory sup- port un- clear	sup- port un- clear	un- clear	sup- port un- clear)

CP: convalescent plasma; **ECMO:** extracorporeal membrane oxygenation; **NIV:** non-invasive ventilation; **NR:** not reported

Table 4. Adverse events: grade 3 or 4

Study	Number of participants	Grade 3 or 4 adverse events[a]
Ahn 2020	2	0
Duan 2020 [b]	10 (convalescent plasma group)	0
Jin 2020	6	0
Li 2020	52 (convalescent plasma group)	3 (in 2 participants) • 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 (convalescent plasma group)	0
Pei 2020	3	1 (anaphylactic shock)
Perotti 2020	46	5 (in 4 participants) • 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)
Salazar 2020 [c]	25	0
Tan 2020	1	1 (fever)
Ye 2020	6	0
Zeng 2020	6 (convalescent plasma group)	0
Zhang 2020a [d]	4	0
Zhang 2020b	1	0

[a]We assume that these adverse events were grade 3 or 4, but the studies did not specify the degree of severity.
[b]One participant with evanescent red face (grade unclear).
[c]One participant with morbilliform rash one day post-transfusion that lasted for several days (grade unclear).

[d]Assessment of adverse events only reported for one individual. Unclear information provided for the other three participants.

Table 1. 'Risk of bias' assessment criteria for observational studies

Heading	Internal validity	External validity
Study group	**Selection bias** (representative: yes/no) • 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 **or** • if it was a random sample with respect to the treatment and important prognostic factors	**Reporting bias** (well defined: yes/no) • if the study population was well described (e.g. severity of disease, age, risk factors) **and** • the intervention was well described (e.g. number of doses, volume)
Follow-up	**Attrition bias** (adequate: yes/no) • if the outcome was assessed for > 90% of the study group of interest (++) **or** • if the outcome was assessed for 60% to 90% of the study group of interest (+)	**Reporting bias** (well defined: yes/no) • if the length of follow-up was mentioned
Outcome	**Detection bias** (blind: yes/no) • if the outcome assessors were blinded to the investigated determinant	**Reporting bias** (well defined: yes/no) • if the outcome definition was objective and precise, and the method of detection was provided
Risk estimation	**Confounding** (adjustment for other factors: yes/no) • if important prognostic factors (i.e. age, co-treatment, comorbidities) or follow-up were taken adequately into account	**Analyses** (well defined: yes/no) • if a risk ratio, odds ratio, attributable risk, linear or logistic regression model, mean difference or Chi^2 statistic was calculated

Table 2. Summary: design and planned completion date of ongoing studies

Study ID	Title	Link	Design	Planned number of participants	Planned completion date	Completed/terminated	Results available	Other study ID
ChiCTR2000029850	Efficacy and safety of convalescent plasma treatment for severe patients with novel coronavirus pneumonia (COVID-19): a prospective cohort study	www.chictr.org.cn/showproj.aspx?proj=49533	Controlled NRSI	20	15 February 2022			
ChiCTR2000030010	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)	www.chictr.org.cn/showproj.aspx?proj=49777	RCT	100	31 May 2020			
ChiCTR2000030039	Clinical study for infusing convalescent plasma to treat patients with new coronavirus pneumonia (COVID-19)	www.chictr.org.cn/showproj.aspx?proj=49544	Controlled NRSI	60	1 February 2020			
ChiCTR2000030179	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19)	www.chictr.org.cn/showproj.aspx?proj=50059	RCT	100	24 February 2020			
ChiCTR2000030627	Study on the application of convalescent plasma therapy in severe COVID-19	www.chictr.org.cn/showproj.aspx?proj=50727	RCT	30	30 May 2020			
ChiCTR2000030702	Convalescent plasma for the treatment of common COVID-19: a prospective RCT	www.chictr.org.cn/showproj.aspx?proj=50537	RCT	30	15 August 2020			
ChiCTR2000030929	A randomized, double-blind,	www.chictr.org.cn/show-	RCT	30	16 June 2020			

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

	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)	pro-j.as-px?proj=50696		
ChiCTR2000031501	The efficacy of convalescent plasma in patients with critical novel coronavirus pneumonia (COVID-19): a pragmatic, prospective cohort study	www.chictr.org.cn/showpro-j.as-px?proj=50254	Controlled NRSI 20	17 July 2020
EUCTR2020-001310-38	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.clinical-trialsregister.eu/ctr-search/search?query=eudract_number:2020-001310-38	RCT 106	NR
IRCT20151228025753N13	Therapeutic effects of plasma of recovered people from COVID-19 on hospitalized patients with this disease	en.irct.ir/trial/46931	Controlled NRSI 12	20 June 2020
IRCT20200310046738N1	Comparison of the therapeutic effect of convalescent plasma and plasma-derived immunoglobulin-enriched solution on COVID-19 patients	en.irct.ir/trial/46424	RCT 45	24 July 2020
IRCT20200325046860N1	Convalescent plasma therapy for COVID-19 patients	en.irct.ir/trial/46759	Non-controlled NRSI 200	20 August 2020
IRCT20200404046944N1	Efficacy and safety of convalescent plasma in the treatment of COVID-19	en.irct.ir/trial/46973	RCT 60	20 June 2020

