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

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

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[Intervention Review]

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

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ABSTRACT

Background

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

Objectives

Using a living systematic review approach, to assess whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in the treatment of people with COVID-19; and to maintain the currency of the evidence.

Search methods

To identify completed and ongoing studies, we searched the World Health Organization (WHO) COVID-19 Global literature on coronavirus disease Research Database, MEDLINE, Embase, the Cochrane COVID-19 Study Register, the Epistemonikos COVID-19 L*OVE Platform, and trial registries. Searches were done on 17 March 2021.

Selection criteria

We included randomised controlled trials (RCTs) evaluating convalescent plasma or hyperimmune immunoglobulin for COVID-19, irrespective of disease severity, age, gender or ethnicity. For safety assessments, we also included non-controlled non-randomised studies of interventions (NRSIs) if 500 or more participants were included.

We excluded studies that included populations with other coronavirus diseases (severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS)), as well as studies evaluating standard immunoglobulin.

Data collection and analysis

We followed standard Cochrane methodology.

To assess bias in included studies, we used the Cochrane 'Risk of Bias 2' tool for RCTs, and for NRSIs, the assessment criteria for observational studies, provided by Cochrane Childhood Cancer. We rated the certainty of evidence, using the GRADE approach, for the following outcomes: all-cause mortality, improvement and worsening of clinical status (for individuals with moderate to severe disease), development of severe clinical COVID-19 symptoms (for individuals with asymptomatic or mild disease), quality of life (including fatigue and functional independence), grade 3 or 4 adverse events, and serious adverse events.

Main results

We included 13 studies (12 RCTs, 1 NRSI) with 48,509 participants, of whom 41,880 received convalescent plasma. We did not identify any completed studies evaluating hyperimmune immunoglobulin. We identified a further 100 ongoing studies evaluating convalescent plasma or hyperimmune immunoglobulin, and 33 studies reporting as being completed or terminated.

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

Eleven RCTs and one NRSI investigated the use of convalescent plasma for 48,349 participants with moderate to severe disease. Nine RCTs compared convalescent plasma to placebo treatment or standard care alone, and two compared convalescent plasma to standard plasma (results not included in abstract).

Effectiveness of convalescent plasma

We included data on nine RCTs (12,875 participants) to assess the effectiveness of convalescent plasma compared to placebo or standard care alone.

Convalescent plasma does not reduce all-cause mortality at up to day 28 (risk ratio (RR) 0.98, 95% confidence interval (CI) 0.92 to 1.05; 7 RCTs, 12,646 participants; high-certainty evidence). It has little to no impact on clinical improvement for all participants when assessed by liberation from respiratory support (RR not estimable; 8 RCTs, 12,682 participants; high-certainty evidence). It has little to no impact on the chance of being weaned or liberated from invasive mechanical ventilation for the subgroup of participants requiring invasive mechanical ventilation at baseline (RR 1.04, 95% CI 0.57 to 1.93; 2 RCTs, 630 participants; low-certainty evidence). It does not reduce the need for invasive mechanical ventilation (RR 0.98, 95% CI 0.89 to 1.08; 4 RCTs, 11,765 participants; high-certainty evidence). We did not identify any subgroup differences.

We did not identify any studies reporting quality of life, and therefore, do not know whether convalescent plasma has any impact on quality of life. One RCT assessed resolution of fatigue on day 7, but we are very uncertain about the effect (RR 1.21, 95% CI 1.02 to 1.42; 309 participants; very low-certainty evidence).

Safety of convalescent plasma

We included results from eight RCTs, and one NRSI, to assess the safety of convalescent plasma. Some of the RCTs reported on safety data only for the convalescent plasma group.

We are uncertain whether convalescent plasma increases or reduces the risk of grade 3 and 4 adverse events (RR 0.90, 95% CI 0.58 to 1.41; 4 RCTs, 905 participants; low-certainty evidence), and serious adverse events (RR 1.24, 95% CI 0.81 to 1.90; 2 RCTs, 414 participants; low-certainty evidence).

A summary of reported events of the NRSI (reporting safety data for 20,000 of 35,322 transfused participants), and four RCTs reporting safety data only for transfused participants (6125 participants) are included in the full text.

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

We identified one RCT reporting on 160 participants, comparing convalescent plasma to placebo treatment (saline).

Effectiveness of convalescent plasma

We are very uncertain about the effect of convalescent plasma on all-cause mortality (RR 0.50, 95% CI 0.09 to 2.65; very low-certainty evidence). We are uncertain about the effect of convalescent plasma on developing severe clinical COVID-19 symptoms (RR not estimable; low-certainty evidence).

We identified no study reporting quality of life.

Safety of convalescent plasma

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

We do not know whether convalescent plasma is associated with a higher risk of grade 3 or 4 adverse events (very low-certainty evidence), or serious adverse events (very low-certainty evidence).

This is a living systematic review. We search weekly for new evidence and update the review when we identify relevant new evidence. Please refer to the Cochrane Database of Systematic Reviews for the current status of this review.

Authors' conclusions

We have high certainty in the evidence that convalescent plasma for the treatment of individuals with moderate to severe disease does not reduce mortality and has little to no impact on measures of clinical improvement. We are uncertain about the adverse effects of convalescent plasma. While major efforts to conduct research on COVID-19 are being made, heterogeneous reporting of outcomes is still problematic. There are 100 ongoing studies and 33 studies reporting in a study registry as being completed or terminated. Publication of ongoing studies might resolve some of the uncertainties around hyperimmune immunoglobulin therapy for people with any disease severity, and convalescent plasma therapy for people with asymptomatic or mild disease.

PLAIN LANGUAGE SUMMARY

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

Key messages

- We are very confident that convalescent plasma has no benefits for the treatment of people with moderate to severe COVID-19.
- We are uncertain about the effects of convalescent plasma for treating people with mild COVID-19 or who have no symptoms.
- We found about 130 ongoing, unpublished and recently published studies. We will update our review with evidence from these studies as soon as possible. New evidence may answer our remaining questions.

What is convalescent plasma?

The body produces antibodies as one of its defences against infection. Antibodies are found in part of the blood called plasma. Plasma from people who have recovered from the COVID-19 virus contains COVID-19 antibodies, and can be used to make two preparations. Firstly, it can be used to make convalescent plasma, which is plasma that contains these antibodies. Secondly, it can be used to make hyperimmune immunoglobulin, which is more concentrated, and therefore contains more antibodies.

Convalescent plasma and hyperimmune immunoglobulin have been used successfully to treat some viruses. These treatments (given by a drip or injection) are generally well-tolerated, but can cause unwanted effects.

What did we want to find out?

We wanted to find out whether convalescent plasma or hyperimmune immunoglobulin are effective treatments for people with confirmed COVID-19. We looked at:

- deaths from any cause after treatment with convalescent plasma or hyperimmune immunoglobulin;
- improvement or worsening of patients' condition, measured by the number of people who needed help from a ventilator (a machine that helps people breathe if they cannot breathe on their own);
- quality of life; and
- unwanted effects.

What did we do?

We searched for studies that investigated convalescent plasma or hyperimmune immunoglobulin to treat people with COVID-19. Studies could take place anywhere in the world and include participants of any age, gender or ethnicity, with mild, moderate or severe COVID-19.

Where possible we pooled the studies' results to analyse them. We rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 13 studies with 48,509 participants that investigated convalescent plasma. All but one of the studies included participants with moderate to severe COVID-19. We did not find any studies that investigated hyperimmune immunoglobulin. Studies mainly took place in hospitals, in countries all over the world.

Moderate to severe COVID-19

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

Convalescent plasma compared to placebo or standard care:

- convalescent plasma makes no difference to **deaths from any cause** at up to 28 days after treatment. About 237 in 1000 people given placebo or standard care died, compared to 233 in 1000 people who had been given convalescent plasma (7 studies, 12,646 people);
- convalescent plasma makes little to no difference to the **improvement of patients' condition in terms of needing less breathing support** for the overall population needing any breathing support before the start of treatment (8 studies, 12,682 people), and also not for the people that were ventilated at the beginning of the study (2 studies, 630 people);
- convalescent plasma makes no difference to the **worsening of patients' condition**. About 126 in 1000 people given placebo or standard care needed invasive mechanical ventilation, compared to 123 in 1000 people who had been given convalescent plasma (4 studies, 11,765 people);
- convalescent plasma may make no difference to **unwanted effects**. The 8 studies that reported unwanted effects measured and reported their results very differently, so we are unable to draw any conclusions.

None of the studies reported **quality of life**.

Mild COVID-19

We do not know if convalescent plasma compared to placebo or standard care makes a difference to number of deaths, improvement or worsening of patients' condition, quality of life or unwanted effects. We found only one study with 160 participants that assessed people with mild COVID-19.

What are the limitations of the evidence?

- We are very confident in the evidence for deaths from any cause and improvement or worsening of patients' condition in people with moderate to severe COVID-19.
- Our confidence in the other evidence for people with moderate and severe, and mild COVID-19 is very limited because the studies were very different and did not measure and record their results using consistent methods.
- We found little useful evidence on unwanted effects and none on quality of life.

How up to date is this evidence?

This is the fourth version of our review. The evidence is up to date to 17 March 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of Findings Table - Convalescent plasma compared to placebo or standard care alone for individuals with moderate to severe disease

Convalescent plasma compared to placebo or standard care alone for individuals with moderate to severe disease

Patient or population: individuals with moderate to severe disease **Setting:** Intervention: convalescent plasma **Comparison:** placebo or standard care alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or standard care alone	Risk with convalescent plasma				
All-cause mortality at up to day 28 - total	237 per 1,000	233 per 1,000 (218 to 249)	RR 0.98 (0.92 to 1.05)	12646 (7 RCTs)	⊕⊕⊕⊕ HIGH	Convalescent plasma does not reduce all-cause mortality at up to day 28.
Clinical improvement, assessed by liberation from respiratory support	Reporting of the clinical status or course of the disease was very heterogeneous across studies and it was not possible to pool data in a meaningful way. The reported evidence in all studies did not suggest any differences in the odds for clinical improvement or time to clinical improvement. ^a			12682 (8 RCTs)	⊕⊕⊕⊕ HIGH	Convalescent plasma has little to no impact on clinical improvement.
Clinical improvement: weaning or liberation from invasive mechanical ventilation in surviving patients, for subgroups of participants requiring invasive mechanical ventilation at baseline	362 per 1,000	377 per 1,000 (206 to 699)	RR 1.04 (0.57 to 1.93)	630 (2 RCTs)	⊕⊕⊕⊖ LOW ^{b, c}	Convalescent plasma may have little to no impact on clinical improvement, if assessed with weaning or liberation from invasive mechanical ventilation in surviving patients.
Clinical worsening: need for invasive mechanical ventilation, for subgroup of participants not requiring invasive mechanical ventilation at baseline	126 per 1,000	123 per 1,000 (112 to 136)	RR 0.98 (0.89 to 1.08)	11765 (4 RCTs)	⊕⊕⊕⊕ HIGH	Convalescent plasma does not reduce clinical worsening if assessed with the need for invasive mechanical ventilation.

Quality of life, including fatigue and neurological functioning; assessed with standardised scales up to longest follow-up	We did not identify any study reporting quality of life on a standardised scale. One study (Agarwal 2020, reporting on 309 participants) assessed resolution of fatigue on day 7 (RR 1.21, 95% CI 1.02 to 1.42, estimated absolute effect with convalescent plasma: 727 of 1000)			309 (1 RCT)	⊕⊕⊕⊕ VERY LOW ^{d, e}	We do not know whether convalescent plasma has any impact on quality of life, and are very uncertain about the effect on resolution of fatigue.
Grade 3 and 4 adverse events - total	64 per 1,000	57 per 1,000 (37 to 90)	RR 0.90 (0.58 to 1.41)	905 (4 RCTs)	⊕⊕⊕⊕ LOW ^{c, f}	We are uncertain whether convalescent plasma reduces or increases the risk of grade 3 and 4 adverse events.
Serious adverse events - total	176 per 1,000	218 per 1,000 (142 to 334)	RR 1.24 (0.81 to 1.90)	414 (2 RCTs)	⊕⊕⊕⊕ LOW ^{c, f}	We are uncertain whether convalescent plasma reduces or increases the risk of serious adverse events.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423533352409190077.

- a.** One study, reporting on 77 participants, provided sufficient data to calculate a relative effect estimate for our predefined outcome "liberation from supplemental oxygen"; for the subgroup of participants that received any supplemental oxygen or ventilator support. We did not identify any evidence for a difference (RR 1.10, 95% CI 0.81 to 1.48, estimated absolute effect with convalescent plasma: 724 per 1000).
- b.** Downgraded one level for serious inconsistency because direction of effect was not consistent in both studies
- c.** Downgraded one level for serious imprecision, because of few participants and wide confidence intervals
- d.** Downgraded two levels for very serious indirectness, because only one symptom impacting quality of life was assessed, not measured on a standardised scale, and after a short observation period.
- e.** Downgraded one level for serious imprecision, because of few participants
- f.** Downgraded one level for publication bias, because safety outcomes were assessed and reported in most studies for convalescent plasma group only

Summary of findings 2. Summary of Findings Table - Convalescent plasma compared to standard plasma for individuals with moderate to severe disease
Convalescent plasma compared to standard plasma for individuals with moderate to severe disease
Patient or population: individuals with moderate to severe disease **Setting:** Intervention: convalescent plasma **Comparison:** standard plasma

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard plasma	Risk with convalescent plasma				
All-cause mortality at up to day 28	216 per 1,000	205 per 1,000 (37 to 1,000)	RR 0.95 (0.17 to 5.29)	252 (2 RCTs)	⊕⊕⊕⊕ VERY LOW a, b	We do not know whether convalescent plasma has any effect on all-cause mortality at up to day 28.
Clinical improvement, assessed by the need for respiratory support	Reporting of the clinical status or course of the disease was heterogeneous across studies. One study reported the odds of a one-point improvement on a six-point scale in clinical status at day 28 (OR 1.5, 95% CI 0.83 to 2.68). The other study reported the median improvement of O2 saturation: 10% (8.2 to 11) in CP group versus 7.5% (4.75 to 9.25) in SP group; and the median improvement in PaO2/FiO2: 231.15 (183.37 to 245.2) in CP group versus 77.01 (56.93 to 96.20) in SP group on up to day 7, respectively. ^c			252 (2 RCTs)	⊕⊕⊕⊕ VERY LOW d, e	We do not know whether convalescent plasma has any effect on clinical improvement.
Clinical worsening: need for invasive mechanical ventilation	67 per 1,000	214 per 1,000 (25 to 1,000)	RR 3.21 (0.38 to 27.40)	29 (1 RCT)	⊕⊕⊕⊕ LOW ^b	Convalescent plasma may increase the need for invasive mechanical ventilation.
Quality of life, assessed with standardised scales at longest follow-up	not pooled	not pooled	-	(0 studies)	-	We did not identify any study reporting this outcome.
Grade 3 and 4 adverse events	The identified studies did not report the number of participants experiencing any grade 3 or 4 adverse events. One study (reporting on 219 participants) reported the number of participants experiencing any event of grade 3 (27/147 in CP group versus 17/72 in SP group), or grade 4 (26/147 in CP group versus 15/72 in SP group). The study also reported the number of participants experiencing at least one event of any grade (96/147 in CP group versus 40/72 in SP group, RR			248 (2 RCTs)	⊕⊕⊕⊕ VERY LOW d, e	We are very uncertain whether or whether not convalescent plasma increases the risk for grade 3 and 4 adverse events.

1.18, 95% CI 0.93 to 1.49). Both identified studies reported on observed transfusion-related events no severe side effects observed in one study (reporting on 29 participants); 4/147 in CP group versus 3/72 in SP group in the other study).^c

Serious adverse events	361 per 1,000	264 per 1,000 (177 to 401)	RR 0.73 (0.49 to 1.11)	219 (1 RCT)	⊕⊕⊕⊕ LOW ^e	Convalescent plasma may decrease the risk of serious adverse events.
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***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_423575562054934976.

- a. Downgraded one level for serious inconsistency, because direction of effect is not consistent in both studies
- b. Downgraded two levels for very serious imprecision, because of few participants, few events and very wide confidence intervals
- c. CP: convalescent plasma; SP: standard plasma
- d. Downgraded one level for serious indirectness, because definition of outcomes was different to the definition used in our review
- e. Downgraded two levels for very serious imprecision, because of few participants, and few events

Summary of findings 3. Summary of Findings Table - Convalescent plasma compared to placebo or standard care alone for individuals with mild disease

Convalescent plasma compared to placebo or standard care alone for individuals with mild disease

Patient or population: individuals with mild disease **Setting:** **Intervention:** convalescent plasma **Comparison:** placebo or standard care alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or standard care alone	Risk with convalescent plasma				

All-cause mortality	50 per 1,000	25 per 1,000 (5 to 133)	RR 0.50 (0.09 to 2.65)	160 (1 RCT)	⊕⊕⊕⊕ VERY LOW a, b	We are very uncertain about the effect of convalescent plasma on all-cause mortality.
Development of severe clinical COVID-19 symptoms assessed with: WHO Clinical Progression Scale ≥ 6	We did not identify any study reporting development of severe clinical COVID-19 symptoms, when assessed according to WHO Clinical Progression Scale. One study (reporting on 160 participants) reported the need for invasive mechanical ventilation (RR 0.50, 95% CI 0.09 to 2.65, estimated absolute effect with convalescent plasma: 25 of 1000), the risk for developing severe respiratory disease (RR 0.52, 95% CI 0.29 to 0.94, estimated absolute effect with convalescent plasma: 313 of 1000), or critical illness with life-threatening disease (RR 0.83, 95% CI 0.27 to 2.62, estimated absolute effect with convalescent plasma: 63 of 1000) c, d, e			160 (1 RCT)	⊕⊕⊕⊕ LOW b	We are uncertain about the effect of convalescent plasma on developing severe clinical COVID-19 symptoms.
Quality of life, assessed with standardised scales at longest follow-up	not pooled	not pooled	-	(0 studies)	-	We did not identify any study reporting this outcome.
Grade 3 and 4 adverse events	We did not identify any study reporting grade 3 or 4 adverse events. One study (reporting on 160 participants) reported that no "solicited" adverse events were observed in any group.			160 (1 RCT)	⊕⊕⊕⊕ VERY LOW f, g	We do not know whether convalescent plasma is associated with a higher risk of grade 3 or 4 adverse events.
Serious adverse events	We did not identify any study reporting serious adverse events. One study (reporting on 160 participants) reported that no serious "solicited" adverse events were observed in any group.			160 (1 RCT)	⊕⊕⊕⊕ VERY LOW f, g	We do not know whether convalescent plasma is associated with a higher risk of serious adverse events.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

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

See interactive version of this table: https://gdt.gradepr.org/presentations/#/isof/isof_question_revman_web_423575913930302502.

- a. Downgraded one level for serious indirectness, because outcome definition did not exactly match our definition (defined as death associated with COVID-19); and because all patients were admitted to hospital after recruitment
- b. Downgraded two levels for very serious imprecision, because CI includes zero effect line, few events, and few participants
- c. Severe respiratory disease defined as a respiratory rate of 30 breaths per minute or more, an oxygen saturation of less than 93% while the person was breathing ambient air, or both.
- d. Life-threatening respiratory disease defined as oxygen supplementation at a fraction of inspired oxygen of 100%, noninvasive or invasive ventilation, admission to an intensive care unit, or any combination of these
- e. Critical systemic illness defined as respiratory failure with a ratio of the partial pressure of oxygen to $F_{iO_2} \leq 200$ mmHg, shock, multiple organ dysfunction syndrome, or any combination of these
- f. Downgraded one level for serious indirectness, because outcome definition did not match our definition
- g. Downgraded two levels for very serious imprecision, because of few participants and only one study was identified

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 22 March 2020, the World Health Organization (WHO) declared the current COVID-19 outbreak to be a pandemic, with the outbreak resulting in more than 119 million confirmed cases and over 2.5 million deaths worldwide (WHO 2020b; WHO 2021a). 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).