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

IRC-T20200409047001N1	Effect of COVID 19 survivors plasma in COVID 19 patients with ARDS	en.irct.ir/trial/47058	RCT	32	15 August 2020	
IRC-T20200413047005N1	Comparison between the efficacy of intravenous immunoglobulin and convalescent plasma in COVID-19	en.irct.ir/trial/47212	RCT	15	19 June 2020	
NCT04264858	An exploratory clinical study on the treatment of acute severe 2019-nCoV pneumonia with immunoglobulin from cured 2019-nCoV pneumonia patients	clinicaltrials.gov/show/NCT04264858	Non-controlled NRSI	10	31 May 2020	ChiCTR2000030841
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	clinicaltrials.gov/show/NCT04292340	Non-controlled NRSI	15	31 July 2020	
NCT04327349	Investigating effect of convalescent plasma on COVID-19 patients outcome: a clinical trial	clinicaltrials.gov/show/NCT04327349	Non-controlled NRSI	30	30 September 2020	
NCT04332380	Convalescent plasma for patients with COVID-19: a pilot study	clinicaltrials.gov/show/NCT04332380	Non-controlled NRSI	10	31 December 2020	
NCT04332835	Convalescent plasma for patients with COVID-19: a randomized, open label, parallel, controlled clinical study	clinical-tri-	RCT	80	31 December 2020	

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

		al-s.gov/show/NCT04332835			
NCT04333251	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 vs best supportive care in hospitalized patients with interstitial pneumonia due to COVID-19	clinicaltrials.gov/show/NCT04333251	RCT	115	31 December 2022
NCT04333355	Phase 1 study to evaluate the safety of convalescent plasma as an adjuvant therapy in patients with SARS-CoV-2 infection	clinicaltrials.gov/show/NCT04333355	Non-controlled NRSI	20	30 Apr 2021
NCT04338360	Expanded access to convalescent plasma for the treatment of patients with COVID-19	ClinicalTrials.gov/show/NCT04338360	Expanded access	NR	NR	Preprint, subset of data
NCT04340050	COVID-19 convalescent plasma	ClinicalTrials.gov/show/NCT04340050	Non-controlled NRSI	10	31 December 2021
NCT04342182	Convalescent plasma as therapy for Covid-19 severe SARS-CoV-2 disease (CONCOVID Study) (ConCoVid-19	ClinicalTrials.gov/show/NCT04342182	RCT	426	1 July 2020

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

NCT04343261	Convalescent plasma in the treatment of COVID 19	ClinicalTrials.gov/show/NCT04343261	Non-controlled NRSI	15	1 April 2021
NCT04343755	Convalescent plasma as treatment for hospitalized subjects with COVID-19 infection	ClinicalTrials.gov/show/NCT04343755	Non-controlled NRSI	55	1 April 2021
NCT04344535	Convalescent plasma vs. standard plasma for COVID-19	ClinicalTrials.gov/show/NCT04344535	RCT	500	31 August 2021
NCT04345289	Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia (CCAP)	ClinicalTrials.gov/show/NCT04345289	RCT	1500	15 June 2021 EUCTR2020-001367-88
NCT04345523	Convalescent plasma therapy vs. SOC for the treatment of COVID19 in hospitalized patients (ConPlas-19)	ClinicalTrials.gov/show/NCT04345523	RCT	278	1 July 2020
NCT04345679	Anti COVID-19 convalescent plasma therapy	ClinicalTrials.gov/show/NCT04345679	Non-controlled NRSI	20	1 April 2021

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

		al-s.gov/show/NCT04345679		
NCT04345991	Efficacy of convalescent plasma to treat COVID-19 patients, a nested trial in the CORIMUNO-19 cohort	ClinicalTrials.gov/show/NCT04345991	RCT	120	1 June 2020
NCT04346446	Efficacy of convalescent plasma therapy in severely sick COVID-19 patients	ClinicalTrials.gov/show/NCT04346446	RCT	20	20 June 2020
NCT04346589	Convalescent antibodies infusion in critically ill COVID 19 patients	ClinicalTrials.gov/ct2/show/NCT04346589	Non-controlled NRSI	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	ClinicalTrials.gov/show/NCT04347681	Non-controlled NRSI	40	11 April 2021
NCT04348656	Convalescent plasma for hospitalized adults with COVID-19 respiratory illness (CONCOR-1)	ClinicalTrials.gov/show/NCT04348656	RCT	1200	31 December 2020

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

NCT04348877	Plasma rich antibodies from recovered patients from COVID19	ClinicalTrials.gov/show/NCT04348877	Non-controlled NRSI	20	1 December 2020
NCT04352751	Experimental use of convalescent plasma for passive immunization in current COVID-19 pandemic in Pakistan in 2020	ClinicalTrials.gov/show/NCT04352751	Non-controlled NRSI	2000	1 April 2021
NCT04353206	Convalescent plasma in ICU patients with COVID-19-induced respiratory failure	ClinicalTrials.gov/show/NCT04353206	Non-controlled NRSI	90	1 May 2021
NCT04354831	A study evaluating the efficacy and safety of high-titer anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19 infection	ClinicalTrials.gov/ct2/show/NCT04354831	Non-controlled NRSI	106	1 May 2023
NCT04355767	Convalescent plasma vs. placebo in emergency room patients with COVID-19	ClinicalTrials.gov/ct2/show/NCT04355767	RCT	206	1 December 2022
NCT04355897	CoVID-19 plasma in treatment of COVID-19 patients	ClinicalTrials.gov/	Non-controlled NRSI	100	1 August 2020

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

		cal-Tri-al-s.gov/ct2/show/NCT04355897		
NCT04356482	Convalescent plasma for ill patients by COVID-19	ClinicalTrials.gov	Non-controlled NRSI	90	1 December 2020
NCT04356534	Convalescent plasma trial in COVID -19 patients	ClinicalTrials.gov	RCT	40	30 June 2020
NCT04357106	COPLA study: treatment of severe forms of coronavirus infection with convalescent plasma	ClinicalTrials.gov	Non-controlled NRSI	10	1 August 2020
NCT04358211	Expanded access to convalescent plasma to treat and prevent pulmonary complications associated with COVID-19	ClinicalTrials.gov	Expanded access	NR	NR
NCT04358783	Convalescent plasma compared to the best available therapy for the treatment of SARS-CoV-2 pneumonia	ClinicalTrials.gov	RCT	30	30 May 2020

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

		s.gov/show/NCT04358783		
NCT04359810	Plasma therapy of COVID-19 in critically ill patients	ClinicalTrials.gov/show/NCT04359810 RCT	105	1 April 2021
NCT04360486	Treatment of COVID-19 with Anti-Sars-CoV-2 convalescent plasma (ASCoV2CP)	ClinicalTrials.gov/show/NCT04360486 Expanded access	NR	NR
NCT04361253	Evaluation of SARS-CoV-2 (COVID-19) antibody-containing plasma therapy	ClinicalTrials.gov/show/NCT04361253 RCT	220	1 December 2021
NCT04362176	Passive immunity trial of Nashville II	ClinicalTrials.gov/show/NCT04362176 RCT	500	1 April 2021
NCT04363034	Arkansas expanded access COVID-19 convalescent plasma treatment program	ClinicalTrials.gov/ct2/show/NCT04363034 Expanded access	NR	NR

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

NCT04364737	Convalescent plasma to limit COVID-19 complications in hospitalized patients	ClinicalTrials.gov/show/NCT04364737	RCT	300	30 April 2023
NCT04365439	Convalescent plasma for COVID-19	ClinicalTrials.gov/show/NCT04365439	Non-controlled NRSI	10	30 June 2020
NCT04366245	Clinical trial to evaluate the efficacy of treatment with hyperimmune plasma obtained from convalescent antibodies of COVID-19 infection	ClinicalTrials.gov/show/NCT04366245	RCT	72	1 December 2021
NCT04372368	Convalescent plasma for the treatment of patients with COVID-19	ClinicalTrials.gov/show/NCT04372368	Expanded access	NR	NR
NCT04372979	Efficacy of convalescent plasma therapy in the early care of COVID-19 patients	ClinicalTrials.gov/show/NCT04372979	RCT	80	1 May 2021
NCT04373460	Convalescent plasma to limit SARS-CoV-2 associated complications	ClinicalTrials.gov/show/	RCT	1344	31 January 2023

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

		al-s.gov/show/NCT04373460			
NCT04374370	SARSCoV2 (COVID-19) convalescent plasma (CP) expanded access protocol (EAP)	ClinicalTrials.gov/show/NCT04374370	Expanded access	NR	NR
NCT04374487	A phase II, open label, RCT to assess the safety and efficacy of convalescent plasma to limit COVID-19 associated complications	ClinicalTrials.gov/show/NCT04374487	RCT	100	9 May 2021
NCT04374526	Early transfusion of convalescent plasma in elderly COVID-19 patients to prevent disease progression	ClinicalTrials.gov/show/NCT04374526	RCT	182	30 June 2021
NCT04374565	Convalescent plasma for treatment of COVID-19 patients with pneumonia	ClinicalTrials.gov/show/NCT04374565	Non-controlled NRSI	29	5 April 2021
NCT04375098	Efficacy and safety of early COVID-19 convalescent plasma in patients admitted for COVID-19 infection	ClinicalTrials.gov/show/NCT04375098	RCT	30	1 December 2021