Approximately 5% of patients with COVID-19 and 20% of those hospitalised experience severe disease requiring intensive care (Wiersinga 2020). Early reports suggested case fatality rates between 0.7% and 4% (WHO 2020a; WHO 2020c). More recent reports estimate wide-ranging case fatality rates, as low as 0.0% in Singapore and up to 9.0% in Mexico (Johns Hopkins 2021). However, these numbers should be interpreted with great care due to testing availability, underreporting of cases and delays from confirmation of a case to time of death (Kim 2020), ethnicity, underlying health conditions, access to health care and socioeconomic status (Williamson 2020).

The median incubation period of SARS-CoV-2 was reported to be five days, with 97.5% of cases developing symptoms within 11.5 days of infection (Lauer 2020). Common signs and symptoms can include fever, dry cough, fatigue and sputum production (WHO 2020a). Postviral olfactory dysfunction is reported in 5% to 85% of cases, with loss of both smell and taste reported (Izquierdo-Dominguez 2020). Other less commonly reported signs and symptoms are shortness of breath, sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhoea, haemoptysis and conjunctival congestion (WHO 2020a). Of the reported cases, 80% are estimated to have a mild or asymptomatic course of infection, and an estimated 5% of cases are admitted to the ICU with acute respiratory distress syndrome (ARDS), septic shock, multiple organ failure, or all three conditions (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). Early reports have suggested that people who are immune-compromised may not have an increased risk of being hospitalised with severe COVID-19 symptoms (D'Antiga 2020). However, evidence has been conflicting, with patients with malignancy and recipients of solid organ and allogeneic transplants reported to have an increased risk of severe COVID-19 disease (Fung 2020; Sharma 2021).

SARS-CoV-2 is a positive-sense, single-stranded ribonucleic acid (RNA) virus with a large genome. There are indications that the virus is capable of inducing an excessive immune reaction in the host, with highly activated but decreased numbers of CD4⁺ and CD8⁺ T

cells detected in the peripheral blood of people with COVID-19 (Xu 2020a). Early reports also showed that people critically ill with COVID-19 frequently exhibit a hypercoagulable state and endothelial inflammation, which is hypothesised to lead to the high burden of thromboembolic events seen in this population (Driggin 2020). SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2). 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 (Tolouian 2020; Van de Veerdonk 2020).

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. Although the included studies were generally small and of low quality, with a moderate to high risk of bias, the review authors concluded that 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 allo-immunisation and haemolytic transfusion reactions have also been described following plasma transfusion, although they are less common (Pandey 2012). Pathogen inactivation can be implemented to decrease the risk of transmitting infections by transfusion (Rock 2011).

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

A theoretical risk related to virus-specific antibodies, which are transferred with convalescent plasma and hyperimmune immunoglobulin administration, is antibody-dependent enhancement of infection (Morens 1994). Here, virus-binding antibodies facilitate the entry and replication of virus particles into monocytes, macrophages and granulocytic cells and thereby increase the risk of more severe disease in the infected host. Although antibody-dependent enhancement has not been demonstrated in COVID-19, it has been seen with previous coronavirus infections when the antibodies given targeted a different serotype of the virus (Wan 2020; Wang 2014). A mechanism for antibody-dependent enhancement in COVID-19 has recently been proposed, with non-neutralising antibodies to variable S domains potentially enabling an alternative infection pathway via Fc receptor-mediated uptake (Ricke 2020). Antibody-dependent enhancement is therefore a potentially harmful consequence of convalescent plasma and hyperimmune immunoglobulin therapy for COVID-19. Safety of convalescent plasma for treatment of COVID-19 has been investigated in a large cohort from the USA Food and Drug Administration (FDA) Expanded Access Program (Joyner

2020). Here, convalescent plasma did not clearly cause an excessive risk of adverse events within seven days of treatment, nor did it show an exceptionally high mortality rate at seven days (8.6%) (Joyner 2020).

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

How the intervention might work

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

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

Preliminary evidence in humans and rhesus macaques has shown that reinfection with SARS-CoV-2 is not likely, with most (but not all) patients who recovered from COVID-19 producing sufficient amounts of neutralising antibodies to protect against reinfection (Bao 2020a; Wu 2020b). This implies that convalescent plasma from people who have recovered from SARS-CoV-2 infection may be capable of conferring passive immunity. Retrospective studies also observed a potential correlation between the level of antibody titres in convalescent plasma and recovery after treatment (Joyner 2021; 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). And, it is unclear exactly how often reinfection occurs, with the burden of reinfection likely to be underestimated, while at the same time a number of case reports of severe reinfection have been published (Iwasaki 2021).

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 and tocilizumab proven to be effective in reducing mortality (Horby 2020; Horby 2021), 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 less severe cases (CDC 2020b; WHO 2020d). Despite these treatments, people hospitalised with COVID-19 are still at a high risk of mortality.

Ongoing vaccination programmes will aid in inducing immunity in the population and may prevent transmission to those who are

at risk for severe disease. Several vaccines have been approved, and many more are in development (WHO 2020g). Mass vaccination programmes have been underway since late 2020 (WHO 2021b). Until these vaccines are globally distributed, convalescent plasma may be a potential therapy for COVID-19 patients. Even with effective vaccines, not everyone can be effectively vaccinated; for example, people who are temporarily or permanently immune-compromised, and very young children. 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

Using a living systematic review approach, to assess whether convalescent plasma or hyperimmune immunoglobulin transfusion is effective and safe in the treatment of people with COVID-19; and to maintain the currency of the evidence.

METHODS

Criteria for considering studies for this review

Types of studies

The main description of methods is based on a template from the Cochrane Haematology review group and in line with a series of Cochrane Reviews investigating treatments and therapies for COVID-19. The protocol for this review was registered with the Center for Open Science on 17 April 2020 (Piechotta 2020a). Amendments that have been made since are summarised in [Differences between protocol and review](#) and [Table 1](#).

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

In case of insufficient evidence available from RCTs we had planned to include prospective and retrospective controlled non-randomised studies of interventions (NRSIs), and prospective and retrospective registered non-controlled NRSIs in a top-down approach as outlined in [Appendix 1](#).

Because large-scale or expanded access studies could still provide valuable information on the safety of convalescent plasma or hyperimmune immunoglobulins, we decided to include prospectively registered single-arm studies, even if upcoming RCTs report safety data for both groups. However, single-arm studies are mostly of lower quality and too heterogeneous to be pooled. We therefore considered prospectively registered single-arm studies for safety assessment only, if 500 or more participants with COVID-19 were included. We followed the methodology as specified in the protocol (Piechotta 2020a).

We followed the suggestions specified in the *Cochrane Handbook* (Higgins 2019a), as far as possible, and applied the methodology outlined in the following sections. We considered RCTs as specified above, and for safety outcomes considered registered single-arm studies including 500 or more participants with COVID-19.

We included full-text publications, pre-print articles, 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 included trials that included participants with any disease severity. We performed separate analyses for populations with ambulatory mild disease and for hospitalised participants with moderate to severe disease, according to the latest WHO clinical progression score (see [Table 2](#); WHO 2020e).

We excluded studies including populations with other coronavirus diseases (SARS or MERS). We also excluded studies that included 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 were allowed, but must have been comparable between intervention groups.
- Convalescent plasma versus standard care or placebo (i.e. saline solution)
- Convalescent plasma versus standard plasma (i.e. fresh frozen plasma)

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

- 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 were allowed, but must have been comparable between intervention groups.

Types of outcome measures

We evaluated core outcomes as predefined by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative for COVID-19 patients (COMET 2020), and additional outcomes that have been prioritised by consumer representatives, referees of previous versions of this review, and the German guideline panel for inpatient therapy of people with COVID-19.

We defined outcome sets for two populations: individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease, and individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease, according to the WHO clinical progression scale (WHO 2020e).

We assessed disease severity with need for respiratory support according to the WHO clinical progression scale (WHO 2020e).

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

Effectiveness of convalescent plasma

Prioritised outcomes (included in the 'Summary of findings' table)

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to day 28, day 60, and up to longest follow-up) including the following.
 - Improvement of clinical status:
 - liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4 on the Clinical Progression Scale (WHO 2020e) (for the subgroup of participants requiring any supplemental oxygen or ventilator support at baseline, i.e. WHO ≥ 5);
 - weaning or liberation from invasive mechanical ventilation in surviving patients i.e. WHO ≤ 6 (for the subgroup of participants requiring invasive mechanical ventilation at baseline, i.e. WHO ≥ 7).
 - Worsening of clinical status:
 - need for invasive mechanical ventilation i.e. WHO 7-9 (for the subgroup of participants not requiring invasive mechanical ventilation at baseline, i.e. WHO ≤ 6);
 - need for non-invasive mechanical ventilation or high flow i.e. WHO = 6 (for the subgroup of participants not requiring

non-invasive or non-invasive mechanical ventilation, or high flow oxygen at baseline, i.e. WHO ≤ 5);

- need for oxygen by mask or nasal prongs i.e. WHO = 5 (for the subgroup of participants not requiring any supplemental oxygen or ventilator support at baseline, i.e. WHO ≤ 4).
- Quality of life, including fatigue and functional independence; assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available

Additional outcomes (not included in the 'Summary of findings' table)

- Duration of hospitalisation, or time-to-discharge from hospital
- Admission to the intensive care unit (ICU)
- Length of stay on the ICU, or time to discharge from ICU
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days
- Need for dialysis (at up to 28 days)

Safety of convalescent plasma

- Adverse events (any grade, grade 1-2, grade 3-4), defined as the number of participants with any event and including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, transfusion-associated dyspnoea (TAD), acute transfusion reactions)
- Serious adverse events, defined as the number of participants with any event

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

Effectiveness of convalescent plasma

Prioritised outcomes (included in the 'Summary of findings' table)

- All-cause mortality at day 28, day 60, time-to-event, and at longest follow-up.
- Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 4 (WHO 2020e), up to longest follow-up
 - Need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow i.e. WHO ≥ 6 , severe disease:
 - need for invasive mechanical ventilation i.e. WHO 7-9;
 - need for non-invasive mechanical ventilation or high flow i.e. WHO = 6.
 - Need for hospitalisation with or without supplemental oxygen i.e. WHO = 4-5, moderate disease:
 - need for oxygen by mask or nasal prongs i.e. WHO = 5;
 - need for hospitalisation without oxygen therapy i.e. WHO = 4.
- Quality of life, including fatigue and functional independence; assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available

Additional outcomes (not included in the 'Summary of findings' table)

- Admission to hospital
- Time to symptom onset

- Length of hospital stay, for subgroup of participants hospitalised during course of disease
- Admission to the ICU
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days

Safety of convalescent plasma

- Adverse events (any grade, grade 1-2, grade 3-4), defined as the number of participants with any event and including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions)
- Serious adverse events, defined as the number of participants with any event

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. Studies reported in all languages are eligible, in order to limit language bias. We check weekly for newly emerging hyperimmune immunoglobulins and review search methods and strategies approximately monthly, to ensure they reflect any terminology changes in the topic area, or in the databases. We adapt the strategy where necessary.

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). One review author (CD) developed the original strategies and Cochrane Haematology's Information Specialist (IM) peer-reviewed and revised them at various times, to reflect the current state of knowledge. In this emerging field, we expected that at least study abstracts 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. Because nowadays, it is mandatory to provide results at least in the trials registry, we had planned to extract and

analyse these data, in case results were not published elsewhere. However, no outcome data have yet been added to the trials registries.

We searched the following databases and sources from 1 January 2019 to 17 March 2021.

- Databases of medical literature
 - MEDLINE (Ovid, 1 January 2019 to 17 March 2021; [Appendix 2](#))
 - Embase (Ovid, 1 January 2019 to 17 March 2021; [Appendix 3](#))
 - Cochrane COVID-19 Study Register ([covid-19.cochrane.org](#); inception to 17 March 2021; [Appendix 4](#))*
 - PubMed (for publications ahead of print only; 1 January 2019 to 17 March 2021; [Appendix 5](#))
 - World Health Organization COVID-19 Global literature on coronavirus disease ([bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov](#); inception to 17 March 2021) without references of MEDLINE and PubMed; [Appendix 6](#))
 - Epistemonikos, L*OVE List Coronavirus disease (COVID-19) ([app.iloveevidence.com/loves](#); inception to 17 March 2021; [Appendix 7](#))

*The Cochrane COVID-19 Study Register is a specialised register built within the Cochrane Register of Studies (CRS) and is maintained by Cochrane Information Specialists. Complete data sources and search methods for the register are available at: [community.cochrane.org/about-covid-19-study-register](#). The register contains study reports from several sources, including:

- daily searches of PubMed;
- daily searches of ClinicalTrials.gov;
- weekly searches of Embase.com;
- weekly searches of the WHO International Clinical Trials Registry Platform (ICTRP);
- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL).

Searching other resources

We handsearched the reference lists of all identified studies, relevant review articles and current treatment guidelines for further literature. We also 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

Using [Covidence](#) software, two review authors (from among SJV, KLC, VP, CK, CI and NS) independently screened the results of the search strategies for eligibility, by reading the abstracts. 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 studies that we excluded after full-text assessment and the reasons for their exclusion in the [Characteristics of excluded studies](#) table.

Data extraction and management

Two review authors (from among SJV, KLC, VP, CK, CI and ED) 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.

Two review authors (from among SJV, KLC, CK, CI, ED and VP) extracted data using a customised data extraction form, developed in Microsoft Excel ([Microsoft Corporation 2018](#)). Another review author (CI, VP, or NS) 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, bias arising from the randomisation process, due to deviations from the intended interventions, due to missing outcome data, in measurement of the outcome, and in selection of the reported results
- 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: as specified in [Types of outcome measures](#)

Assessment of risk of bias in included studies

Randomised controlled trials

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

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

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

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

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

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

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

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

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

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

We used the RoB 2 Excel tool to implement RoB 2 (available on the riskofbiasinfo.org website), added our judgements to the analysis for each assessed study and outcome, and stored our detailed RoB 2 assessments as supplementary online material ([Piechotta 2021](#)). We used the overall 'risk of bias' judgement, derived from the RoB 2 Excel tool, to inform our GRADE decision on downgrading for risk of bias.

Controlled non-randomised studies of interventions

As reported above, we had planned to include NRSI trials if there was insufficient evidence from RCTs. Please refer to [Appendix 1](#) for detailed information on how we would have assessed risk of bias for controlled NRSIs.

Non-controlled non-randomised studies of interventions

As specified in the 'Types of studies' section, we also included safety data from prospective non-controlled NRSIs, if 500 or more participants with COVID-19 were included.

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 3](#); [Mulder 2019](#)). We performed and presented any 'Risk of bias' judgements per outcome per study.

The quality assessment strongly depends upon information on the design, conduct and analysis of the study. The two review authors (VP, NS) resolved any disagreements regarding the quality assessments by discussion; in case of disagreement they would have consulted a third review author (SJV, KLC or CK).

We assessed the following domains of bias.

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

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

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

Measures of treatment effect

Randomised controlled trials

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

For continuous outcomes using the same scale we performed analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales we performed analyses using the standardised mean difference (SMD). For interpreting SMDs, we re-expressed 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 (e.g. discharge from hospital). 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 provided HRs, we used 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

Please refer to [Appendix 1](#) for detailed information on how we had planned to extract and report different treatment measures of outcome data from controlled NRSIs.

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 non-controlled NRSIs, as described above. Instead, we reported and presented results narratively.

As recommended in Chapter 6 of the *Cochrane Handbook* ([Higgins 2019d](#)), for studies with multiple treatment groups, we had planned to combine arms if they could be regarded as subtypes of the same intervention.

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

Dealing with missing data

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

We requested missing data from the study authors. We contacted 11 principal investigators from included studies (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Bajpai 2020; Gharbharan 2020; Hamdy Salman 2020; Horby 2021; Li 2020; Libster 2020; Ray 2020; Simonovich 2020). We received six responses: one each from Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Gharbharan 2020; Horby 2021 and Li 2020, providing all requested information; one from Balcells 2020 providing breakdowns of adverse events that occurred in the study; and one from Rasheed 2020, stating that all or most requested information will be included in the journal publication. Partly based on the additional requested data, we decided to exclude Balcells 2020 and Rasheed 2020.

As we received all outcome data from included studies that we had requested, we did not have to make any assumptions. For updates of this review, if data are still missing, we will have to make explicit assumptions of any methods used in the included studies. 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.

We further contacted all principal investigators from ongoing studies, asking for their prospective completion dates, as well as completed studies without published results, and invited them to share their data with us for this update. We received 11 responses: one each from Beltran 2021 and NCT04438694, informing us that their trials were completed and that they are willing to share their data for this update (no data were received from the investigators until submission of our review, however, Beltran 2021 published a preprint of their anticipated journal publication after we submitted the review); one each from NCT04433910, ISRCTN85216856 and NCT04397757 informing us that randomisation was completed at the end of December 2020, and that they are willing to share their data with us once analysed (no data were received from the investigators until submission of our review); one from NCT04429854, informing us that their trial was completed by January 2021, and one each from NCT04388410 and NCT04428021, informing us that their trials were completed by February 2021, and that they are willing to share their data with us once analysed (no data were received from the investigators until submission of our review); and one each from Bennett-Guerrero 2021, NCT04348656 and NCT04377568, informing us that there is not yet any information to share, however, Bennett-Guerrero 2021 published a preprint

of their anticipated journal publication after we submitted the review. We will contact the principal investigators of ongoing and completed studies without published results again for our next update.

Assessment of heterogeneity

We did not combine any data from different study designs. Meta-analysis was not appropriate for the non-controlled NRSIs, as described above. Instead, we reported and presented results in tables.

We assessed heterogeneity of treatment effects between trials using a Chi² test with a significance level at $P < 0.1$, and visual examination. We used the I^2 statistic (Higgins 2003), to quantify possible heterogeneity ($I^2 > 30\%$ to signify moderate heterogeneity, $I^2 > 75\%$ to signify considerable heterogeneity; Deeks 2019). If heterogeneity had been above 80%, we would have explored potential causes through sensitivity and subgroup analyses. If we had not found a reason for heterogeneity, we would not have performed a meta-analysis, but would have only commented on results from all studies and presented these in tables.

Assessment of reporting biases

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

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

Data synthesis

If the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we pooled the data in meta-analysis. We performed separate analyses for populations with ambulatory mild disease and for hospitalised participants with moderate to severe disease, according to the latest WHO clinical progression score (WHO 2020e). We performed analyses according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2019). We did not conduct meta-analyses that included different study designs. We conducted separate meta-analyses for each comparison.

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

We used the random-effects model for all analyses, as we anticipated that for included studies, true effects would be related, but would not be the same. For binary outcomes, we based the estimation of the between-study variance using the Mantel-Haenszel method. We used the inverse variance method for continuous outcomes, outcomes that include data from cluster-RCTs, or outcomes where HRs are available. We planned to explore heterogeneity above 80% with subgroup analyses. If we could not

find a cause for the heterogeneity or if study outcomes were too clinically heterogeneous to be combined, we did not perform a meta-analysis, but commented on the results in a narrative analysis, with the results from all studies presented in tables.