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

NCT04376034	Convalescent plasma collection and treatment in pediatrics and adults	ClinicalTrials.gov/show/NCT04376034	Non-controlled NRSI	240	30 Mar 2021
NCT04376788	Exchange transfusion versus plasma from convalescent patients with methylene blue in patients with COVID-19	ClinicalTrials.gov/show/NCT04376788	RCT	15	1 June 2020
NCT04377568	Efficacy of human coronavirus-immune convalescent plasma for the treatment of COVID-19 disease in hospitalized children	ClinicalTrials.gov/show/NCT04377568	RCT	100	1 May 2022
NCT04377672	Human convalescent plasma for high risk children exposed or infected with SARS-CoV-2	ClinicalTrials.gov/show/NCT04377672	Non-controlled NRSI	30	18 May 2022
NCT04380935	Effectiveness and safety of convalescent plasma therapy on COVID-19 patients with acute respiratory distress syndrome	ClinicalTrials.gov/show/NCT04380935	RCT	60	31 August 2020
NCT04381858	Convalescent plasma vs human immunoglobulin to treat COVID-19 pneumonia	ClinicalTrials.gov/show/	RCT	500	30 September 2020

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

		al-s.gov/show/NCT04381858			
NCT04381936	Randomised evaluation of COVID-19 therapy (RECOVERY)	ClinicalTrials.gov/ct2/show/NCT04381936	RCT	12000	30 June 2021	ISRCTN50189673
NCT04383535	Convalescent plasma and placebo for the treatment of COVID-19 severe pneumonia	ClinicalTrials.gov/show/NCT04383535	RCT	333	20 August 2020	
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	ClinicalTrials.gov/show/NCT04383548	Non-controlled NRSI	100	1 January 2021	
NCT04384497	Convalescent plasma for treatment of COVID-19: an exploratory dose identifying study	ClinicalTrials.gov/show/NCT04384497	Non-controlled NRSI	50	1 December 2020	
NCT04384588	COVID19-convalescent plasma for treating patients with active symptomatic COVID 19 infection (FALP-COVID)	ClinicalTrials.gov/show/NCT04384588	Controlled NRSI	400	6 April 2021	

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

NCT04385043	Hyperimmune plasma in patients with COVID-19 severe infection	ClinicalTrials.gov/show/NCT04385043	RCT 400	15 May 2021
NCT04385186	Inactivated convalescent plasma as a therapeutic alternative in patients with CoViD-19	ClinicalTrials.gov/show/NCT04385186	RCT 60	30 November 2020
NCT04385199	Convalescent plasma for patients with COVID-19	ClinicalTrials.gov/show/NCT04385199	RCT 30	1 August 2020
NCT04388410	Safety and efficacy of convalescent plasma transfusion for patients with SARS-CoV-2 infection	ClinicalTrials.gov/show/NCT04388410	RCT 250	31 December 2020
NCT04388527	COVID-19 convalescent plasma for mechanically ventilated population	ClinicalTrials.gov/show/NCT04388527	Non-controlled NRSI 50	30 September 2020
NCT04389710	Convalescent plasma for the treatment of COVID-19	ClinicalTrials.gov/	Non-controlled NRSI 100	14 April 2021

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

		al-s.gov/show/NCT04389710		
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	ClinicalTrials.gov/show/NCT04389944	Non-controlled NRSI	15	30 June 2020
NCT04390178	Convalescent plasma as treatment for acute coronavirus disease (COVID-19)	ClinicalTrials.gov/show/NCT04390178	Non-controlled NRSI	10	1 December 2020
NCT04390503	Convalescent plasma for COVID-19 close contacts	ClinicalTrials.gov/ct2/show/NCT04390503	RCT	200	1 April 2021
NCT04391101	Convalescent plasma for the treatment of severe SARS-CoV-2 (COVID-19)	ClinicalTrials.gov/show/NCT04391101	RCT	231	31 December 2021
NCT04392232	A phase 2 study of COVID 19 convalescent plasma in high risk patients with COVID 19 infection	ClinicalTrials.gov/show/NCT04392232	Non-controlled NRSI	100	31 December 2020

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

NCT04392414	Hyperimmune convalescent plasma in moderate and severe COVID-19 disease	ClinicalTrials.gov/show/NCT04392414	RCT 60	15 September 2020
NCT04393727	Transfusion of convalescent plasma for the early treatment of pneumonia due to SARSCoV2	ClinicalTrials.gov/show/NCT04393727	RCT 126	30 August 2020
NCT04395170	Convalescent plasma compared to anti-COVID-19 human immunoglobulin and standard treatment (TE) in hospitalized patients	ClinicalTrials.gov/show/NCT04395170	RCT 75	1 June 2021
NCT04397523	Efficacy and safety of COVID-19 convalescent plasma	ClinicalTrials.gov/show/NCT04397523	Non-controlled NRSI 20	29 April 2021
NCT04397757	COVID-19 convalescent plasma for the treatment of hospitalized patients with pneumonia caused by SARS-CoV-2	ClinicalTrials.gov/show/NCT04397757	RCT 80	13 November 2020
NCT04403477	Convalescent plasma therapy in severe COVID-19 infection	ClinicalTrials.gov/show/NCT04403477	RCT 20	30 October 2020

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

		al-s.gov/show/NCT04403477		
NCT04404634	Convalescent plasma to limit coronavirus associated complications	ClinicalTrials.gov/show/NCT04404634 RCT	300	31 January 2023
NCT04405310	Convalescent plasma of Covid-19 to treat SARS-COV-2 a randomized double blind 2 center trial	ClinicalTrials.gov/show/NCT04405310 RCT	80	20 July 2020
NCT04407208	Convalescent plasma therapy in patients with COVID-19	ClinicalTrials.gov/show/NCT04407208 Non-controlled NRSI	10	1 August 2020
NCT04408040	Use of convalescent plasma for COVID-19	ClinicalTrials.gov/show/NCT04408040 Non-controlled NRSI	700	1 June 2022
NCT04408209	Convalescent plasma for the treatment of patients with severe COVID-19 infection	ClinicalTrials.gov/show/NCT04408209 Non-controlled NRSI	60	15 September 2021

Table 2. Summary: design and planned completion date of ongoing studies *(Continued)*

NCT04412486	COVID-19 convalescent plasma (CCP) transfusion	Clinical-Trials.gov/show/NCT04412486	Non-controlled NRSI	100	31 May 2022
U1111-1251-9285	Effect of convalescent plasma in patients with severe COVID-19	www.saiotlie-cos.gov.br/rg/RBR-4vm3yy/	Non-controlled NRSI	20	31 May 2022

NR: not reported; **RCT:** randomised controlled trial; **NRSI:** non-randomised study of intervention

Table 5. Serious adverse events

Study	Number of participants	Serious adverse events
Ahn 2020	2	0
Duan 2020	10 (convalescent plasma group)	0
Jin 2020	6	0
Joyner 2020	5000	Within 4 hours after transfusion • 15 dead (4 potentially, probably, or definitely related) • 7 TACO (7 potentially, probably, or definitely related) • 11 TRALI (11 potentially, probably, or definitely related) • 3 severe allergic reaction (3 potentially, probably, or definitely related)
Li 2020	52 (convalescent plasma 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 (convalescent plasma group)	0
Pei 2020	3	1 (anaphylactic shock)
Perotti 2020	46	3 • anaphylaxis/hypersensitivity (relation possible) • TRALI (relation possible) • subsegmental pulmonary embolism (relation unlikely/excluded)
Salazar 2020	25	0
Tan 2020	1	0
Ye 2020	6	0
Zeng 2020	6 (convalescent plasma group)	0
Zhang 2020a	4	0
Zhang 2020b	1	0

TACO: transfusion-associated circulatory overload; **TRALI:** transfusion-related acute lung 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 antiflu* 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 antiflu* 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 antiflu* or antifluenza*).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 virusinactived 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-lg).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 inactived 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 antiflu*) 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 coronovirinae* 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 antiflu* 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 antiflu* 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 antiflu* 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 antiflu* OR anti-flu

Appendix 6. Planned methodology for randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSIs)

Data extraction and management

Assessment of risk of bias in included studies

Randomised controlled trials

We had planned to use 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 would have performed all assessments with RoB 2 on this effect. The outcomes that we would have 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).

One review author would have assessed the risk of bias for each study result. A second review author would have verified the accuracy and the plausibility. In case of discrepancies among their judgements or inability to reach consensus, we had planned to consult a third review author to reach a final decision. We would have assessed the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a).

- 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

To address these types of bias we had planned to use the signalling questions recommended in RoB 2 and make 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 for the 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 unfilled 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 unfilled 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 had planned to use 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 had planned to derive a 'Risk of bias' rating for each prespecified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': the trial is judged to be at low risk of bias for all domains for this result.
- 'Some concerns': the trial is judged 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': the trial is judged to be at high risk of bias in at least one domain for the result or the trial is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the results.

Data synthesis

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

We had planned to use the Review Manager Web software for analyses (Review Manager Web). One review author would have entered the data into the software, and a second review author would have checked the data for accuracy.

We had planned to use the random-effects model for all analyses as we anticipate that true effects will be related but will not be the same for included studies. If we could not perform a meta-analysis, we had planned to comment on the results as a narrative with the results from all studies presented in tables.

For RCTs, when meta-analysis had been feasible, we had planned to use the random-effects model for pooling the data. For binary outcomes, we had planned to base the estimation of the between-study variance using the Mantel-Haenszel method. We had planned to use 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.

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).