Please see [Appendix 1](#) for detailed information on how we had planned to synthesise data from 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.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses of the following characteristics for our prioritised outcomes, as specified in the 'Summary of Findings' section.

- Severity of condition (divided into moderate and severe disease, assessed with need for respiratory support according to WHO clinical progression scale ([WHO 2020e](#)))
- Duration since symptom onset (divided into up to 7 days and more than 7 days)
- Antibodies in recipients detected at baseline (divided into detected in a maximum of 20% of recipients versus detected in at least 80% of recipients)

For the outcome domain of clinical status, we used additional subdivisions to analyse the changes of the need for respiratory support more precisely, and targeted to the baseline need (see [Types of outcome measures](#)).

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

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

- Age of participants (divided into applicable age groups, e.g. children; 18 to 65 years, 65 years and older)
- Pre-existing conditions (diabetes, respiratory disease, hypertension, immunosuppression)
- Level of antibody titre in donors (divided into high and low titres, using the studies definition)
- SARS-CoV-2 variants (e.g. B.1.1.7, B.1.351, P.1, and other variants that may occur in the future)

Sensitivity analysis

We performed sensitivity analyses for the following.

- 'Risk of bias' assessment components (studies with a low risk of bias or some concerns versus studies with a 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, and prepared one 'Summary of findings' table per population.

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

- All-cause mortality; all-cause mortality at hospital discharge most favourable. If not reported, all-cause mortality day 60, followed by day 28, or time-to-event estimate, will be included in the 'Summary of findings' table.
- Improvement of clinical status; assessed with liberation from respiratory support, i.e. supplemental oxygen support or invasive mechanical ventilation, in accordance with WHO Clinical Progression Scale ([WHO 2020e](#)) at longest follow-up available
 - For all participants requiring any supplemental oxygen or ventilator support at baseline (WHO ≥ 5 at baseline on the WHO Clinical Progression Scale ([WHO 2020e](#))): Liberation from supplemental oxygen in surviving patients
 - For all participants requiring invasive mechanical ventilation at baseline (WHO ≥ 7 at baseline on the WHO Clinical Progression Scale ([WHO 2020e](#))): Liberation from invasive mechanical ventilation in surviving patients
- Worsening of clinical status; assessed with the need for invasive mechanical ventilation i.e. WHO 7-9 (only for participants not requiring invasive mechanical ventilation at baseline, i.e. WHO ≤ 6) on the WHO Clinical Progression Scale ([WHO 2020e](#)) at longest follow-up available
- Quality of life, including fatigue and functional independence; assessed with standardised scales (e.g. WHOQOL-100) at longest follow-up available
- Grade 3 or 4 adverse events
- Serious adverse events

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

- All-cause mortality; all-cause mortality at longest follow-up and greater than 60 days most favourable. If not reported, all-cause mortality day 60, followed by day 28, or time-to-event estimate, will be included in the 'Summary of findings' table.
- Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 ([WHO 2020e](#)) at longest follow-up available
- Quality of life, including fatigue and functional independence; assessed with standardised scales (e.g. WHOQOL-100) at longest follow-up available
- Grade 3 or 4 adverse events
- Serious adverse events

We followed the current GRADE guidance for these assessments in its entirety, as recommended in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2020](#)). We used [GRADEpro GDT](#) software to create a 'Summary of findings' table ([Schünemann 2020](#)). For RCTs, we used the overall 'risk of bias' judgement, derived from the RoB 2 Excel tool, to inform our decision on downgrading for risk of bias. We assessed the certainty of the evidence for non-controlled NRSIs as reported in the GRADE guidance 3, starting from low-certainty evidence ([Balshem 2011](#)). 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 14,714 new records, in addition to the 7856 potentially relevant records from the previous versions

(altogether 22,570 references). After removing duplicates, we screened 10,312 new records for this update (altogether 15,812 records) based on their titles and abstracts, and we excluded 15,492 records that did not meet the prespecified inclusion criteria. We evaluated the remaining 316 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

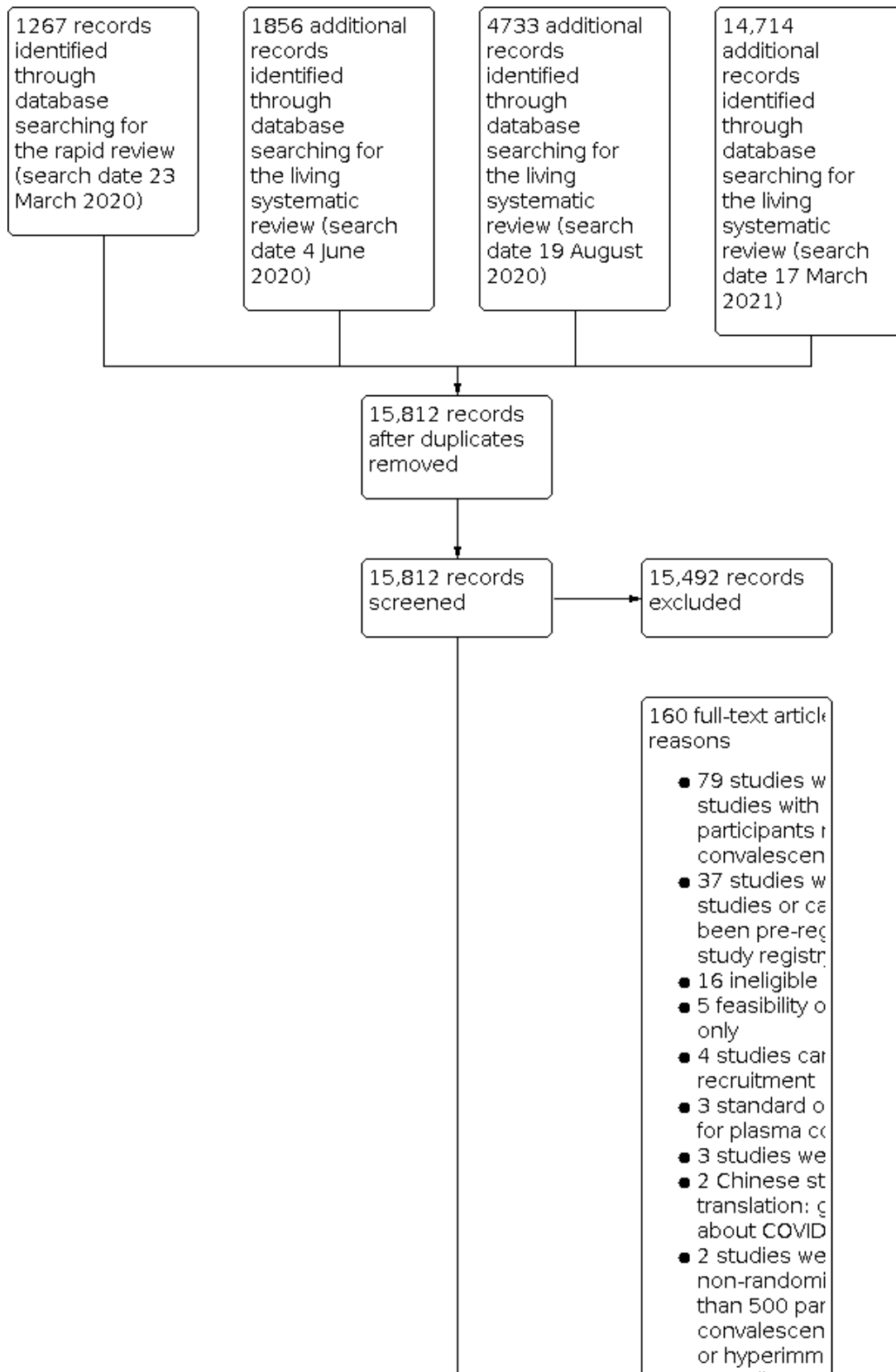


Figure 1. (Continued)

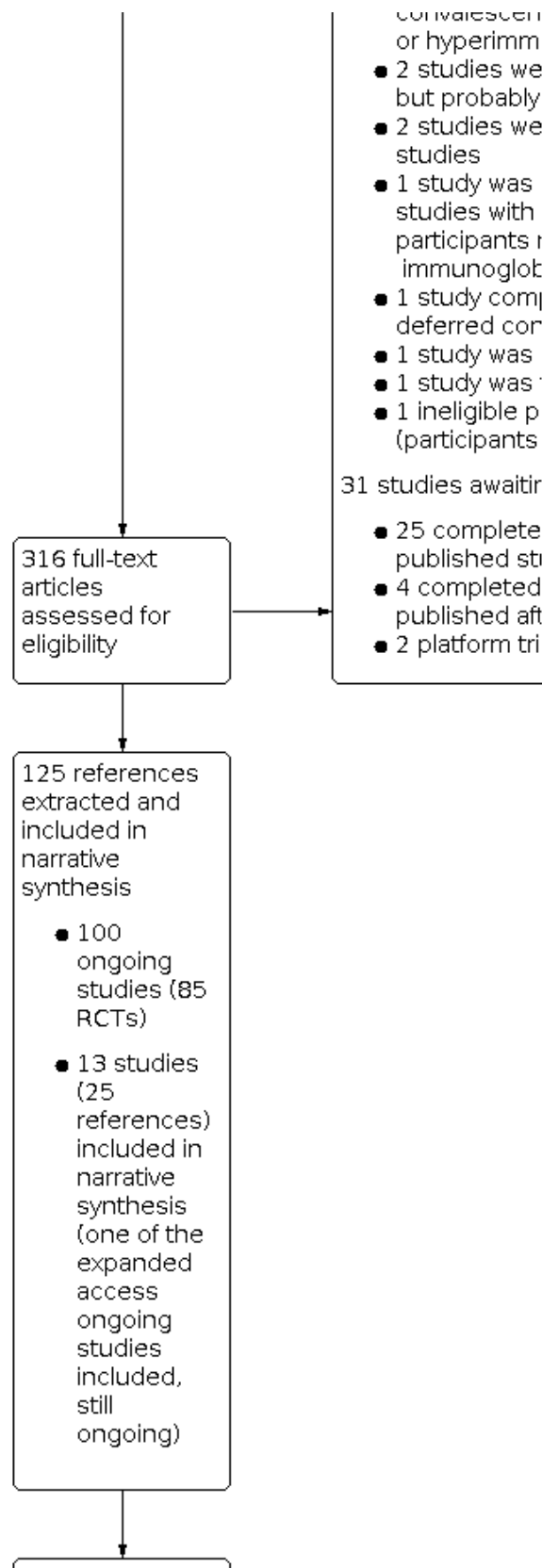
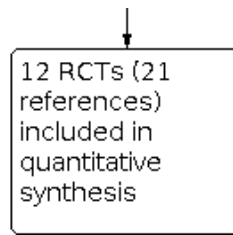


Figure 1. (Continued)



We identified 113 potentially eligible studies within 125 citations: 13 included studies (25 records) (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Bajpai 2020; Gharbharan 2020; Hamdy Salman 2020; Horby 2021; Joyner 2020; Li 2020; Libster 2020; O'Donnell 2021; Ray 2020; Simonovich 2020) and 100 ongoing studies (see 'Ongoing studies' below).

Included studies

We included 13 studies reporting on 48,509 participants, of whom 41,880 received convalescent plasma (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Bajpai 2020; Gharbharan 2020; Hamdy Salman 2020; Horby 2021; Joyner 2020; Li 2020; Libster 2020; O'Donnell 2021; Ray 2020; Simonovich 2020).

Design and sample size

We included 12 RCTs (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Bajpai 2020; Gharbharan 2020; Hamdy Salman 2020; Horby 2021; Li 2020; Libster 2020; O'Donnell 2021; Ray 2020; Simonovich 2020) and one non-controlled NRSI (Joyner 2020).

Setting

The included studies differed considerably in their settings.

Among the RCTs, three were conducted in India (Agarwal 2020; Bajpai 2020; Ray 2020), one was in Bahrain (AlQahtani 2020), one was conducted in Spain (Avendano-Sola 2020), one was in the Netherlands (Gharbharan 2020), one was conducted in Egypt (Hamdy Salman 2020), one was from the UK (Horby 2021), one was done in China (Li 2020), two were conducted in Argentina (Libster 2020; Simonovich 2020), and one was conducted partly in the USA and partly in Brazil (O'Donnell 2021). The non-controlled NRSI that we included for safety outcomes was conducted in the USA (Joyner 2020).

Three studies are single-centre studies (Bajpai 2020; Hamdy Salman 2020; Ray 2020) and nine are multi-centre studies (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Gharbharan 2020; Joyner 2020; Li 2020; Libster 2020; O'Donnell 2021; Simonovich 2020), with a minimum of two centres for AlQahtani 2020 and a maximum of 2807 centres for Joyner 2020.

Among the RCTs, 11 were performed in an inpatient setting (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Bajpai 2020; Gharbharan 2020; Hamdy Salman 2020; Horby 2021; Li 2020; O'Donnell 2021; Ray 2020; Simonovich 2020). One study was performed in an outpatient setting, for the recruitment of participants; but after randomisation, all participants were admitted to hospital for administration of convalescent plasma (Libster 2020).

Participants

The RCTs by Agarwal 2020, AlQahtani 2020, Avendano-Sola 2020 and Simonovich 2020 included participants with moderate disease and the RCTs by Gharbharan 2020 and Li 2020 included individuals with severe disease, according to the latest WHO clinical progression score (WHO 2020e). The RCTs by Bajpai 2020, Horby 2021, O'Donnell 2021, Ray 2020 and Hamdy Salman 2020 included individuals with both moderate and severe disease, according to the latest WHO clinical progression score (WHO 2020e). The RCT by Libster 2020 included populations with mild disease.

The non-controlled NRSI by Joyner 2020 transfused convalescent plasma in individuals with severe or life-threatening disease.

Interventions

All included RCTs evaluated convalescent plasma in comparison to a control arm, but not all studies had the same comparisons. We did not identify any completed studies evaluating hyperimmune immunoglobulin (IgG). All of the included studies that we evaluated for efficacy and safety outcomes transfused different doses and volumes of convalescent plasma.

Randomised controlled trials

Ten RCTs compared convalescent plasma with standard care, with or without placebo (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Gharbharan 2020; Hamdy Salman 2020; Horby 2021; Li 2020; Libster 2020; Ray 2020; Simonovich 2020), and two RCTs compared convalescent plasma with standard plasma (Bajpai 2020; O'Donnell 2021).

In these 11 RCTs that we evaluated for efficacy and safety, the dose and volume of plasma also varied. The total volume of convalescent plasma transfused varied between 200 mL and 600 mL of plasma, with participants receiving between one dose of plasma (Avendano-Sola 2020; Hamdy Salman 2020; Libster 2020; O'Donnell 2021; Simonovich 2020), and two or more doses of plasma (Agarwal 2020; AlQahtani 2020; Bajpai 2020; Gharbharan 2020; Horby 2021; Li 2020; Ray 2020).

Non-controlled, non-randomised studies of interventions

In the one non-controlled NRSI by Joyner 2020, that we evaluated for safety outcomes, a volume of 200 mL convalescent plasma was transfused, in one or more doses. The antibody titre test in donors was not performed.

Plasma donors

All included RCTs determined antibody titres in donors, of which five RCTs reported antibody titres in donors' plasma (AlQahtani 2020; Horby 2021; Libster 2020; Ray 2020;

Simonovich 2020), and eight RCTs reported neutralising antibody titres in donors' plasma (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Bajpai 2020; Gharbharan 2020; Hamdy Salman 2020; Li 2020; O'Donnell 2021).

Of the included studies, 11 RCTs reported the donors' eligibility criteria (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Bajpai 2020; Gharbharan 2020; Hamdy Salman 2020; Li 2020; Libster 2020; O'Donnell 2021; Ray 2020; Simonovich 2020). They also reported some descriptive information about donors, such as their age, gender, disease severity, or their timing from disease recovery and/or the RT-PCR virus detection. Among those RCTs reporting the sex of donors, in Agarwal 2020, Avendano-Sola 2020, Gharbharan 2020 and O'Donnell 2021, most of the donors were male (94%, 88%, 91% and 66%, respectively). In Bajpai 2020, all donors were male.

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

Outcomes

We evaluated efficacy and safety outcomes from 12 RCTs (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Bajpai 2020; Gharbharan 2020; Hamdy Salman 2020; Horby 2021; Li 2020; Libster 2020; O'Donnell 2021; Ray 2020; Simonovich 2020) with 12,878 participants, of whom 6555 received convalescent plasma. For the safety outcomes, we also evaluated one non-controlled NRSI (Joyner 2020) with 35,322 participants, all having received convalescent plasma.

Efficacy outcomes

Different efficacy outcomes were prioritised, based on the setting and the disease severity in participants of the included RCTs (see Types of outcome measures).

Among the RCTs that included individuals with moderate to severe disease, nine studies reported 28-day mortality (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Bajpai 2020; Horby 2021; Li 2020; O'Donnell 2021; Ray 2020; Simonovich 2020), and three studies also reported all-cause mortality at hospital discharge (Agarwal 2020; AlQahtani 2020; Gharbharan 2020). Improvement of clinical status, assessed by liberation from supplemental oxygen, was reported in one RCT (Gharbharan 2020). Clinical improvement, assessed by liberation from invasive mechanical ventilation, was reported in two RCTs (Gharbharan 2020; Horby 2021). Worsening of clinical status, assessed by the need for invasive mechanical ventilation, was reported in five RCTs (Agarwal 2020; AlQahtani 2020; Bajpai 2020; Horby 2021; Simonovich 2020). None of the included RCTs reported quality of life. The safety outcome for any grade adverse event was reported in two RCTs (Simonovich 2020; O'Donnell 2021); the outcome of grade 3 or 4 adverse events was reported in four RCTs (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Simonovich 2020); and serious adverse events were reported in three RCTs (Avendano-Sola 2020; O'Donnell 2021; Simonovich 2020).

The sole RCT that included individuals with asymptomatic or mild disease reported only all-cause mortality (Libster 2020), at an undefined time point.

Safety outcomes

For safety outcomes, we also evaluated the non-controlled NRSI (Joyner 2020). Five RCTs (Agarwal 2020; AlQahtani 2020; Avendano-

Sola 2020; O'Donnell 2021; Simonovich 2020) and the one non-controlled NRSI (Joyner 2020) reported adverse events or serious adverse events, or both, for all the participants. From these six studies, we extracted safety data from 21,154 participants, with safety data for 20,687 participants who received convalescent plasma and 464 participants who did not receive convalescent plasma. All the other included RCTs reported transfusion-related adverse events, for the participants receiving convalescent plasma (Bajpai 2020; Gharbharan 2020; Hamdy Salman 2020; Horby 2021; Li 2020; Libster 2020; Ray 2020) and for the participants receiving standard plasma (Bajpai 2020). From these eight studies, we extracted safety data from 6266 participants who received convalescent plasma only and 15 participants who received the standard plasma.

Two RCTs were terminated early, Gharbharan 2020 because most of the participants were found to have SARS-CoV-2 antibodies present at baseline and Li 2020 because there were no more eligible participants, due to containment of the epidemic in Wuhan, China. Neither of these studies cited safety concerns as the reasons for early termination.