Appendix 7. 'Risk of bias' assessment of randomised controlled trials (RCTs), using RoB 1.0

We assessed methodological quality and risk of bias using the 'Risk of bias' tool recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

'Risk of bias' assessment of Li 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Mortality Clinical improvement Adverse events	Low	Quote: "Patients were randomly assigned via computer-generated random numbering (1:1) to receive standard treatment coupled with convalescent plasma transfusion or standard treatment alone (control group) (Figure 1). The randomization was stratified based on the severity of COVID-19 (severe or life-threatening) and a randomization schedule was generated using block randomization with block size of 4 for each type of COVID-19 by SAS software."
Allocation concealment (selection bias)	Mortality Clinical improvement Adverse events	Low	Quote: "This random number will connect the subject to the designated treatment group (experimental group or control group) for treatment. [...] Staff responsible for randomization will only be responsible for the assignment of random groups and will not be involved in any specific trial operations."
Blinding of participants and personnel (performance bias)	Mortality Clinical improvement Adverse events	High	Quote: "open-label" Co-interventions not balanced across arms
Blinding of outcome assessment (detection bias)	Mortality	Low	Quote: "To avoid assessment bias, the evaluation of clinical outcomes was performed by an investigator who was blind to the study group allocation."
	Clinical improvement Adverse events	Low	Quote: "To avoid assessment bias, the evaluation of clinical outcomes was performed by an investigator who was blind to the study group allocation."
Selective reporting (reporting bias)	Mortality	Low	Reported as determined at protocol stage
	Clinical improvement	Unclear	Quote: "A post hoc analysis was added to compare rates of improvement at days 7, 14, and 28."
	Adverse events	High	Only transfusion-related adverse events reported
Incomplete outcome data (attrition bias)	Mortality	Low	ITT population reported
	Clinical improvement	Low	ITT population reported
	Adverse events	High	No safety data for control group available
Other bias	Mortality	Unclear	Quote: "Due to the containment of the COVID-19 epidemic in Wuhan, China, the numbers of patients with COVID-19 decreased in late March 2020. [...]

(Continued)

	Clinical improvement	The trial was terminated early after 103 of a planned 200 patients were enrolled."
	Adverse events	The study expressed effect estimates as odds ratios. Therefore we recalculated relative effects as risk ratios. We noticed that our calculation arrived at the same numerical values, and therefore highlight that effect estimates, which are indicated as odds ratios in the primary study, are in fact risk ratios.

Appendix 8. 'Risk of bias' assessment of controlled non-randomised studies of interventions (NRSIs), using ROBINS-I

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 Duan 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Bias due to confounding	Mortality Clinical improvement	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.
	Adverse events	Not applicable	Paper only reports transfusion-related adverse events for intervention group
Bias in selection of participants into the study	Mortality Clinical improvement	Critical	Small sample size, unclear how participants were selected into intervention group, unclear how long participants of historical control group were followed
	Adverse events	Not applicable	Paper only reports transfusion-related adverse events for intervention group
Bias in classification of interventions	Mortality Clinical improvement	Critical	Assignment to control group was done retrospectively. Treatment details of control group are not provided, and it is unclear whether patients 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.
	Adverse events	Not applicable	Paper only reports transfusion-related adverse events for intervention group
Bias due to deviations from intended interventions	Mortality Clinical improvement Adverse events	Low	All participants received the intended intervention.

(Continued)

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 Clinical improvement	Critical	Study was registered as single-arm trial and control group was retrospectively selected
	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 yet insufficient.
	Clinical improvement	Critical	The study is too problematic to provide any useful evidence, however better evidence is yet insufficient.
	Adverse events	Critical	The study is too problematic to provide any useful evidence, however better evidence is yet insufficient.

Risk of bias assessment of Liu 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Bias due to confounding	Mortality Clinical improvement	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
	Adverse events	Not applicable	Paper only reports transfusion-related adverse events for intervention group
Bias in selection of participants into the study	Mortality Clinical improvement	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. 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

(Continued)

			potential for plasma therapy based on time series data obtained at baseline upon admission, prior to transfusion, and the day of 107 transfusion."
	Adverse events	Not applicable	Paper only reports transfusion-related adverse events for intervention group
Bias in classification of interventions	Mortality Clinical improvement	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.
	Adverse events	Not applicable	Paper only reports transfusion-related adverse events for intervention group
Bias due to deviations from intended interventions	Mortality Clinical improvement	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
	Adverse events		
Bias due to missing data	Mortality Clinical improvement	Low	Data were reasonably complete
	Adverse events	Critical	No safety data for control group available
Bias in measurement of outcomes	Mortality Clinical improvement	Moderate	Median follow-up comparable between groups. However, outcome assessors were not blinded to intervention and the study was performed retrospectively.
	Adverse events	Critical	Only transfusion-related adverse events reported
Bias in selection of the reported results	Mortality Clinical improvement	Critical	Retrospective study; selection of all reported results are likely biased
	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 yet insufficient.
	Clinical improvement	Critical	The study is too problematic to provide any useful evidence, however better evidence is yet insufficient.
	Adverse events	Critical	The study is too problematic to provide any useful evidence, however better evidence is yet insufficient.