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

Ongoing studies

Of the 100 ongoing studies, seven are expanded access studies from the USA (NCT04338360; NCT04360486; NCT04363034; NCT04374370; NCT04472572; NCT04420988; NCT04445207). As the NCT04338360 study has reported on the first 35,322 participants (with safety data for 20,000 participants; Joyner 2020), and has enrolled a further 86,805 participants (of whom 57,630 received convalescent plasma) into the study as of 7 August 2020 (US Covid Plasma 2020), we decided to treat this record as an ongoing study.

Eighty-five studies are RCTs (see Table 4 and Table 5), and 10 of these are investigating the effect of hyperimmune immunoglobulin (see Table 4). Of the 85 RCTs, 18 were scheduled to be completed in 2020 and planned to evaluate between 15 and 414 participants, but according to the trial registry, three are not yet recruiting, and 15 are still recruiting. Forty-nine RCTs are expected to be completed in 2021, and plan to evaluate between 16 and 1200 participants. Of these, 11 were scheduled to be completed by the time of writing, but according to the trial registry, five are not yet recruiting, three are still recruiting and three are active, but not recruiting. Four further, large RCTs are planned to be completed in 2021: NCT04418518, randomising 1200 participants; NCT04345289, evaluating 1100 participants; NCT02735707, evaluating 7100 participants; and NCT04483960, randomising 2400 participants. Another eight RCTs are expected to be completed in 2022 and plan to evaluate between 115 and 1344 participants. One study is expected to be completed in 2023 and plans to evaluate 1000 participants (NCT04364737). Please refer to Table 4 and Table 5 for further details on the planned completed dates and planned number of participants per study.

Two single-arm studies, including between 500 and 2000 participants, are expected to be completed in 2021 (NCT04352751) and in 2022 (NCT04642014). Two non-RCTs, including between 500 and 700 participants, are expected to be completed in 2021 (NCT04432272) and in 2022 (NCT04408040). Four studies are

pre-registered observational studies, including between 500 and 10,000 participants, of which three are expected to be completed in 2021 (NCT04497779; NCT04545047; NCT04669990). One is expected to be completed in 2022 (NCT04463823).

Please refer to Characteristics of ongoing studies and Table 4 and Table 5 for more detailed information.

Studies awaiting assessment

In the process of finalising the review, one of our ongoing studies was terminated early for futility and the trial stopped recruiting participants (NCT04355767). As this study was not yet completed, we decided to keep it under 'Awaiting classification'.

According to the trial registry, 24 studies have been completed, or had their recruitment completed, but no results have yet been published (IRCT20200404046948N1; IRCT20200409047007N1; IRCT20200413047056N1; ISRCTN85216856; NCT04332835; NCT04392414; NCT04405310; NCT04442958; CTRI/2020/05/025299; CTRI/2020/05/025328; CTRI/2020/09/027903; IRCT20120215009014N353; IRCT20150808023559N21; IRCT20200503047281N1; IRCT20200525047562N1; IRCT20201004048922N1; jRCT2031200174; NCT04521309; NCT04433910; NCT04492501; NCT04542941; NCT04547127; NCT04547660; NCT04610502).

For this reason, we have placed these studies in the category of 'Awaiting classification'. Of these, one study was a non-randomised controlled study with 600 participants (NCT04492501). All the others were RCTs.

According to the trial registry, expanded access is no longer available for two studies, but no results have been published yet and we are waiting until the sample size is available, which is why we have kept them under 'Awaiting classification' (NCT04358211; NCT04372368).

Two studies are platform trials, which are not yet completed and do not include our intended interventions. A platform trial is an adaptive, multistage study design in which numerous interventions can be evaluated through interim analyses. Additionally, in a platform trial new study arms can be added within the study period to examine further interventions (Park 2020). However, we want to track these studies, in case they add arms on convalescent plasma or hyperimmune immunoglobulin (NCT04501978; NCT04315948).

We identified full texts of four ongoing studies in our weekly searches, after the submission of the current review version (Beltran 2021; Bennett-Guerrero 2021; Lopardo 2021; Pouladzadeh 2021). We have categorised them as 'Awaiting classification' and will include them in the next version of this living systematic review. Of these four studies, one is investigating the effect of hyperimmune immunoglobulin (Lopardo 2021).

Excluded studies

We excluded 157 references that did not match our inclusion criteria as follows.

- Seventy-seven studies were single-arm studies with fewer than 500 participants receiving convalescent plasma (Abdullah 2020; Abolghasemi 2020; Bradfute 2020; ChiCTR2000029850; ChiCTR2000030039; ChiCTR2000031501; ChiCTR2000033798; CTRI/2020/04/024804; CTRI/2020/08/027285; Donato

2020; Duan 2020; Dulipsingh 2020; Ibrahim 2020; IRCT20151228025732N53; IRCT20200406046968N2; IRCT20200414047072N1; IRCT20200416047099N1; Jin 2020; Liu 2020; Madariaga 2020; NCT04264858; NCT04292340; NCT04321421; NCT04327349; NCT04332380; NCT04333355; NCT04345679; NCT04346589; NCT04348877; NCT04353206; NCT04354831; NCT04355897; NCT04356482; NCT04365439; NCT04374565; NCT04376034; NCT04377672; NCT04384497; NCT04388527; NCT04389710; NCT04389944; NCT04390178; NCT04392232; NCT04397523; NCT04407208; NCT04408209; NCT04411602; NCT04412486; NCT04418531; NCT04432103; NCT04458363; NCT04462848; NCT04471051; NCT04474340; NCT04476888; NCT04502472; NCT04513158; NCT04516954; NCT04535063; NCT04554992; NCT04565197; NCT04569188; NCT04570982; NCT04614012; NCT04616976; NCT04622826; NCT04644198; Olivares-Gazca 2020; PER-031-20; Perotti 2020; RBR-4vm3yy; RPCEC00000323; Salazar 2020a; Xia 2020; Zeng 2020; NCT04383548; NCT04438694).

- Thirty-seven studies were single-arm studies or case series that had not been pre-registered in a clinical study registry (Ahn 2020; Anderson 2020; Bao 2020b; Bobek 2020; Cantore 2020; Clark 2020; Enzmann 2020; Erkurt 2020; Fan 2020; Figlerowicz 2020; Grisolia 2020; Im 2020; Jamous 2020; Jiang 2020a; Karatas 2020; Kong 2020; Liu 2020a; Martinez-Resendez 2020; McCuddy 2020; Mira 2020; Niu 2020; Pei 2020; Peng 2020; Salazar 2020b; Shen 2020; Soleimani 2020; Taher 2020; Tan 2020; Wang 2020; Wright 2020; Xu 2020b; Yang 2020; Ye 2020; Zhang 2020a; Zhang 2020b; Zhang 2020c; Çınar 2020).
- Sixteen studies were performed with an intervention other than convalescent plasma or hyperimmune immunoglobulin (Cao 2020a; Chen 2020b; Chen 2020c; Díez 2020; Hu 2020; ISRCTN86534580; Jiang 2020b; Lin 2020; NCT04261426; NCT04344379; NCT04350580; NCT04368013; Robbiani 2020; Shi 2020; Xie 2020; de Assis 2020; CTRI/2020/10/028547).
- Five studies pertained to feasibility of collection of convalescent plasma only (Budhai 2020; Hashim 2020; NCT04344015; NCT04344977; NCT04360278).
- Four studies were cancelled by the investigator before recruiting participants into the study (ChiCTR2000030312; ChiCTR2000030381; ChiCTR2000030442; NCT04325672; NCT04467151).
- 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.
- Two studies were controlled, non-randomised studies with fewer than 500 participants receiving convalescent plasma or hyperimmune immunoglobulin (NCT04347681; NCT04384588).
- Two studies were controlled studies, but probably not truly randomised (Baklaushev 2020; Rasheed 2020).
- Two studies were pharmacokinetics studies (NCT04638634; NCT04661839).

- One study included an irrelevant participant population (participants exposed to COVID-19) ([NCT04323800](#)).
- One study was a single-arm study with fewer than 500 participants receiving hyperimmune immunoglobulin ([NCT04721236](#)).
- One study compared early to deferred convalescent plasma ([Balcells 2020](#)).
- One study was on plasma donors ([NCT04555109](#)).
- One study was terminated early and stopped because the sponsor was changed and a new study on convalescent plasma sponsored by the Italian Medicines Agency (AIFA) was started in Italy ([NCT04393727](#)).

Risk of bias in included studies

We assessed methodological quality and risk of bias for 12 RCTs ([Agarwal 2020](#); [AlQahtani 2020](#); [Avendano-Sola 2020](#); [Bajpai 2020](#); [Gharbharan 2020](#); [Hamdy Salman 2020](#); [Horby 2021](#); [Li 2020](#); [Libster 2020](#); [O'Donnell 2021](#); [Ray 2020](#); [Simonovich 2020](#)), using the 'Risk of Bias 2' (RoB 2) tool recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2019c](#)). For one non-controlled NRSI ([Joyner 2020](#)), we used the 'Risk of bias' assessment criteria tool for observational studies provided by Cochrane Childhood Cancer (see [Table 3](#); [Mulder 2019](#)). For the non-controlled NRSI, we only assessed risk of bias for safety outcomes. The completed RoB 2 tool with responses to all assessed signalling questions is available online at zenodo.org/record/4715089#.YIKvBOj7RaQ ([Piechotta 2021](#)).

Overall judgements for studies including individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

All-cause mortality

Among those studies reporting a mortality outcome, we rated the overall risk of bias to be of some concern in [Agarwal 2020](#), [AlQahtani 2020](#), [Gharbharan 2020](#) and [Ray 2020](#). We assessed this outcome on a study level at day 28, day 60, time-to-event, and at hospital discharge. For [Agarwal 2020](#), there were some inconsistencies in the adherence to the allocated interventions, which could be due to awareness of the intervention in this open-label trial (see [Risk of bias table for Analysis 1.1](#); [Risk of bias table for Analysis 1.3](#)). [Gharbharan 2020](#) provided insufficient information on whether co-interventions were balanced across arms (see [Risk of bias table for Analysis 1.2](#); [Risk of bias table for Analysis 1.3](#)). In one study ([AlQahtani 2020](#)), the produced result analysed was not in accordance with the pre-specified analysis plan, as the time point of the mortality outcome was not specified in the study protocol (see [Risk of bias table for Analysis 1.1](#); [Risk of bias table for Analysis 1.3](#)). In [Ray 2020](#), the preprint available gave no clear information on allocation concealment; only a preliminary statement of concealment via case record numbers could be retrieved from the trial registry, which led to a high risk of bias from the randomisation process (see [Risk of bias table for Analysis 1.1](#); [Risk of bias table for Analysis 1.2](#)).

Clinical status

Among those studies reporting at least one of the outcomes addressing clinical status and progression of disease, we rated the overall risk of bias to be of some concern for [Agarwal 2020](#) and [Gharbharan 2020](#). We assessed clinical status on a

study level, in accordance with the WHO Clinical Progression Scale ([WHO 2020e](#)), and including both improvement of clinical status and worsening of clinical status. For [Gharbharan 2020](#), we judged the risk of bias for improvement of clinical status to be of some concern, as the study provided insufficient information on whether co-interventions were balanced across arms (see [Risk of bias table for Analysis 1.4](#); [Risk of bias table for Analysis 1.5](#)). For [Agarwal 2020](#), we judged the risk of bias for worsening of clinical status to be of some concern, because of some inconsistencies in the adherence to the allocated interventions, which could be due to awareness of the intervention in this open-label trial, as well as because the outcome analysed was not prespecified in the trial registry and a study protocol was not available (see [Risk of bias table for Analysis 1.6](#)).

Quality of life

We could not assess the risk of bias for quality of life, as none of the studies reported this outcome.

Safety

Risk of bias in randomised controlled trials

Among those studies reporting at least one of the safety outcomes, we rated the overall risk of bias to be of some concern for [Agarwal 2020](#) and [AlQahtani 2020](#) (see [Risk of bias table for Analysis 1.14](#)). We assessed safety outcomes on a study level and included any adverse events, grade 3 to 4 adverse events and serious adverse events. For [Agarwal 2020](#), we judged the risk of bias for grade 3 to 4 adverse events to be of some concern, because of some inconsistencies in the adherence to the allocated interventions, which could be due to awareness of the intervention in this open-label trial. For both studies ([Agarwal 2020](#); [AlQahtani 2020](#)), the safety data was provided on our request by the study investigator, and it is not clear whether data for this outcome was collected from all, or nearly all the participants randomised. There is also no information available on how safety was measured.

Risk of bias in non-controlled, non-randomised studies of interventions

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 the study ([Joyner 2020](#)) to be low. Please refer to our detailed assessment in [Appendix 8](#).

Overall judgements for studies including individuals with a confirmed diagnosis of COVID-19 and asymptomatic or mild disease

We assessed risk of bias for one outcome, and did not identify any concerns suggesting a risk of bias for [Libster 2020](#), the only study including individuals with asymptomatic or mild disease.

Effects of interventions

See: [Summary of findings 1](#) Summary of Findings Table - Convalescent plasma compared to placebo or standard care alone for individuals with moderate to severe disease; [Summary of findings 2](#) Summary of Findings Table - Convalescent plasma compared to standard plasma for individuals with moderate to severe disease; [Summary of findings 3](#) Summary of Findings Table - Convalescent plasma compared to placebo or standard care alone for individuals with mild disease

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

We present the summary of findings and the certainty of the evidence for our prioritised outcomes for individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease in [Summary of findings 1](#) and [Summary of findings 2](#). [Summary of findings 1](#) includes the comparison of convalescent plasma versus placebo or standard care alone. [Summary of findings 2](#) includes the comparison of convalescent plasma versus standard plasma. We assessed disease severity with the need for respiratory support according to the WHO clinical progression scale ([WHO 2020e](#)).

We have not yet identified any completed studies on hyperimmune immunoglobulins, but continue to closely monitor ongoing studies (see [Table 4](#)).

Effectiveness of convalescent plasma

Prioritised outcomes (included in the 'Summary of findings' table)

All-cause mortality

We assessed all-cause mortality at day 28, day 60, time-to-event, and at hospital discharge.

Convalescent plasma versus placebo or standard care alone

Eight studies reported all-cause mortality for 12,550 participants. Considering the reported event rates across studies, we estimated that 237 of 1000 participants die at up to 28 days when treated with placebo or standard care alone. Treatment with convalescent plasma results in little to no difference in all-cause mortality at up to day 28 (RR 0.98, 95% CI 0.92 to 1.05; 233 per 1000; 7 studies, 12,646 participants; $I^2 = 0\%$; high-certainty evidence; [Analysis 1.1](#)); when measured over time (HR 0.99, 95% CI 0.92 to 1.07; 5 studies, 11,827 participants; $I^2 = 0\%$; [Analysis 1.2](#)); or at hospital discharge (RR 0.90, 95% CI 0.53 to 1.53; 3 studies, 577 participants; $I^2 = 18\%$; [Analysis 1.3](#)). All-cause mortality at day 60 was not reported in any study.

Subgroup analyses

Severity of disease

We identified no evidence for a difference in the effectiveness of convalescent plasma with regard to all-cause mortality for people with moderate disease (WHO score 4-5) or severe disease (WHO score ≥ 6), according to the WHO Clinical Progression Scale ([WHO 2020e](#)); see [Analysis 1.1](#); [Analysis 1.2](#); [Analysis 1.3](#).

Duration since symptom onset

We identified no evidence for a difference in the effectiveness of convalescent plasma with regard to the duration since symptom onset; see [Analysis 4.1](#).

Antibodies in recipients detected at baseline

We identified no evidence for a difference in the effectiveness of convalescent plasma with regard to the detection of antibodies in the recipients at baseline; see [Analysis 5.1](#).

Other subgroups

We could not perform any other of our planned subgroup analyses for the comparison of convalescent plasma versus standard plasma and the outcome all-cause mortality. We had planned to investigate

potential differences in the age of participants (children; age 18 to 65 years; and age 65 years and older), but none of the studies performed subgroup analyses, using our cut-offs. [Horby 2021](#) reported subgroup analyses for participants up to 70 years of age, 70 to 79 years of age, and 80 years or older, and did not identify any evidence for a difference. [Ray 2020](#) reported subgroup analyses for participants up to 67 years of age, and 67 years or older, and noted a potential survival benefit for the younger age group when receiving convalescent plasma. However, the study size was small (80 participants) and it was unclear how many participants informed subgroup analyses.

In addition to our pre-planned subgroup analyses, [Horby 2021](#) conducted further analyses for the following characteristics: sex, ethnicity, respiratory support received, and use of corticosteroids. The principal investigators did not identify evidence for a difference for any of the performed subgroup analyses.

Sensitivity analyses

We summarised the effects of sensitivity analyses in [Table 6](#). Reported effects of our main analysis were robust when removing studies at high risk of bias, preprint articles, or studies that were stopped early.

Convalescent plasma versus standard plasma

Two studies reported all-cause mortality for 252 participants. Considering the reported event rates within the study, we estimated that 216 of 1000 participants die at up to 28 days when treated without convalescent plasma. We are uncertain about the effect of convalescent plasma on all-cause mortality at up to day 28 when compared to standard plasma (RR 0.95, 95% CI 0.17 to 5.29; 205 per 1000; $I^2 = 62\%$, very low-certainty evidence, see [Analysis 2.1](#)). Our main reasons for downgrading were serious inconsistency because direction of effect was not consistent in both studies, and very serious imprecision due to few participants, few events, and wide confidence intervals. All-cause mortality at day 60, over time, or at hospital discharge were not reported in the study.

Subgroup analyses

We could not perform any of our planned subgroup analyses for the comparison of convalescent plasma versus standard plasma and the outcome all-cause mortality.

Sensitivity analyses

We could not perform any of our planned sensitivity analyses for the comparison of convalescent plasma versus standard plasma and the outcome all-cause mortality.

Clinical status

We assessed the clinical status of participants by the need for respiratory support in accordance with standardised scales (e.g. WHO Clinical Progression Scale ([WHO 2020e](#)), WHO Ordinal Scale for Clinical Improvement ([WHO 2020f](#))) at up to day 28, day 60, and up to longest follow-up). We targeted outcomes that were included in this domain to subgroups of our population to assess clinical improvement and clinical worsening (see Types of outcome measures).

Convalescent plasma versus placebo or standard care alone

Reporting of the clinical status or progression of disease was very heterogeneous across studies. We summarised all reported or additionally received data per study in [Table 7](#).

Improvement of clinical status

The reported evidence in all eight studies (12,682 participants) did not suggest any differences in the odds for clinical improvement or time to clinical improvement when assessed by liberation from respiratory support (high-certainty evidence, see [Table 7](#)).

One study ([Gharbharan 2020](#)), reporting on 77 participants, provided sufficient data to calculate a relative effect estimate for our predefined outcome 'liberation from supplemental oxygen' for the subgroup of participants that received any supplemental oxygen or ventilator support (i.e. WHO \geq 5). Considering the reported event rates within the study, we estimated that 614 of 1000 participants had the chance to be liberated from supplemental oxygen when treated with placebo or standard care alone. Evidence suggests little to no difference in the chance of being liberated from supplemental oxygen when treated with convalescent plasma (RR 1.10, 95% CI 0.81 to 1.48; 675 per 1000; low-certainty evidence, [Analysis 1.4](#)). Our main reasons for downgrading were very serious imprecision due to few participants, and very wide confidence intervals.