'Risk of bias' assessment of Zeng 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Bias due to confounding	Mortality Clinical improvement	Serious	Not adjusted for confounding factors
	Adverse events	Not applicable	Paper only reports adverse events after plasma transfusion for intervention group
Bias in selection of participants into the study	Mortality Clinical improvement	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."
	Adverse events	Not applicable	Paper only reports adverse events after plasma transfusion for intervention group
Bias in classification of interventions	Mortality Clinical improvement	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.
	Adverse events	Not applicable	Paper only reports adverse events after plasma transfusion for intervention group
Bias due to deviations from intended interventions	Mortality Clinical improvement	Low	All participants received intended intervention. Co-interventions (e.g. antiviral therapy, traditional Chinese medicine, etc.) seem to be balanced across treatment groups.
	Adverse events	Low	All assessed participants received intended intervention
Bias due to missing data	Mortality	Low	Data were reasonably complete
	Clinical improvement	Low	Living participants discharged
	Adverse events	Critical	No safety data for control group available
Bias in measurement of outcomes	Mortality Clinical improvement	Low	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 Clinical improvement	Critical	Retrospective study; selection of all reported results are likely biased
	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 yet insufficient.
	Clinical improvement	Critical	The study is too problematic to provide any useful evidence, however better evidence is yet insufficient.
	Adverse events	Critical	The study is too problematic to provide any useful evidence, however better evidence is yet insufficient.

Appendix 9. 'Risk of bias' assessment of non-controlled non-randomised studies of interventions (NRSIs), using the 'Risk of bias' assessment criteria for observational studies tool provided by Cochrane Childhood Cancer

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 Ahn 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Not available	High	2 participants only
Outcome detectors blinded to intervention (detection bias)	Adverse events	High	Not blinded, awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Low	Assessed and reported for both cases
Well-defined study group (reporting bias)	Not available	Low	Population and intervention are well described
Well-defined outcome (reporting bias)	Adverse events	High	No adverse reaction occurred after the administration of convalescent plasma in both cases. Observation period not reported
Well-defined risk estimates (analyses)	Adverse events	Not applicable	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Not available	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)	Not available	High	6 of 146 COVID-19 patients in Guizhou Jiangjunshan Hospital who received convalescent plasma therapy included in report
Outcome detectors blinded to intervention (detection bias)	Adverse events	High	Not blinded, awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Unclear	Assessed for all participants over study period, observation period unclear
Well-defined study group (reporting bias)	Not available	Unclear	Study population well described, but intervention scarcely described
Well-defined outcome (reporting bias)	Adverse events	High	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)	Not available	High	Not adjusted for confounding, results only reported for 6 of 146 participants receiving convalescent plasma

'Risk of bias' assessment of Joyner 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Not available	Low	Large population size, prospective study, interim analysis of first 5000 patients
Outcome detectors blinded to intervention (detection bias)	Adverse events	High	Not blinded, awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Unclear	Preliminary results; only serious adverse events assessed, 4-h follow-up
Well-defined study group (reporting bias)	Adverse events	Unclear	Study population well described, intervention scarcely described
Well-defined outcome (reporting bias)	Adverse events	Unclear	Preliminary results; serious adverse events only
Well-defined risk estimates (analyses)	Adverse events	Not available	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Not available	High	Not adjusted for confounding factors

'Risk of bias' assessment of Pei 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Not available	High	3 participants only
Outcome detectors blinded to intervention (detection bias)	Adverse events	High	Not blinded, awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Unclear	Serious adverse events reported for 1 participant, not reported whether other participants experienced any adverse events
Well-defined study group (reporting bias)	Not available	High	Study population and intervention insufficiently described
Well-defined outcome (reporting bias)	Adverse events	High	Observation period not described
Well-defined risk estimates (analyses)	Adverse events	Not available	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Not available	High	Comorbidities and disease presentation and course not clearly reported; 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)	Not available	High	46 participants only
Outcome detectors blinded to intervention (detection bias)	Adverse events	High	Not blinded, but awareness of intervention can bias assessment of subjective outcomes
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)	Not available	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 available	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Not available	High	Not adjusted for confounding factors

'Risk of bias' assessment of Salazar 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Not available	High	25 participants only
Outcome detectors blinded to intervention (detection bias)	Adverse events	High	Not blinded, but awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Low	All participants observed for occurrence of adverse events
Well-defined study group (reporting bias)	Not available	Low	Study population and intervention well described
Well-defined outcome (reporting bias)	Adverse events	Low	All observed adverse events described
Well-defined risk estimates (analyses)	Adverse events	Not available	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Not available	High	Not adjusted for confounding factors