Two studies reported weaning or liberation from invasive mechanical ventilation in surviving patients for 630 participants; the subgroup of participants that were ventilated at baseline (i.e. WHO \geq 7). Considering the reported event rates across studies, we estimated that 362 of 1000 participants had the chance to be weaned or liberated from invasive mechanical ventilation when treated without convalescent plasma. Evidence suggests that treatment with convalescent plasma may have little to no impact on being weaned or liberated from invasive mechanical ventilation (RR 1.04, 95% CI 0.57 to 1.93; 377 per 1000; $I^2 = 75\%$; low-certainty evidence, [Analysis 1.5](#)). Our main reasons for downgrading were serious inconsistency because direction of effect was not consistent in both studies, and serious imprecision due to few participants, and wide confidence intervals.

Worsening of clinical status

Four studies reported the need for invasive mechanical ventilation for 11,765 participants. Considering the reported event rates within the study, we estimated that 126 of 1000 participants had a need for invasive mechanical ventilation when treated without convalescent plasma. Evidence suggests that treatment with convalescent plasma results in little to no difference in the need for invasive mechanical ventilation when compared to no convalescent plasma (RR 0.98, 95% CI 0.89 to 1.08; 123 per 1000; $I^2 = 0\%$; high-certainty evidence, [Analysis 1.6](#)). Need for non-invasive mechanical ventilation or high-flow oxygen and need for oxygen by mask or nasal prongs were not reported in any study, in the way that we had defined the outcomes.

Subgroup analyses

Severity of disease

We identified no evidence for a difference in the effectiveness of convalescent plasma with regard to the need for invasive mechanical ventilation for people with moderate disease (WHO score 4-5), according to WHO Clinical Progression Scale ([WHO](#)

[2020e](#)), when compared to the main analysis that also included participants with more severe disease, receiving non-invasive ventilation or high-flow oxygen at baseline (WHO score 6); see [Analysis 1.6](#).

Other subgroups

We could not perform any other of our planned subgroup analyses for the comparison of convalescent plasma versus standard plasma for any outcome summarised under 'clinical status'.

Sensitivity analyses

We summarised the effects of sensitivity analyses in [Table 6](#). Reported effects of our main analysis for the outcome need for invasive mechanical ventilation were robust when removing studies preprint articles. We did not include any studies at high risk of bias, or studies that were stopped early in the main analysis of this outcome.

Convalescent plasma versus standard plasma

Reporting of the clinical status or progression of disease was heterogeneous across studies. We summarised reported data per study in [Table 7](#).

Improvement of clinical status

Both studies assessed improvement of clinical status with the need for respiratory support or oxygenation indices (see [Table 7](#)). The reported evidence in both studies was of very low-certainty and we do not know whether convalescent plasma has any effect on clinical improvement. Our main concerns were serious indirectness because definition of outcomes differed from the definitions used in our review, and very serious imprecision because of few participants and few events.

Worsening of clinical status

One study reported the need for invasive mechanical ventilation for 29 participants ([Bajpai 2020](#)). Considering the reported event rates within the study, we estimated that 67 of 1000 participants had a need for invasive mechanical ventilation when treated with standard plasma. Evidence is uncertain whether treatment with convalescent plasma increases the need for invasive mechanical ventilation when compared to standard plasma (RR 3.21, 95% CI 0.38 to 27.40; 214 per 1000; low-certainty evidence; [Analysis 2.2](#)). Our main reasons for downgrading were very serious imprecision due to few participants, few events, and very wide confidence intervals. Need for non-invasive mechanical ventilation or high-flow oxygen and need for oxygen by mask or nasal prongs were not reported in any study.

Subgroup analyses

We could not perform any of our planned subgroup analyses for the comparison of convalescent plasma versus standard plasma for any outcome summarised under 'clinical status'.

Sensitivity analyses

We could not perform any of our planned sensitivity analyses for the comparison of convalescent plasma versus standard plasma for any outcome summarised under 'clinical status'.

Quality of life

We had planned to assess quality of life, including fatigue and neurological functioning of participants, if assessed with standardised scales (e.g. WHOQOL-100) for the following time points: at up to 7 days, up to 30 days, and longest follow-up available. However we did not identify any studies reporting quality of life on a standardised scale.

Convalescent plasma versus placebo or standard care alone

None of the identified studies reported quality of life on a standardised scale. One study ([Agarwal 2020](#), reporting on 309 participants) assessed resolution of fatigue on day 7 (RR 1.21, 95% CI 1.02 to 1.42, estimated absolute effect with convalescent plasma: 727 of 1000 with symptom resolution, very low-certainty evidence). We do not know whether convalescent plasma has any impact on quality of life, and are very uncertain about the effect on resolution of fatigue. Our main reasons for downgrading were very serious indirectness and serious imprecision, because only one symptom impacting quality of life was assessed, the outcome was not measured on a standardised scale, after a short observation period, and only for few participants.

Convalescent plasma versus standard plasma

We did not identify any study reporting this outcome.

Additional outcomes (not included in the 'Summary of findings' table)

Duration of hospitalisation, or time to discharge from hospital

Convalescent plasma versus placebo or standard care alone

Mean duration of hospitalisation was not reported in any study. Five studies reported time to discharge from hospital for 683 participants. Evidence suggests that more people treated with convalescent plasma may be discharged earlier than people treated without convalescent plasma (HR 1.15, 95% CI 0.95 to 1.40; $I^2 = 17.6%$; [Analysis 1.7](#)).

Convalescent plasma versus standard plasma

One study reported duration of hospitalisation for 29 participants ([Bajpai 2020](#)). The study reported a mean duration of hospitalisation of 12.1 days (SD 4.1) in the convalescent plasma group and 16.1 days (SD 5.6) in the standard plasma group (MD -4.00, 95% CI -7.56 to -0.44; [Analysis 2.3](#)). Time to discharge from hospital was not reported in any study.

Admission to the ICU

Convalescent plasma versus placebo or standard care alone

One study reported admission to the ICU for 333 participants ([Simonovich 2020](#)). Evidence suggests that fewer people treated with convalescent plasma may have to be admitted to the ICU (RR 0.90, 95% CI 0.74 to 1.09; [Analysis 1.8](#)).

Convalescent plasma versus standard plasma

We did not identify any study reporting this outcome.

Length of stay on the ICU, or time to discharge from ICU

Convalescent plasma versus placebo or standard care alone

We did not identify any study reporting this outcome.

Convalescent plasma versus standard plasma

We did not identify any study reporting this outcome.

Viral clearance

We included data of viral clearance if assessed with RT-PCR test for SARS-CoV-2 for the following time points: at baseline, up to 3, 7, and 15 days.

Convalescent plasma versus placebo or standard care alone

Four studies reported viral clearance for 552 participants. Evidence suggests that more people treated with convalescent plasma may achieve viral clearance at up to day 3 (RR 1.73, 95% CI 0.98 to 3.04; 4 studies, 552 participants; $I^2 = 76%$; [Analysis 1.9](#)) day 7 (RR 1.55, 95% CI 0.99 to 2.43; 3 studies, 485 participants; $I^2 = 75%$; [Analysis 1.10](#)), and day 15 (RR 1.59, 95% CI 0.74 to 3.43; 2 studies, 129 participants; $I^2 = 83%$; [Analysis 1.11](#)).

Convalescent plasma versus standard plasma

We did not identify any study reporting this outcome.

Need for dialysis

Convalescent plasma versus placebo or standard care alone

One study reported the need for dialysis for 11,442 participants ([Horby 2021](#)). Evidence suggests little to no difference between participants receiving convalescent plasma or not (RR 1.03, 95% CI 0.87 to 1.22; [Analysis 1.12](#)).

Convalescent plasma versus standard plasma

We did not identify any study reporting this outcome.

Safety of convalescent plasma

In addition to RCT data, we included data from controlled NRSIs, and non-controlled NRSIs for safety outcomes, if the study was prospectively registered and reported on 500 or more participants receiving convalescent plasma.

Adverse events

We defined the outcome as the number of participants with any event and were interested in events of any grade, grade 1-2, and grade 3-4. We summarised data, including the potential relationship between intervention and adverse reaction, as reported in the primary studies in [Table 8](#).

Convalescent plasma versus placebo or standard care alone

One study reported any grade adverse events for both groups and a total of 333 participants ([Simonovich 2020](#)). Considering the reported event rates across studies, we estimated that 629 of 1000 participants experience any adverse event when treated without convalescent plasma. Evidence suggests little to no difference in the occurrence of any adverse events when treated with convalescent plasma (RR 1.06, 95% CI 0.89 to 1.26; 667 per 1000; [Analysis 1.13](#)).

Four RCTs reported grade 3 or 4 events for both groups and a total of 905 participants. Considering the reported event rates across studies, we estimated that 64 of 1000 participants experience a grade 3 or 4 adverse event when treated without convalescent

plasma. We are uncertain whether convalescent plasma reduces or increases the risk of grade 3 and 4 adverse events (RR 0.90, 95% CI 0.58 to 1.41; 57 per 1000; $I^2 = 0\%$; low-certainty evidence, [Analysis 1.14](#)). Our main reasons for downgrading were serious imprecision due to few participants, wide confidence intervals, and suspected publication bias, because most studies assessed and reported transfusion-related events only; i.e. reported safety data only for the intervention group.

Grade 1-2 adverse events were not reported in any study in a way that we could pool data. We summarised any reported adverse reactions in [Table 8](#), including potential relationships between events and transfusion.

Subgroup analyses

Severity of disease

All studies included in the main analysis for the outcome grade 3 or 4 adverse events, included participants with moderate disease (WHO score 4-5), according to WHO Clinical Progression Scale ([WHO 2020e](#)); see [Analysis 1.14](#). We could therefore not investigate subgroup differences between participants with moderate and severe disease.

Other subgroups

We could not perform any other of our planned subgroup analyses for the comparison of convalescent plasma versus standard plasma for any outcome summarised adverse events.

Sensitivity analyses

We summarised the effects of sensitivity analyses in [Table 6](#). Reported effects of our main analysis for the outcome grade 3 or 4 adverse events were robust when removing studies preprint articles. We did not include any studies at high risk of bias, or studies that were stopped early in the main analysis of this outcome.

Convalescent plasma versus standard plasma

One study reported any grade adverse events for both groups and a total of 219 participants ([O'Donnell 2021](#)). Considering the reported event rates across studies, we estimated that 556 of 1000 participants experience any adverse event when treated without convalescent plasma. Evidence suggests an increase of any adverse events when treated with convalescent plasma (RR 1.18, 95% CI 0.93 to 1.49; 656 per 1000; very low-certainty evidence; [Analysis 2.4](#)). None of the studies reported the number of participants experiencing any grade 1 or 2, or grade 3 or 4 adverse events. However, [O'Donnell 2021](#) reported the number of participants experiencing grade 1, 2, 3, and 4 events, respectively (see [Table 8](#)). We are very uncertain whether or whether not convalescent plasma increases the risk of grade 3 or 4 adverse events, when compared to standard plasma. Our main concerns were serious indirectness because definition of outcomes differed from the definitions used in our review, and very serious imprecision because of few participants and few events.

Both studies further reported incidence of transfusion-related events. [Bajpai 2020](#) reported that one participant per group (14 participants in convalescent plasma group, and 15 participants in standard plasma group) experienced a mild transfusion

reaction; [O'Donnell 2021](#) reported that four of 147 participants in the convalescent plasma group, and two of 72 participants in the standard plasma group, experienced events that were probably or definitely transfusion-related (see [Table 8](#)).

Convalescent plasma (no comparison)

We did not identify any study that matched our inclusion criteria and reported this outcome.

Serious adverse events

We defined the outcome as the number of participants with any event. Two RCTs (414 participants) reported serious adverse events for both groups. Further, four RCTs (6125 participants in convalescent plasma groups) reported on serious adverse events only in participants who received convalescent plasma, with no reporting in the control group. One of the included studies was a single-arm expanded access study, reporting safety data for 20,000 of 35,322 transfused participants ([Joyner 2020](#)). A detailed report of the observed events of the five RCTs and the expanded access study is provided in [Table 9](#), including potential relationships between events and transfusion.

Convalescent plasma versus placebo or standard care alone

Considering the reported event rates reported across the control groups of the two RCTs, we estimated that 176 of 1000 participants experience a serious adverse event when treated without convalescent plasma. Convalescent plasma may or may not result in an increase of serious adverse events (RR 1.24, 95% CI 0.81 to 1.90; 218 per 1000; 2 studies, 414 participants; $I^2 = 0\%$; low-certainty evidence, [Analysis 1.15](#)). Our main reasons for downgrading were serious imprecision due to few participants, and wide confidence intervals, and suspected publication bias because most studies assessed and reported transfusion-related events only; i.e. reported safety data only for the intervention group.

Subgroup analyses

Severity of disease

Both studies included in the main analysis for the outcome serious adverse events, included participants with moderate disease (WHO score 4-5), according to WHO Clinical Progression Scale ([WHO 2020e](#)); see [Analysis 1.15](#). We could therefore not investigate subgroup differences between participants with moderate and severe disease.

Other subgroups

We could not perform any other of our planned subgroup analyses for the comparison of convalescent plasma versus standard plasma for any outcome summarised adverse events.

Sensitivity analyses

We summarised the effects of sensitivity analyses in [Table 6](#). Reported effects of our main analysis for the outcome grade 3 or 4 adverse events were robust when removing studies preprint articles. We did not include any studies at high risk of bias, or studies that were stopped early in the main analysis of this outcome.

Convalescent plasma versus standard plasma

One study reported serious adverse events for both groups and a total of 219 participants (O'Donnell 2021). Considering the reported event rates across studies, we estimated that 316 of 1000 participants experience any serious adverse event when treated without convalescent plasma. Treatment with convalescent plasma may decrease the risk of serious adverse events when compared to standard plasma (RR 0.73, 95% CI 0.49 to 1.11; 246 per 1000, see Analysis 2.5), but the evidence is uncertain. Our main reasons for downgrading were very serious imprecision because of few participants and few events.

Convalescent plasma without a comparison

Agarwal 2020 (227 participants, intervention arm from the included RCT) reported that three observed deaths in the convalescent plasma group could be related to the transfusion. Gharbharan 2020 (43 participants, intervention arm from the included RCT) did not observe any serious transfusion-related adverse events. Horby 2021 (5795 participants, intervention arm from the included RCT) assessed serious adverse events according to SHOT (serious hazards of transfusion), and reported that 13 transfused individuals experienced at least one event. Joyner 2020 reported safety data for 20,000 of 35,322 transfused participants from an ongoing USA FDA 'Expanded Access Program'. The study authors evaluated the incidence of serious adverse events in the first four hours after convalescent plasma transfusion, and additionally, within seven days after transfusion. Overall, 1282 events were reported, 146 of which occurred during the first four hours of observation, and 1136 additional events occurred within seven days after transfusion of convalescent plasma. Li 2020 (52 participants, intervention arm from the included RCT) mentioned that one participant suffered from shortness of breath, cyanosis, and severe dyspnoea within six hours of convalescent plasma transfusion, which they classified as possible severe transfusion-associated dyspnoea (TAD). After medical treatment, the symptoms gradually improved over two hours.

Reporting of serious adverse events was variable across the included studies. The duration of follow-up for observation of serious adverse events varied across all studies. Some, but not all, studies included death as a serious adverse event. In addition, it was difficult to ascertain whether some of the adverse events were related to convalescent plasma transfusion, or due to underlying disease or other treatments, or both. There was insufficient evidence to determine whether convalescent plasma therapy results in a clinically relevant increased risk of serious adverse events and our certainty in the evidence is low.

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

In Summary of findings 3 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) for individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease, and the comparison of convalescent plasma versus placebo or standard care alone.

We did not identify any completed studies on hyperimmune immunoglobulins, yet, but monitor ongoing studies closely (see Table 4).

Effectiveness of convalescent plasma

One study included and analysed individuals with asymptomatic or mild disease (Libster 2020). The included study did not provide all the data on the effectiveness of the intervention in accordance with our pre-specified outcomes.

Prioritised outcomes (included in the 'Summary of findings' table)

All-cause mortality

We assessed all-cause mortality at day 28, day 60, time-to-event, and at longest follow-up available. One RCT reported mortality at an undefined time point, including 160 participants, from which 2 out of 80 participants had died due to COVID-19 in the convalescent plasma group and 4 out of 80 participants in the comparison group (Libster 2020). We are very uncertain about the effect of convalescent plasma on all-cause mortality when compared to placebo or standard care alone (RR 0.50, 95% CI 0.09 to 2.65; very low-certainty evidence, Analysis 3.1). Our main reasons for downgrading were serious indirectness and very serious imprecision, because the study investigators defined the outcome as deaths associated with COVID-19, and may not have reported other causes of mortality; and because we only identified one study with few participants and few events.

Development of moderate to severe clinical COVID-19 symptoms

We defined moderate and severe clinical COVID-19 symptoms according to the WHO clinical progression scale (WHO 2020e).

Development of severe disease

We assessed this outcome by the need for invasive mechanical ventilation, non-invasive mechanical ventilation or high flow (i.e. score 6 or higher on WHO clinical progression scale, WHO 2020e). Need for invasive mechanical ventilation was reported by one RCT (Libster 2020), including 160 participants, from which 2 out of 80 participants developed the need for invasive mechanical ventilation in the convalescent plasma group compared to 4 out of 80 participants in the comparison group (RR 0.50, 95% CI 0.09 to 2.65; Analysis 3.2). The study authors further reported the risk for developing severe respiratory disease (RR 0.52, 95% CI 0.29 to 0.94), or critical illness with life-threatening disease (RR 0.83, 95% CI 0.27 to 2.62), see Table 7. We are uncertain about the effect of convalescent plasma on the development of severe clinical symptoms when compared to placebo or standard care alone (very-low certainty). Our main reason for downgrading was very serious imprecision due to few events and the small information size.

Development of moderate disease

We assessed this outcome by the need for hospitalisation with supplemental oxygen by mask or nasal prongs or without oxygen therapy (i.e. scores 4 and 5 on WHO clinical progression scale, WHO 2020e). We did not identify any study reporting this outcome.

Quality of life

We did not identify any study reporting this outcome.

Additional outcomes (not included in the 'Summary of findings' table)

Admission to hospital

Libster 2020 recruited all participants via home visits but admitted all for observational purposes at study enrolment to

the hospital. We did not identify any other study reporting this outcome.

Time to symptom onset

We did not identify any study reporting this outcome.

Length of hospital stay (for hospitalised patients)

We did not identify any study reporting this outcome.

Admission to the intensive care unit (ICU)

This outcome was reported by one RCT (Libster 2020), including 160 participants, from which 2 out of 80 participants were admitted to the intensive care unit in the convalescent plasma group and 6 out of 80 participants were admitted to ICU in the comparison group. Convalescent plasma therapy may decrease the rate of ICU admissions when compared to placebo treatment or standard care alone (RR 0.33, 95% CI 0.07 to 1.60; see Analysis 3.3), but the evidence is very uncertain.

Viral clearance (assessed with RT-PCR)

We did not identify any study reporting this outcome.

Safety of convalescent plasma

In addition to RCT data, we had planned to include data from controlled NRSIs, and non-controlled NRSIs for safety outcomes, if the study was prospectively registered and reported on 500 or more participants receiving convalescent plasma. However, we did not identify any non-randomised study matching our inclusion criteria for individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease.

Adverse events

We defined the outcome as the number of participants with any event and were interested in events of any grade, grade 1-2, and grade 3-4. We summarised data, including the potential relationship between intervention and adverse reaction, as reported in the primary study, in Table 8.

One study reported that convalescent plasma was not associated with any solicited adverse events (Libster 2020). Because the definition was unclear whether only drug-related adverse events were assessed, and we did not receive additional information from the study investigators, we did not include this outcome in analysis. We do not know whether convalescent plasma is associated with a higher risk for adverse events (very low-certainty evidence).

We identified no study reporting adverse events of any grade, grade 1-2, or grade 3-4.

Serious adverse events

One study reported that convalescent plasma was not associated with any solicited serious adverse events (Libster 2020). Because the definition was unclear whether only drug-related serious adverse events were assessed, and we did not receive additional information from the study investigators, we did not include this outcome in analysis. We do not know whether convalescent plasma is associated with a higher risk for serious adverse events (very low-certainty evidence).

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 COVID-19. This is the fourth version of our living systematic review.

We identified 12 RCTs (Agarwal 2020; AlQahtani 2020; Avendano-Sola 2020; Bajpai 2020; O'Donnell 2021; Gharbharan 2020; Hamdy Salman 2020; Horby 2021; Li 2020; Libster 2020; Ray 2020; Simonovich 2020), and one non-controlled NRSI (Joyner 2020). The studies evaluated 48,509 participants, of whom 41,880 received convalescent plasma. We did not identify any completed studies that evaluated hyperimmune immunoglobulin. We identified a further 100 ongoing studies evaluating convalescent plasma or hyperimmune immunoglobulin. We also identified 24 completed but not yet published studies, one study not yet completed but terminated early for futility, two studies where expanded access is no longer available but without results published yet and four completed studies with full texts in our weekly searches after the submission of the current review version, that we categorised as 'Awaiting classification', as well as two platform trials that we have placed in that category.

Risk of bias

Among those studies reporting a mortality outcome, we judged the risk of bias to be of some concern for three RCTs (Agarwal 2020; AlQahtani 2020; Gharbharan 2020) and high for one RCT (Ray 2020). Among those studies reporting at least one of the outcomes addressing clinical status and progression of disease, the risk of bias was of some concern for two RCTs (Agarwal 2020; Gharbharan 2020). As none of the studies reported quality of life, we could not assess the risk of bias for this outcome. The risk of bias of safety outcomes was of some concern for two RCTs (Agarwal 2020; AlQahtani 2020).

For safety outcomes, we also included and assessed non-controlled NRSIs. 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 the study to be low (Joyner 2020).

Effects of interventions

Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease

Eleven RCTs and one NRSI investigated the use of convalescent plasma for 48,349 participants with moderate to severe disease, of which nine RCTs compared convalescent plasma to placebo or standard care alone, and two compared convalescent plasma to standard plasma.

Effectiveness of convalescent plasma

We included data on all RCTs (13,127 participants) to assess effectiveness of convalescent plasma. Nine RCTs (12,875 participants) compared convalescent plasma to placebo or standard care alone, and two RCTs (252 participants) compared convalescent plasma to standard plasma.

Convalescent plasma versus placebo or standard care alone

Convalescent plasma does not reduce all-cause mortality at up to day 28 (RR 0.98, 95% CI 0.92 to 1.05; 7 RCTs, 12,646 participants; high-certainty evidence), it has little to no impact on clinical improvement when assessed by liberation from respiratory support (RR not estimable; 8 RCTs, 12,682 participants; high-certainty evidence) for all participants, or on the chance of being weaned or liberated from invasive mechanical ventilation for the subgroup of participants requiring invasive mechanical ventilation at baseline (RR 1.04, 95% CI 0.57 to 1.93; 2 RCTs, 630 participants; low-certainty evidence), and does not reduce the need for invasive mechanical ventilation (RR 0.98, 95% CI 0.89 to 1.08; 4 RCTs, 11,765 participants; high-certainty evidence). We identified no subgroup differences.

We did not identify any studies reporting quality of life, and therefore, do not know whether convalescent plasma has any impact on quality of life. One RCT (309 participants) assessed resolution of fatigue on day 7, but we are very uncertain about the effect (RR 1.21, 95% CI 1.02 to 1.42; very low-certainty evidence).

Convalescent plasma versus standard plasma

We do not know whether convalescent plasma has any effect on all-cause mortality at up to day 28 (RR 0.95, 95% CI 0.17 to 5.29; 2 RCTs, 252 participants; very low-certainty evidence), and clinical improvement (RR not estimable; 2 RCTs, 252 participants; very low-certainty evidence). Convalescent plasma may increase the need for invasive mechanical ventilation (RR 3.21, 95% CI 0.38 to 27.40; 1 RCT, 29 participants; low-certainty evidence).

No study reported quality of life.

Safety of convalescent plasma

We included results from eight RCTs, and one NRSIs assessing safety of convalescent plasma. Reporting of safety data and duration of follow-up was variable. Some of the RCTs reported on adverse events and serious adverse events only in participants receiving convalescent plasma. Some, but not all, studies included death as a serious adverse event.

Convalescent plasma versus placebo or standard care alone

We are uncertain whether convalescent plasma increases or reduces the risk of grade 3 and 4 adverse events (RR 0.90, 95% CI 0.58 to 1.41; 4 RCTs, 905 participants; low-certainty evidence), and serious adverse events (RR 1.24, 95% CI 0.81 to 1.90; 2 RCTs, 414 participants; low-certainty evidence), when compared to placebo treatment or standard care alone.

Convalescent plasma versus standard plasma

We are very uncertain whether or not convalescent plasma increases the risk for grade 3 or 4 adverse events (very low-certainty evidence), because the identified studies did not report the number of participants experiencing any grade 3 or 4 adverse event. One study (219 participants) reported the number of participants experiencing any event of grade 3 (27/147 in convalescent plasma group versus 17/72 in standard plasma group), or grade 4 (26/147 in convalescent plasma group versus 15/72 in standard plasma group). The study also reported the number of participants experiencing at least one event of any grade (96/147 in convalescent plasma group versus 40/72 in standard plasma group, RR 1.18, 95% CI 0.93 to 1.49). Both identified studies reported on

observed transfusion-related events, with no severe side effects observed in one study (reporting on 29 participants); 4/147 in convalescent plasma group versus 3/72 in standard plasma group in the other study).

Convalescent plasma may decrease the risk of serious adverse events (RR 0.73, 95% CI 0.49 to 1.11; 1 RCT, 219 participants; low-certainty evidence).

Convalescent plasma (no comparison)

We included data of one NRSI (reporting safety data for 20,000 of 35,322 transfused participants), and four RCTs reporting safety data only for participants that received convalescent plasma (6125 participants). The NRSI reported on SAEs within the first four hours and within an additional seven days after transfusion. There were 63 deaths, 12 were possibly related and one was probably related to transfusion. There were 146 SAEs within four hours and 1136 SAEs within seven days post-transfusion. These were predominantly allergic or respiratory, thrombotic or thromboembolic and cardiac events. The four RCTs observed severe or serious transfusion-related adverse events in 0 to 1.3% of participants receiving convalescent plasma, including severe transfusion-associated dyspnoea, and probably-transfusion-related deaths.

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease

We identified one RCT reporting on 160 participants, and comparing convalescent plasma to placebo treatment (saline).

Effectiveness of convalescent plasma

We are very uncertain about the effect of convalescent plasma on all-cause mortality (RR 0.50, 95% CI 0.09 to 2.65; very low-certainty evidence). Convalescent plasma may decrease the risk for developing severe clinical COVID-19 symptoms (RR not estimable; low-certainty evidence), but the evidence is uncertain.

We identified no study reporting quality of life.

Safety of convalescent plasma

The identified study reported solicited adverse events only and reported that none have been observed in either group. We do not know whether convalescent plasma is associated with a higher risk of grade 3 or 4 adverse events (very low-certainty evidence), or serious adverse events (very low-certainty evidence).

Overall completeness and applicability of evidence

We identified 12 RCTs, and one NRSI (for safety outcomes only), evaluating convalescent plasma in adults. These studies included 48,509 participants, of whom 41,880 received convalescent plasma. Most of the participants had also received different treatment options, including antivirals, antimicrobials, corticosteroids, hydroxychloroquine, respiratory support (extracorporeal membrane oxygenation, mechanical ventilation or oxygen), or a combination of those.

Eleven RCTs and the NRSI investigated the use of convalescent plasma for moderately to severely ill individuals, of which nine RCTs compared convalescent plasma to placebo treatment or standard care alone, and two compared convalescent plasma to standard plasma. We included data of all RCTs (13,127 participants) to

assess effectiveness of convalescent plasma therapy for individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease. We have high certainty in the evidence that treatment with convalescent plasma does not reduce all-cause mortality at up to 28 days, and has little to no impact on clinical improvement when compared to placebo treatment or standard care alone. We have low certainty about the effect of convalescent plasma on all-cause mortality at up to 28 days, and clinical improvement when compared to treatment with standard plasma. Not all of the included RCTs reported adverse events for the control arm. One large, non-controlled NRSI provided serious adverse events data (reported data for 20,000 of 35,322 transfused participants) within seven days after convalescent plasma transfusion. Convalescent plasma therapy may result in a clinically relevant increased risk of serious adverse events, when compared to treatment with placebo or standard care alone (low-certainty evidence). When compared to standard plasma, convalescent plasma therapy may result in a decreased risk of serious adverse events. The evidence for grade 3 and 4 adverse events is uncertain, but treatment with convalescent plasma therapy may result in a slight reduction of grade 3 and 4 adverse events (low-certainty evidence). None of the studies comparing convalescent and standard plasma therapy reported other than transfusion-related grade 3 or 4 adverse events.

The remaining RCT (160 participants) investigated the efficacy and safety of convalescent plasma compared to placebo treatment for individuals with pre-existing co-morbidities and mild symptoms. We are uncertain about the effect of convalescent plasma therapy on all-cause mortality (very-low certainty), the risk for developing severe clinical COVID-19 symptoms (low-certainty evidence), or the risk for experiencing severe or serious adverse events (very low-certainty evidence).

We identified 31 studies (28 RCTs, two expanded access studies and one NRSI with a planned enrolment of 600 participants) that were completed, terminated or no longer available as expanded access according to the trials registry entry. Of these, we identified the full texts of four studies in our weekly searches, after we submitted this version of the review. We have categorised these studies as 'Awaiting classification'. We will include them in the next version of this living systematic review. For the remaining studies, no outcome data were yet available; study investigators did not reply to our requests, or contact details of principal investigators were not reported in the trials registry. In addition, we identified two platform trials, which do not include our intended interventions. However, we wish to keep track of them, in the event that they may add arms on convalescent plasma or hyperimmune immunoglobulins. Therefore, we categorised these as 'Awaiting classification'. We will consider including them in an update of this review, once results are available.

We identified 100 ongoing studies, of which 85 are RCTs, seven are expanded access studies from the USA, two are single-arm studies, two are non-randomised controlled studies and four are pre-registered observational studies. Of the ongoing studies, 90 are assessing the benefits and safety of convalescent plasma therapy for the treatment of COVID-19 and ten studies are assessing the benefits and safety of hyperimmune immunoglobulins for the treatment of COVID-19.

Certainty of the evidence

We included data of nine RCTs to assess effectiveness and safety of convalescent plasma for individuals with a confirmed diagnosis of COVID-19 disease and moderate to severe symptoms when compared to treatment with placebo or standard care alone. We had high certainty in the identified evidence for effectiveness outcomes, and very low- to low certainty in the identified evidence for safety outcomes. Our main concerns were that safety outcomes were assessed and reported in most studies for the convalescent plasma group only, indicating selective reporting and publication bias and serious imprecision due to the small information size with comparative evidence.

We included data of two RCTs to assess effectiveness and safety of convalescent plasma for individuals with a confirmed diagnosis of COVID-19 disease and moderate to severe symptoms when compared to treatment with standard plasma. We had very low- to low certainty in the identified evidence. Our main concerns were serious inconsistency for mortality outcomes, and very serious imprecision due to the small information size, and wide confidence intervals for mortality, and safety outcomes, as well as clinical worsening.

We included data of one RCT to assess effectiveness and safety of convalescent plasma for individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease when compared to treatment with placebo or standard care alone. We had very-low to low certainty in the identified evidence. Our main concerns were very serious imprecision due to the small information size and serious indirectness for mortality and safety outcomes, because reported outcomes did not precisely match our outcome definition.

Potential biases in the review process

To avoid potential biases in the review process, we had planned to include the best available evidence and adhered to the guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019a) in any step of the review. However, as COVID-19 is a novel disease, high quality evidence is still rare, although more RCTs became available since the last update (Chai 2020). For this update, we were able to include 12 RCTs and one non-controlled NRSI. To increase the informative value of our review, we are tracking all registered trials and will continually update this review as more evidence becomes available. There are currently still many new trials being registered in trials registries, as can be seen from the additional 86 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.

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 investigated robustness of our analysis results in sensitivity analyses.

The necessary adaptation of review methods to the development of research output, as described in Table 1, is in general a potential

source of bias in the review process. Since the available evidence changed rapidly in a comparably short period of time in the COVID-19 pandemic, we needed to take this approach to give a comprehensive answer to the review question. Before starting with an update process, our interdisciplinary team of review authors meets to review the methods and to discuss necessary amendments. We follow the methods we agree upon, before starting with the update, and adhere to these decisions throughout each update process.

For this review update, we introduced separate analyses for ambulatory and hospitalised participants because of clinical heterogeneity between people with asymptomatic to mild symptoms, and people with moderate to severe symptoms. Furthermore, we added in the first version of this review (Valk 2020) that studies with the intervention 'standard immunoglobulin' will be excluded and 'standard immunoglobulin' and 'standard plasma' were added as eligible control treatments because of substantial biological differences of these treatment options, compared to the eligible interventions. We do not think that the bias arising from these adaptations was substantial, since these changes were driven by objective reasons.

For changes in outcomes and outcome measurement, we specified and redefined the outcome 'clinical status (assessed by need for respiratory support)' from self-set cut-offs until version 2 of this review (Piechotta 2020b) to standardised scales (WHO 2020e; WHO 2020f) from version 3 (Chai 2020) onward, as they became available later in the course of the COVID-19 pandemic. We do not think that this change has led to any bias in the review process. Instead, we think that changing the inclusion criteria for outcome measurement to a standardised scale can facilitate identifying studies with objective and higher quality results and, additionally, can contribute to a lower heterogeneity among included studies. We also added a new secondary outcome 'quality of life' from version 2 of this review (Piechotta 2020b) onward, but do not suspect that this had an impact on bias since the outcome was suggested by an external patient representative.

For inclusion criteria regarding different study designs, we tried to anticipate possible changes of the evidence landscape already at protocol stage and therefore excluded study designs of lower level evidence as more RCTs were published. Nonetheless, for this update we decided that we needed to deviate from our previous specification by not excluding prospectively registered single-arm studies with inclusion of 500 or more participants, even if upcoming RCTs report safety data for both groups. That was because we decided that data of large single-arm studies like Joyner 2020 could still provide valuable information for safety outcomes and their results could not be neglected in our analyses. To mitigate risk of bias arising from the changes in inclusion criteria, we planned to only use safety data of such studies and to only include prospectively registered studies.

Regarding other changes in methods, it must also be noted that in a previous versions of this review (Piechotta 2020b), we used the former 'Risk of bias' tool to assess risk of bias for RCTs (Higgins 2011). Since the last update (Chai 2020), we assessed RCTs using 'Risk of Bias 2' (Sterne 2019). This led to changes in the risk of bias rating and the GRADE assessment for the outcomes mortality, clinical status and safety outcomes of one included study (Li 2020). We think using the revised 'Risk of Bias 2' tool (Sterne 2019)

corrected our judgement from potential personal biases, since it is less sensitive to subjective interpretations.

Agreements and disagreements with other studies or reviews

This update of our systematic review identified moderate- to high-certainty evidence that treatment with convalescent plasma is not effective for the treatment of COVID-19, in individuals with moderate to severe disease, when compared to placebo treatment or standard care alone. Further, we identified low-certainty evidence about the effects of convalescent plasma when compared to standard plasma in individuals with moderate to severe COVID-19 and very low to low-certainty evidence about the effects of convalescent plasma when compared to placebo or standard care alone in individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease.

To date, there have been published several systematic reviews on effectiveness and safety of convalescent plasma in the treatment of COVID-19. For example, Janiaud 2021 analysed data of four peer-reviewed RCTs, including 1,060 participants, and six other publicly available RCTs, including 10,722 participants. All but one included trial (Libster 2020) included participants with moderate to severe disease and they meta-analysed trials that compared convalescent plasma to placebo and/or standard care. In contrast to our review, they did not differentiate populations by disease severity. However, they already included preliminary published data of Horby 2021, which had a big impact on overall meta-analysis results, since the study contributed data from 10,406 participants. A meta-analysis including all 10 RCTs indicated that there is moderate-certainty evidence for no association of convalescent plasma on all-cause mortality (RR 1.02, 95% CI 0.92 to 1.12). Furthermore, the analyses including all 10 RCTs showed that convalescent plasma use was not associated with length of hospital stay (HR 1.07, 95% CI 0.79 to 1.45) or the relative risk for the initiation of mechanical ventilation (RR 0.81 95% CI 0.42 to 1.58). Certainty of evidence for both outcomes were rated as low due to imprecision. The authors conducted no meta-analysis for clinical improvement, clinical deterioration, or serious adverse events, due to inconsistent reporting. In concordance with our results, Janiaud 2021 concluded that convalescent plasma compared to standard care or placebo is not associated with all-cause mortality or other clinical outcomes that were considered in their analysis. Janiaud 2021 included data from the same studies as we did, but we included additional safety data from one non-RCT (Joyner 2020).

Klassen 2021 aggregated patient outcome data of 35,055 participants for the outcome mortality with varying length of follow-up (2-118 days). They included 10 RCTs, 20 matched-control studies, two dose-response studies, and 96 case-reports or case-series. They found a 42% reduction in mortality rate of participants treated with convalescent plasma (20%) compared to participants receiving standard treatment (28%), when combining results of RCTs and matched-control studies (OR 0.58, 95% CI 0.47 to 0.71). When they synthesised results of RCTs only, they found no association between convalescent plasma therapy and mortality (OR 0.76, 95% CI 0.54 to 1.09). In a sensitivity analysis, the authors excluded Agarwal 2020 because approximately 70 percent of participants in the convalescent plasma arm received plasma with an antibody level of less than 1:80. Based on that, they found a reduction of 35% in mortality odds ratio of the plasma arm (11%) compared to the control group (16%) (OR 0.65, 95% CI 0.43 to

0.98). In contrast to our results, [Klassen 2021](#) concluded that there is moderate to high certainty evidence favouring convalescent plasma over standard care.

[Klassen 2021](#) did not include data of [Horby 2021](#), since it was not available in the format of a preprint or peer-reviewed publication at the time of their publication; this is likely to be one reason for the differences between their results and ours. Further reasons may be the post-hoc exclusion of [Agarwal 2020](#), and the inclusion of [Rasheed 2020](#), since they classified the study as a RCT. [Rasheed 2020](#) reported that controls were matched to participants according to the disease stage, age, and sex, and assigned participants to convalescent plasma based on ABO compatibility and limited availability of plasma. In our opinion, this does not fit the criteria for a randomised allocation method and we classified it as a controlled NRSI. We also wrote to the authors of [Rasheed 2020](#) to clarify their methods of randomisation, but their answer did not give any new insights.