'Risk of bias' assessment of Tan 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Not available	High	1 participant only
Outcome detectors blinded to intervention (detection bias)	Adverse events	High	Not blinded, but awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Unclear	Only fever reported, not reported whether other adverse events occurred
Well-defined study group (reporting bias)	Not available	High	1 participant only, not much information (e.g. age, comorbidities, clinical symptoms), intervention not described in detail
Well-defined outcome (reporting bias)	Adverse events	High	Only fever reported, not reported whether other adverse events occurred
Well-defined risk estimates (analyses)	Adverse events	Not available	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Not available	High	Not adjusted for confounding factors

'Risk of bias' assessment of Ye 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Not available	High	6 participants only
Outcome detectors blinded to intervention (detection bias)	Adverse events	High	Not blinded, but awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Low	None occurred (3-day follow-up)
Well-defined study group (reporting bias)	Not available	Low	Study population and intervention well described
Well-defined outcome (reporting bias)	Adverse events	Low	3-day follow-up
Well-defined risk estimates (analyses)	Adverse events	Not available	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Not available	High	Not adjusted for confounding factors

'Risk of bias' assessment of Zhang 2020a

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Not available	High	4 participants only
Outcome detectors blinded to intervention (detection bias)	Adverse events	High	Not blinded, but awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Unclear	Clinical course reported, but not whether adverse events occurred
Well-defined study group (reporting bias)	Not available	Unclear	Study group well described but not intervention
Well-defined outcome (reporting bias)	Adverse events	High	Not described in detail, unclear whether adverse events occurred
Well-defined risk estimates (analyses)	Adverse events	Not available	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Not available	High	Not adjusted for confounding factors

'Risk of bias' assessment of Zhang 2020b			
Domain	**Assessed outcomes**	**Authors' judgement**	**Support for judgement**
Representative study group (selection bias)	Not available	High	1 participant only
Outcome detectors blinded to intervention (detection bias)	Adverse events	High	Not blinded, awareness of intervention can bias assessment of subjective outcomes
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Low	Reported that no transfusion-related acute lung injuries were observed
Well-defined study group (reporting bias)	Not available	Unclear	Participant not described in detail
Well-defined outcome (reporting bias)	Adverse events	Low	No adverse events occurred
Well-defined risk estimates (analyses)	Adverse events	Not available	No analyses performed
Important prognostic factors or follow-up taken adequately into account (confounding)	Not available	High	Not adjusted for confounding factors

WHAT'S NEW

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.

HISTORY

Review first published: Issue 5, 2020

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

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 sought funding support from Australian Medical Research Future Fund for a trial of convalescent plasma. I will not be involved in bias assessment, data extraction or interpretation, but will serve as a content expert.

AL: none known

CK: none known

ZM: I have sought funding support from Australian Medical Research Future Fund for a trial of convalescent plasma. I will not be involved in bias assessment, data extraction or interpretation, but will serve as a content expert.

CS-O: is a member of the BEST Collaborative Clinical Study Group. I will not be involved in bias assessment, data extraction or interpretation, but will serve as a content expert.

LJE: co-lead of the COVID-19 immunoglobulin domain of the REMAP-CAP trial. I will not be involved in bias assessment, data extraction or interpretation, but will serve 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

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of studies

As the evidence we found from the RCT was at unclear or high risk of bias and at serious 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 prospective and retrospective non-comparative study designs (e.g. case series) and followed the methodology as specified in the protocol (Piechotta 2020). 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 revised the secondary outcome 'Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 to 15 days; 16 to 30 days' and added to the fourth bullet point: 'plus high-flow oxygen', to differentiate from the third bullet point. It now reads:

Improvement of clinical symptoms, assessed by need for respiratory support at up to 7 days; 8 to 15 days; 16 to 30 days:

- oxygen by mask or nasal prongs
- oxygen by NIV (non-invasive ventilation) or high flow
- intubation and mechanical ventilation
- mechanical ventilation plus high-flow oxygen
- extracorporeal membrane oxygenation (ECMO)

We added the outcome, 'quality of life' after discussion with a patient representative.

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).

Assessment of risk of bias in included studies

Randomised controlled trials

We had planned to use the Risk of Bias 2.0 (RoB 2) tool to analyse the risk of bias in the underlying study results (Sterne 2019). However, RoB 2 is not yet available in RevMan Web (Review Manager Web), and the Cochrane Editorial and Methods Department recommended for us to use the former 'Risk of bias' tool for this version of the review (Higgins 2011), instead. Please refer to Appendix 6 for further information on the planned bias assessment with RoB 2.

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)

Betacoronavirus; *Coronavirus Infections [therapy]; Critical Care; Critical Illness; Immunization, Passive [adverse effects] [methods]; *Immunoglobulins [therapeutic use]; *Inpatients; *Pandemics; *Pneumonia, Viral [therapy]; Randomized Controlled Trials as Topic; Respiration, Artificial; Severity of Illness Index; Treatment Outcome

MeSH check words

Humans