The large-scale clinical administration of convalescent plasma in the USA was regulated under an expanded access programme by the FDA with individual patient authorisation and collection of data ([Joyner 2020](#)). The initial purpose of the analysis was to provide data to establish the safety of administration of convalescent plasma ([Joyner 2020](#)). However, the data were thought to contain signals of efficacy and therefore re-analysed, and although the data set did not include any data from a control cohort, the FDA and the USA government considered that there was sufficient evidence of efficacy to widen access to convalescent plasma under the 'Emergency Use Authorization' (EUA) issued on 23 August 2020 ([FDA 2020](#)). On 11 February 2021, the FDA revised the EUA of convalescent plasma. The authorization is now limited to the use of high titre convalescent plasma for hospitalised individuals at an early stage of disease ([FDA 2021](#)).

On 2 March 2021, the USA National Institutes of Health announced that a large trial of COVID-19 convalescent plasma for participants with mild symptoms in the emergency department ([NCT04355767](#)) was halted because no strong evidence for a benefit of convalescent plasma was found ([NIH 2021](#)). They stated that they do not expect a change in results, even if enrolment was continued.

The adverse events associated with plasma transfusions are well characterised. Critically ill participants 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. To date, there is no sufficient comparative safety data available for adverse events.

In this systematic review of the literature, which mainly identified studies that included people with COVID-19 with severe or critical illness, we identified a small proportion of participants experiencing any grade 3 or 4 adverse events, or serious adverse events. With the information available at this moment from published trials registry entries, it is apparent that the majority of clinical trials are enrolling people with COVID-19 who have progressed to moderate or severe disease. Despite there being some evidence from other infectious diseases that early therapy might be more effective ([Mair-Jenkins 2015](#)), targeting this population is justifiable given the evident lack of effective interventions for COVID-19. Recent subgroup analysis in RECOVERY

([Horby 2021](#)) did not identify strong evidence for a difference between receipt of intervention within seven days of symptom onset or after seven days, and results of our review show that evidence concerning safety and effectiveness of convalescent plasma for individuals with mild disease still is not sufficient.

AUTHORS' CONCLUSIONS

Implications for practice

We currently have high certainty in the evidence that convalescent plasma for the treatment of individuals with moderate to severe disease does not reduce mortality and has little to no impact on measures of clinical improvement. We are uncertain about the safety of convalescent plasma in such patients, again when compared to placebo or standard care. Further, we identified very low- to low-certainty evidence about the effects of convalescent plasma when compared to standard plasma in individuals with moderate to severe COVID-19; very low- to low-certainty evidence about the effects of convalescent plasma when compared to placebo or standard care alone in individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease; and no evidence on effectiveness or safety of hyperimmune immunoglobulins.

Implications for research

For the fourth version of this living systematic review investigating the use of convalescent plasma or hyperimmune immunoglobulin for people with COVID-19, we included data from 12 randomised controlled trials (RCTs) reporting on the effectiveness and safety of convalescent plasma, and in total considered the experience of almost 50,000 participants. We did not identify any completed studies that evaluated hyperimmune immunoglobulin, but there are currently still new studies being registered in trials registries. Studies should report outcomes in the same way, and should consider the importance of maintaining comparability in terms of co-interventions administered in all study arms. There are 100 ongoing studies evaluating convalescent plasma and hyperimmune immunoglobulin and 27 studies reporting in a study registry as being completed, terminated or no longer available as expanded access. After submitting this version of the review, our weekly searches identified four completed studies with full texts. We will also keep track of two platform trials. Of the 100 ongoing studies, 10 are investigating the effect of hyperimmune immunoglobulins. Publication of the results might dissolve some of the uncertainties around hyperimmune immunoglobulin therapy for people with any severity of disease, and convalescent plasma therapy for people with asymptomatic or mild disease.

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* Indicates the major publication for the study

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

Agarwal 2020
Study characteristics

Methods	<ul style="list-style-type: none"> • Trial design: RCT, open-label • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 22 April 2020-14 July 2020 • Country: India • Language: English • Number of centres: 39
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Agarwal 2020 (Continued)

	<ul style="list-style-type: none"> • Trial registration number: CTRI/2020/04/024775 • Date of trial registration: 12 April 2020
Participants	<ul style="list-style-type: none"> • Age: median age 52 (IQR 42-60) years in intervention group; 52 (IQR 41-60) years in control group • Sex: 75% of males in the intervention group and 77% of males in the control group • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 1210/464 (CP 235, SC 229)/464 • Severity of condition according to study definition: moderate (partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO₂/FiO₂) ratio between 200 mm Hg and 300 mm Hg or a respiratory rate of more than 24/min with oxygen saturation 93% or less on room air) • Severity of condition according to WHO score: level 4 and 5 • Comorbidities: diabetes mellitus, hypertension, coronary artery disease, obesity, tuberculosis, chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular disease, cirrhosis and history of cancer • Inclusion criteria <ul style="list-style-type: none"> ◦ Participants admitted with RT-PCR-confirmed COVID-19 illness ◦ Age > 18 years ◦ Moderate illness with one of two: <ul style="list-style-type: none"> ■ PaO₂/FiO₂: 200-300 ■ respiratory rate > 24/min with oxygen saturation (SaO₂) < 93% or less on room air ◦ Availability of matched donor plasma at the point of enrolment ◦ Written informed consent obtained before recruitment • Exclusion criteria <ul style="list-style-type: none"> ◦ Pregnant or breastfeeding women ◦ Known hypersensitivity to blood products ◦ Receipt of pooled immunoglobulin in last 30 days ◦ Critically ill patients: <ul style="list-style-type: none"> ■ PaO₂/FiO₂ ratio < 200 mmHG (moderate - severe ARDS) or ■ shock (requiring vasopressors to maintain a mean arterial pressure (MAP) of ≥ 65 mm Hg or MAP of < 65 mm Hg) ◦ Participating in any other clinical trial ◦ Clinical status precluding infusion of blood product • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR • Donor eligibility criteria <ul style="list-style-type: none"> ◦ Men or nulliparous women <ul style="list-style-type: none"> ■ Aged between 18 and 65 years ■ Weight of more than 50 kg ■ Received a diagnosis of COVID-19 confirmed by a RT-PCR test result ■ Had experienced symptoms of COVID-19 with at least fever and cough: <ul style="list-style-type: none"> □ the symptoms must have completely resolved for 28 consecutive days before donation or □ a period of 14 days before donation with two negative RT-PCR test results for SARS-CoV-2 from nasopharyngeal swabs collected 24 h apart • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP <ul style="list-style-type: none"> ◦ Type of plasma: used from 262 donors (male (94.3%), with mean (SD) age of 34.3 (9.3) years) ◦ Volume: 200 mL ◦ Number of doses: 2 doses ◦ Type of antibody test and antibody-titre: micro-neutralisation test, median (IQR) titre of 1:40 (1:30 to 1:80) ◦ Pathogen inactivated or not: NR ◦ RT-PCR tested: NR

Agarwal 2020 (Continued)

- Details of donors
 - Sex: 94.3% males
 - HLA and HNA antibody-negative: NR
 - Severity of disease:
 - mild (fever and cough with no oxygen requirement): 94.2%
 - moderate (fever and cough with oxygen requirement): 5.8%
 - Timing from recovery from disease: symptoms must have completely resolved for 28 consecutive days before donation or a period of 14 days before donation with two negative RT-PCR test results for SARS-CoV-2 from nasopharyngeal swabs collected 24 h apart.
 - RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): first dose of convalescent plasma was transfused at randomisation, and the second dose after 24 h.
- For studies including a control group: comparator (type): randomised 1:1 to CP and standard of care versus standard care including any drugs that are being used in clinical practice
- Concomitant therapy: standard care for COVID-19 disease (antivirals (hydroxychloroquine, remdesivir, lopinavir/ritonavir, oseltamivir), broad spectrum antibiotics, immunomodulators (steroids, tocilizumab), and supportive management (oxygen through a nasal cannula, face mask, non-rebreathing face mask; noninvasive or invasive mechanical ventilation; awake proning))
- Duration of follow-up: 28 days
- Treatment cross-overs: none
- Compliance with assigned treatment: 3 participants from the control group received the convalescent plasma treatment

Outcomes

- Primary study outcome
 - Composite of progression to severe disease ($\text{PaO}_2/\text{FiO}_2 < 100$ mm Hg) or all-cause mortality at 28 days post-enrolment
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: 28-day mortality 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): yes, transfusion-related AEs only
 - Number of participants with SAEs: yes (transfusion-related mortality)
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: assessed, but NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission on the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR

Agarwal 2020 (Continued)

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

Notes

- Preprint published on 10 September 2020
- Journal article accepted on 12 October 2020
- Sponsor/funding: this multicentric study was funded by ICMR, an autonomous government-funded medical research council

AlQahtani 2020
Study characteristics

Methods

- Trial design: RCT, open-label
- Type of publication: preprint publication
- Setting: ICU (hospitalised patients)
- Recruitment dates: April 2020 to June 2020
- Country: Bahrain
- Language: English
- Number of centres: 2
- Trial registration number: NCT04356534
- Date of trial registration: April 22, 2020

Participants

- Age: mean age CP arm: 52.6 and control arm: 50.7
- Sex: 75% of males in the intervention group and 85% of males in the control group
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 40/40/40 (20 in CP arm and 20 in control arm)
- Severity of condition according to study definition: severe (requiring oxygen therapy and radiological evidence of pneumonia)
- Severity of condition according to WHO score: according to WHO 10 point scale: level 5-7
- Comorbidities: diabetes, hypertension, cardiac disease, chronic kidney disease, chronic lung disease, chronic liver disease

AlQahtani 2020 (Continued)

- Inclusion criteria
 - Signed informed consent
 - Aged at least 21 years
 - COVID-19 diagnosis based on polymerase chain reaction (PCR) testing
 - Hypoxia (oxygen saturation of less than or equal 92% on air, or $PO_2 < 60$ mmHg in arterial blood gas, or arterial partial pressure 90 of oxygen (PaO₂)/fraction of inspired oxygen (FIO₂) of 300 or less) and patient requiring oxygen therapy
 - Pneumonia confirmed by chest imaging
- Exclusion criteria
 - Mild disease not requiring oxygen therapy
 - Normal chest X-ray and CT scan
 - Requiring ventilatory support (invasive or non-invasive)
 - History of allergy to plasma, sodium citrate or methylene blue
 - History of autoimmune disease or selective IGA deficiency
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation):
- Donor eligibility criteria
 - Ability to give informed consent
 - Men or nulliparous women (all women had a pregnancy test except for postmenopausal women)
 - PCR COVID-19 negative from respiratory tract
 - Patients were symptom free
 - Recovered from COVID-19 and discharged from hospital for more than 2 weeks
 - Patients above the ages of 21
 - Body weight more than 50 kg
 - Met all donor selection criteria employed for routine plasma collection and plasmapheresis procedures at the collection centre
- Donor exclusion criteria: NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP
 - Type of plasma: NR
 - Volume: 400 mL
 - Number of doses: 200 mL x 2 (2 consecutive days)
 - Type of 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: patients who had recovered from COVID-19 and had been discharged from hospital for more than 2 weeks were approached to be volunteer donors
 - RT-PCR tested: yes (negative)
- 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: standard of care for COVID-19 disease (standard supportive treatment included control of fever (paracetamol) and possible therapy including antiviral medications, Tocilizumab and antibacterial medication)
- Duration of follow-up: NR
- Treatment cross-overs: NR
- Compliance with assigned treatment: good compliance

Outcomes

- Primary study outcome: requirement for ventilation (invasive or noninvasive)

AlQahtani 2020 (Continued)

- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: 28-day mortality reported
- Secondary review outcomes
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR
 - Number of participants with SAEs: yes, but transfusion reactions reported
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: not reported with WHO scale
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission on the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
- Additional outcomes
 - 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)

Notes

- Preprint published: November 4, 2020
- Sponsor/funding: Royal College of Surgeons in Ireland - Medical University of Bahrain

Avendano-Sola 2020

Study characteristics

Methods

- Trial design: multicentre, RCT
- Type of publication: preprint
- Setting: hospital
- Country: Spain
- Language: English
- Number of centres: 14
- Trial registration: NCT04345523
- Date of trial registration: 14 April 2020

Participants

- Age: 60.8 (\pm 15.5) mean age (\pm SD)
- Sex: 54.3% of males in the intervention and control group together
- Number of participants (recruited/allocated/evaluated): 278/81/81
- Severity of condition according to study definition: patients requiring hospitalisation for COVID-19 without mechanical ventilation (invasive or non-invasive) or high-flow oxygen devices
- Severity of condition according to WHO score: level 4 and 5

Avendano-Sola 2020 (Continued)

- Comorbidities: diabetes mellitus, hypertension, cardiac disorder, chronic lung disease, chronic kidney disease, immunodeficiency
- Inclusion criteria
 - Written informed consent prior to performing study procedures. Witnessed oral consent will be accepted in order to avoid paper handling. Written consent by participant or representatives will be obtained as soon as possible
 - Not > 12 days between the onset of symptoms (fever or cough) and treatment administration day
 - Participants 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
 - Laboratory-confirmed SARS-CoV-2 infection as determined by PCR in naso/oropharyngeal swabs or any other relevant specimen
 - Male or female adult patient ≥ 18 years of age at time of enrolment
- 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)
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
- Donor eligibility criteria
 - Subjects willing and able to provide written informed consent
 - Fulfilling all the current requirements to be a plasma apheresis donor according to the regulations for donation of blood products (European Guidelines and RD 1088/2005 in Spain)
 - Absence of COVID-19 symptoms within the last 14 days
 - Anti SARS-CoV-2 IgG antibodies detectable in peripheral blood
 - ≥ 18 years of age at time of donation
 - Weight > 50 kg and good vein access are standard criteria, for which exceptions could be considered according to the criteria of the blood bank and haematologists
- Donor exclusion criteria
 - Plasmapheresis in the previous seven days
 - Whole blood donation in the previous 30 days
 - Donation of more than 25 litres of plasma in the previous 12 months

 Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP

Avendano-Sola 2020 (Continued)

- Details of CP
 - Type of plasma: all administered plasma units had neutralizing antibodies
 - Volume: 250 mL to 300 mL
 - Number of doses: 1
 - Type of antibody test and antibody-titre:
 - VMNT-ID50: all titers > 1:80 (median titre 1:292, IQR 238-451)
 - pseudovirus neutralising ID50 assay: median titre 1:327, IQR 168-882
 - two CP units had ID50 titre <1:80)
 - semiquantitative results for anti SARS-Cov-2 antibodies (ELISA): median 3.65 (IQR 2.0-5.3)
 - ID50 for D614 pseudovirus neutralizing assay: median 327.3 (IQR 168.1-882.1)
 - PRNT50 neutralising AB titre: median 292.2 (IQR 237.7- 450.7)
 - Pathogen inactivated or not: pathogen reduced
 - RT-PCR tested:
 - in nasopharyngeal/oropharyngeal swabs on days 3, 5, 8, 11 (while hospitalised); and day 15 and 29 (if able to return to clinic or still hospitalised)
 - in blood on days 3, 5, 8, 11 (while hospitalised)
- Details of donors
 - Age: 37.85 (±11.60) mean age (±SD)
 - Gender: 23 (88.46%) male, 3 (11.54%) female
 - HLA and HNA antibody-negative: yes (tested only in two cases with infusion-related AE and suspected TRALI)
 - Severity of disease: mild (but recovered from severe disease was not an exclusion criteria)
 - Timing from recovery from disease: absence of COVID-19 symptoms within the last 14 days
 - RT-PCR tested: 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): 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
- Duration of follow-up: 29 days
- Treatment cross-overs: none
- Compliance with assigned treatment: good (all compliant)

Outcomes

- Primary study outcome: proportion of patients in categories 5, 6 or 7 (seven-category ordinal scale, see: additional outcomes) at day 15 of the study
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: mortality of any cause at 29 days (time frame: 29 days)
- Secondary review outcomes
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - Number of participants with SAEs: yes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up

Avendano-Sola 2020 (Continued)

- to 7 days, 8 to 15 days, 16 to 30 days: No (but assessment of improvement with seven-category ordinal scale (see: additional outcomes))
- o Time to death: yes (up to 29 days)
- o 90-day mortality: NR
- o Time to discharge from hospital: yes (Kaplan-Meier curve, median (95 % CI): Figure 2D)
- o Admission on the ICU: NR
- o Length of stay on the ICU: NR
- o Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: yes (RT-PCR tests on days 0, 3, 5, 8, 11, 15, and 29)
- o QoL: NR
- Additional study outcomes
 - o Category changes in ordinal scale (time frame: 15 days)
 - Proportion of participants in categories 5, 6 or 7 of the 7-point ordinal scale at day 15 ordinal scale:
 - not hospitalised, no limitations on activities
 - not hospitalised, limitation on activities
 - hospitalised, not requiring supplemental oxygen
 - hospitalised, requiring supplemental oxygen
 - hospitalised, on non-invasive ventilation or high-flow oxygen devices
 - hospitalised, on invasive mechanical ventilation or ECMO
 - death
 - o 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
 - o Oxygenation-free days (time frame: 29 days)
 - o Ventilator-free days
 - o 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
 - o Antibodies levels in CP donors recovered from COVID-19 (time frame: 3 months)
 - quantitative total antibodies and neutralising antibody activity against SARS-CoV-2 in the sera from donors and participants using viral pseudotypes
 - o Viral load (time frame: days 1, 3, 5, 8, 11 and 29)
 - Change in PCR for SARS-CoV-2 in naso/oropharyngeal swabs and blood at baseline and on days 3, 5, 8, 11 (while hospitalised); and days 15 and 29 (if able to return to clinic or still hospitalised)

Notes

- Interim analysis after randomisation of 81 participants, study terminated afterwards due to fall in recruitment
- First published: 1 September 2020; latest version: 29 September 29
- Sponsor/funding: "This research is funded by the Government of Spain, Ministry of Science and Innovation, Instituto de Salud Carlos III, grant number COV20/00072 (Royal Decree-Law 8/2020, of 17 March, on urgent extraordinary measures to deal with the economic and social impact of COVID-19), co-financed by the European Regional Development Fund (FEDER) A way to make Europe."
- COIs: none

Bajpai 2020

Study characteristics

Methods

- Trial design: RCT, open label
- Type of publication: preprint publication
- Setting: hospital (inpatient and ICU)
- Recruitment dates: 21 April 2020 until final follow-up on 30 May 2020
- Country: India
- Language: English

Bajpai 2020 (Continued)

- Number of centres: 1
- Trial registration number: NCT04346446
- Date of trial registration: 15 April 2020

Participants

- Age: mean 48.2 ± 9.8
- Sex: 75.9% of males in the intervention and control group together
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 51/31/29
- Severity of condition according to study definition: severe (respiratory rate (RR) ≥ 30/min, oxygen saturation level less than 93% in resting state, the partial pressure of oxygen (PaO₂)/oxygen concentration (FiO₂) ≤ 300 mmHg, lung infiltrates > 50% within 24 to 48 h)
- Severity of condition according to WHO score: level 5-7
- Comorbidities: BMI
- Inclusion criteria
 - Written informed consent
 - SARS-CoV-2 infection (positive by real-time PCR assay) patient
 - Severe COVID-19 (respiratory rate (RR) ≥ 30/min, oxygen saturation level less than 93% in resting state, the partial pressure of oxygen (PaO₂)/oxygen concentration (FiO₂) ≤ 300 mmHg, lung infiltrates > 50% within 24 to 48 h)
- Exclusion criteria
 - Failure to obtain informed consent
 - Patients less than 18 years or more than 65 years of age
 - Those with co-morbid conditions (cardiopulmonary disease-structural or valvular heart disease, coronary artery disease, COPD, chronic liver disease, chronic kidney disease)
 - Patients presenting with multi-organ failure or on mechanical ventilation
 - Pregnant females
 - Individuals with HIV
 - Viral hepatitis, cancer, morbid obesity with a BMI > 35 kg/m²
 - Extremely moribund patients with an expected life expectancy of < 24 h,
 - Haemodynamic instability requiring vasopressors
 - Previously known history of allergy to plasma, or a PaO₂/FiO₂ ratio less than 150
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation)
- Donor eligibility criteria
 - From COVID-19 recovered patients after 14 days of complete resolution of symptoms by plasmapheresis
 - Two consecutive test negative results (RT-PCR) 24 h apart
 - Due consent
 - Medical history, physical examination and laboratory tests
- Donor exclusion criteria: NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP
 - Type of plasma: COPLA convalescent plasma transfusion (ABO blood group compatible plasma)
 - Volume: 500 mL (either convalescent or FFP)
 - Number of doses: 2 divided doses on consecutive days
 - Type of antibody test and antibody-titre: the titre was determined by ELISA (SARS-CoV-2 Spike S1-RBD IgG Detection Kit, Genscript, USA) using positive, negative controls and sample dilutions (1:80, 1:160, 1:320, 1:640 and 1:1000). The S1 RBD IgG titre of 1:80 or above was preferred.
 - Pathogen inactivated or not: NR
 - RT-PCR tested: yes

Bajpai 2020 (Continued)

- Details of donors
 - Sex: 14 male, 0 female
 - HLA and HNA antibody-negative: NR
 - Severity of disease: NR
 - Timing from recovery from disease: 14 days of complete resolution of symptoms
 - RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): transfusion within three days of onset of symptoms of severe COVID-19
- For studies including a control group: comparator (type): fresh frozen plasma (FFP)
- Concomitant therapy: standard care
 - Medically, all patients received a course of Hydroxychloroquine 400 mg (twice daily) on day 1, followed by 200 mg (twice daily) for five days along with oral azithromycin 500 mg (once daily) for five days. Standard medications for the control of diabetes and hypertension were given when required.
- Duration of follow-up: between 21 April and 30 May 2020
- Treatment cross-overs: no
- Compliance with assigned treatment: yes

Outcomes

- Primary study outcome
 - Proportion of participants remaining free of mechanical ventilation (Day 7)
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: yes (mortality at day 28)
- 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): any AEs reported
 - Number of participants with SAEs: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: yes (duration of hospital stay)
 - Admission on the ICU: NR
 - Length of stay on the ICU: yes
 - Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
- Additional review outcomes
 - Improvement in PaO₂/FiO₂ ratio (day 2, day 7)
 - SOFA scores reduction (day 2, day 7)
 - Requirements of Vasopressor (day 28)
 - Days free of dialysis (day 28)
 - Clinical assessment of patients was done by assessing reduction in respiratory rate, and improvement in oxygen saturation (day 2 and day 7)
 - Laboratory effects of plasma therapy by improvement in lymphocyte count Ct value (day 7)
 - Any adverse transfusion events with plasma transfusion

Notes

- Preprint published: 27 October 2020
- Sponsor/funding: Institute of Liver and Biliary Sciences, India

Gharbharan 2020
Study characteristics

Methods	<ul style="list-style-type: none"> • Trial design: RCT, open label • Type of publication: preprint • Setting: hospital (ICU) • Recruitment dates: 8 April 2020-10 June 2020 • Country: Netherlands • Language: English • Number of centres: 18 • Trial registration number: NCT04342182 • Date of trial registration: 10 April 2020
Participants	<ul style="list-style-type: none"> • Age: median age 61 (IQR 56-70) years in intervention group; 63 (IQR 55-77) years in control group • Sex: 72% of males in the intervention and control group together • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 204/86/86 • Severity of condition according to study definition: moderate to severe (defined in the study according to the old WHO 8-point COVID-19 disease severity score: moderate is hospitalised, no oxygen, and oxygen by mask or nasal prongs; and severe is noninvasive ventilation or high-flow oxygen, intubation and mechanical ventilation, and ventilation with additional organ support) • Severity of condition according to WHO score <ul style="list-style-type: none"> ◦ CP arm had 16% ≤ score 4 and 84% ≥ score 5 ◦ SoC arm had 2% ≤ score 4 and 98% ≥ score 5 • Comorbidities: diabetes mellitus, hypertension, cardiac, pulmonary, cancer, immunodeficiency, chronic kidney disease, liver cirrhosis • Inclusion criteria: PCR-confirmed COVID-19 disease, admitted to the hospital, most recent PCR-positive sample is < 96 h old, written informed consent by patient or LAR, age ≥ 18 years • Exclusion criteria: participation in another intervention trial on the treatment of COVID-19 that falls under the Dutch law human research (WMO) and in which individual patients are randomised to different treatment options, known IgA deficiency, invasive ventilation for > 96 h already • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR • Donor eligibility criteria: donors with a history of COVID infection that was documented by PCR, known ABO-rhesus (D) blood group, negative screening for irregular antibodies, asymptomatic for at least 24 h, written informed consent regarding the plasmapheresis procedure • Donor exclusion criteria: if age < 18 years and > 66 years, weight < 45 kg, medical history of heart failure, history of transfusion with red blood cells, platelets or plasma
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP therapy • Details of CP <ul style="list-style-type: none"> ◦ Type of plasma: <ul style="list-style-type: none"> ■ serum samples of donors analysed for the presence of neutralising antibodies by performing a PRNT with the SARS-CoV-2 virus (German isolate; GISAID ID EPI_ISL_406862; European Virus Archive Global #026V-03883) ■ for each participant, we selected the plasma with the highest PRNT50 titre from the ABO compatible donor pool ◦ Volume: 300 mL ◦ Number of doses: 1; participants without a clinical response and a persistently positive RT-PCR could receive a second plasma unit after 5 days ◦ Type of antibody test(s) and antibody-titre(s): antiSARS-CoV-2 neutralising antibodies confirmed by a SARS-COV-2 PRNT and a PRNT50 titre > 1:80 ◦ Pathogen inactivated or not: NR ◦ RT-PCR tested: NR

Gharbharan 2020 (Continued)

- Details of donors
 - CP for treatment was collected from 115 donors. The median age was 43 years (IQR 31-52 years)
 - Gender: 105 male (91%)
 - HLA and HNA antibody-negative: yes
 - Severity of disease: NR
 - Timing from recovery from disease: NR
 - RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): administered on the day of inclusion
- For studies including a control group: comparator (type): standard of care; off-label use of EMA-approved drugs (e.g. chloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, anakinra) as a treatment for COVID-19 was allowed in hospitals where this was part of the standard of care
- Concomitant therapy: NR
- Duration of follow-up: NR; followed for at least 15 days after inclusion and 75 (87%) and 32 (37%) for at least 30 and 60 days respectively
- Treatment cross-overs: not applicable
- Compliance with assigned treatment: good (all compliant)

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: all-cause mortality reported
 - 30-day mortality: 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: reported for transfusion related
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: reported for day 15 and day 30
 - Time to death: yes
 - 90-day mortality: NR
 - Time to discharge from hospital: yes
 - Admission on the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
- Additional study outcomes: NR

Notes

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

Hamdy Salman 2020

Study characteristics

Methods	<ul style="list-style-type: none"> • Trial design: RCT, double-blinded • Type of publication: journal publication • Setting: hospital (inpatient and ICU) • Recruitment dates: June 2020 to August 2020 • Country: Egypt • Language: English • Number of centres: 1 • Trial registration number: NCT04530370 • Date of trial registration: August 28, 2020
Participants	<ul style="list-style-type: none"> • Age: median (IQR): 57.0 (50.0–66.0) • Sex: 70% of males in the intervention and control group together • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 45/30/30 • Severity of condition according to study definition: patients with COVID-19 severe conditions (no clear definition reported) • Severity of condition according to WHO score: not clear • Comorbidities: diabetes and respiratory disease • Inclusion criteria <ul style="list-style-type: none"> ◦ Hospitalised patients \geq 18 years ◦ Confirmed positive nasopharyngeal/oropharyngeal COVID-19 swab ◦ With two or more of a four-category illness-severity scale: <ul style="list-style-type: none"> ■ respiratory frequency \geq 24/min ■ blood oxygen saturation \leq 93% on room air ■ partial pressure of arterial oxygen to fraction of inspired oxygen ratio $<$ 300 mmHg ■ pulmonary infiltrates occupying more than 50% of both lungs • Exclusion criteria <ul style="list-style-type: none"> ◦ Any patient with prior allergic history to plasma or plasma products or septic shock or multiple organ failure was excluded from the study. • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): all patients received steroid and oxygen supportive therapy as required. • Donor eligibility criteria <ul style="list-style-type: none"> ◦ A history of COVID-19 infection confirmed by positive nasopharyngeal swab/oropharyngeal swab test ◦ Complete recovery of symptoms for at least 2 weeks prior to donation, documented with negative nasopharyngeal/oropharyngeal swab ◦ All blood products followed standard blood handling and processing procedures and regulations • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP <ul style="list-style-type: none"> ◦ Type of plasma: NR ◦ Volume: 250 mL ◦ Number of doses: 1 ◦ Type of antibody test and antibody-titre: neutralising antibody, Cusabio, ELISA Kit Catalog Number. CSBEL23253HU for the qualitative determination of SARS-CoV-2 ◦ Pathogen inactivated or not: NR ◦ RT-PCR tested: NR

Hamdy Salman 2020 (Continued)

- Details of donors
 - Gender: NR
 - HLA and HNA antibody-negative: NR
 - Severity of disease: NR
 - Timing from recovery from disease: complete recovery of symptoms for at least 2 weeks prior to donation
 - RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group
 - Comparator (type): standard care
 - Concomitant therapy: available standard therapy, when appropriate, included:
 - supplemental oxygen
 - noninvasive and invasive ventilation
 - antibiotic medication
 - inotrope drugs
 - renal-replacement therapy
 - anticoagulants
 - glucocorticoids
 - intravenous fluids
 - interferon
 - extracorporeal membrane oxygenation (ECMO)
- Duration of follow-up: 5 days
- Treatment cross-overs: NA
- Compliance with assigned treatment: yes

Outcomes

- Primary study outcome
 - 50% Improvement of severity of illness was defined as achieving a minimum of two-point reduction on the four-category illness severity scale:
 - respiratory frequency ≥ 24 /min
 - blood oxygen saturation $\leq 93\%$ on room air
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 mmHg; pulmonary infiltrates occupying more than 50% of both lungs, during 5 days study period
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: 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): transfusion-related complications
 - Number of participants with SAEs: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission on the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: yes at day 3
 - QoL: NR

Hamdy Salman 2020 *(Continued)*

- Additional review outcomes
 - Laboratory biomarkers of severe COVID-19 infections were assessed, included serum levels of: ferritin, D-dimer, troponin, lactic dehydrogenase creatine phosphokinase, lymphocytic count, and C-reactive protein.

Notes

- Journal published: 3 November 2020
- Sponsor/funding: South Valley University

Horby 2021
Study characteristics

Methods

- Trial design: multicentre, randomised adaptive trial
- Type of publication: preprint
- Setting: inpatient
- Recruitment dates: 28 May 2020 - 15 January 2021
- Country: UK
- Language: English
- Number of centres: multiple (currently 176 active sites)
- Trial registration number: NCT04381936
- Date of trial registration: 11 May 2020

Participants

- Age: mean 63.5 (SD 14.7)
- Sex: 63% of males in the intervention group and 66% of males in the control group
- Ethnicity
 - White 75% in CP and 74% in SOC
 - Black, Asian, and minority ethnic 15% in CP and 15% in SOC
 - Unknown 10% in CP and 10% in SOC
- Number of participants (recruited/allocated/evaluated): 40,000/5795 CP and 5763 SOC/5795 CP and 5763 SOC
- Severity of condition according to study definition: 87 % oxygen only, includes non-invasive ventilation
- Severity of condition according to WHO score: severe WHO ≥ 6
- Comorbidities: diabetes, heart disease, chronic lung disease, TB, HIV, severe liver disease, severe kidney impairment
- Inclusion criteria
 - Hospitalised patients at any age
 - 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
 - Written informed consent
- Exclusion criteria
 - If the attending clinician believes that there is a specific contra-indication to one of the active drug treatment arms 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
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): yes

Horby 2021 (Continued)

- Donor eligibility criteria
 - Only plasma donations with sample to cut-off (S/CO) ratio of 6.0 or above on the EUROIMMUN IgG enzyme-linked immunosorbent assay (ELISA) test targeting the spike (S) glycoprotein (PerkinElmer, London, UK) were supplied for the RECOVERY trial use
- Donor exclusion criteria: NR

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 versus lopinavir-ritonavir versus low-dose corticosteroids versus 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 versus tocilizumab
- Details of CP
 - Type of plasma: ABO-identical if possible
 - Volume: 275 mL +/- 75 mL
 - Number of doses: 2 (with a minimum of 12-h interval between 1st and 2nd units)
 - Type of antibody test and antibody-titre: only plasma donations with sample to cut-off (S/CO) ratio of 6.0 or above on the EUROIMMUN IgG enzyme-linked immunosorbent assay (ELISA) test targeting the spike (S) glycoprotein (PerkinElmer, London, UK) were supplied for the RECOVERY trial use
 - 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
- For studies including a control group: comparator (type): 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 or sarilumab, remdesivir
- Duration of follow-up: 6 months
- 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 versus tocilizumab. New trial arms can be added as evidence emerges that other candidate therapeutics should be evaluated.
- Compliance with assigned treatment: yes

Outcomes

- Primary study outcome: all-cause mortality (time frame: within 28 days after randomisation)
- Primary review outcomes
 - All-cause mortality at hospital discharge: yes
 - 30-day mortality: yes (up to 6 months after main randomisation)
- 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): transfusion related adverse events at 72 h 185 following randomisation (worsening respiratory status, suspected transfusion reaction, 186 fever, hypotension, haemolysis, and thrombotic events), cause-specific mortality, and 187 major cardiac arrhythmia
 - Number of participants with SAEs: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: yes (within 28 days and up to 6 months after the main randomisation)

Horby 2021 *(Continued)*

- Mortality (time to event): yes
- 90-day mortality: NR (up to 6 months after main randomisation)
- Time to discharge from hospital: yes
- Admission on the ICU: NR
- Length of stay on the ICU: NR
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: NR
- QoL: NR
- Additional outcomes
 - Need for renal replacement
 - Development of new major cardiac arrhythmias
 - Proportion of patients discharged from hospital

Notes

- Preprint published 10 March 2021
- Sponsor/funding: UK Research and Innovation (Medical Research Council) and National 48 Institute of Health Research (Grant refs: MC_PC_19056; COV19-RECPLA)

Joyner 2020
Study characteristics

Methods

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

Participants

- Age: 18 to > 80 years
- Sex: 60.2% of males in the intervention group and 0.1% of people in gender/sex categories other than males or females
- Ethnicity: Asian (4.2%), black (18.8%), white (50.4%), unknown (26.6%)
- Number of participants (recruited/allocated/evaluated):
 - recruited: 47,047 patients
 - transfused: 36,226 patients
 - evaluated: the first 35,322 patients
- Severity of disease: hospitalised adults with severe or life-threatening COVID-19
- Comorbidities: NR
- 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

Joyner 2020 (Continued)

	<ul style="list-style-type: none"> • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP therapy • Details of CP <ul style="list-style-type: none"> ◦ Type of plasma: ABO-compatible COVID-19 CP ◦ Volume: approximately 200 mL ◦ Number of doses: ≥ 1 ◦ Type of antibody test(s) and antibody-titre(s): Ortho-Clinical IgG CLIA (qualitative assay) ◦ Pathogen inactivated or not: NR ◦ RT-PCR tested: NR • Details of donors <ul style="list-style-type: none"> ◦ Sex: NR ◦ HLA and HNA antibody-negative: NR ◦ Severity of disease: NR ◦ Timing from recovery from disease: symptom-free for 14 days ◦ RT-PCR tested: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): variable (day 0-day 11+) • Comparator: none • Concomitant therapy: NR • Duration of follow-up: 4 h for safety (first version), 7 days for safety (second version), 30 days for mortality (third version) • Treatment cross-overs: not applicable • Compliance with assigned treatment: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome(s) <ul style="list-style-type: none"> ◦ Provide access to COVID-19 CP, assessed as the availability of CP • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: 7-day and 30-day mortality rate reported for third version ◦ Time to death: NR • Secondary review outcomes <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): serious transfusion-related AEs reported for 20,000 participants (second version) ◦ Number of participants with SAEs: reported for 20,000 participants (up to one week post transfusion in the second version) ◦ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: NR ◦ 30-day and 90-day mortality: reported for 30-day mortality in the third version ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: NR ◦ QoL: NR ◦ Virological response: NR • Additional study outcomes: none
Notes	<ul style="list-style-type: none"> • 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 Coun-

Joyner 2020 (Continued)

cil 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

Li 2020

Study characteristics

Methods

- Trial design: RCT
- Type of publication: journal publication
- Setting: hospital (ICU)
- 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
- Sex: 58.3% of males in the intervention and control group together
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 103 (52 CP, 51 standard treatment)
- Severity of condition according to study definition: severe (respiratory distress and/or hypoxaemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation)
- Severity of condition according to WHO score: level 4 - 9
- Comorbidities: hypertension, cardiovascular disease, cerebrovascular disease, diabetes, liver disease, cancer, kidney disease
- Inclusion criteria
 - Signed informed consent
 - Aged at least 18 years
 - COVID-19 diagnosis based on PCR testing
 - Positive PCR result within 72 h prior to randomisation
 - Pneumonia confirmed by chest imaging
 - Clinical symptoms meeting the definitions of severe or life-threatening COVID-19
 - Acceptance of random group assignment
 - Hospital admission
 - Willingness to participate in all necessary research studies and be able to complete the study follow-up
 - No participation in other clinical trials, such as antiviral trials, during the study period

Li 2020 (Continued)

- Exclusion criteria
 - Pregnancy or lactation
 - Immunoglobulin allergy
 - IgA deficiency
 - Pre-existing comorbidity that could increase the risk of thrombosis
 - Life expectancy < 24 h
 - Disseminated intravascular coagulation
 - Severe septic shock
 - PaO₂/FIO₂ of < 100
 - Severe congestive heart failure
 - Detection of high titre of S protein–RBD-specific IgG antibody (≥ 1:640)
 - Other contraindications as determined by the patient’s physicians
 - Participation in any antiviral clinical trials for COVID-19 within 30 days prior to enrolment
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): antivirals, antibiotics, steroids, human Ig, Chinese herbal medicines, interferon
- Donor eligibility criteria
 - Age 18 through 55 years, suitable for blood donation, initially diagnosed with COVID-19 but with 2 negative PCR test results from nasopharyngeal swabs (at least 24 h apart) prior to hospital discharge, discharged for more than 2 weeks from the hospital, and no persisting COVID-19 symptoms.
- Donor exclusion criteria: NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP
 - Type of plasma: plasmapheresis
 - Volume: 4-13 mL/kg of recipient body weight, median 200 mL, IQR 200-300 mL
 - Number of doses: 1 (96%) or more
 - Antibody test and antibody-titre: only the plasma units with an S-RBD-specific IgG titre of at least 1:640 were used correlating to serum neutralisation titre of 1:80
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors
 - Age: 18-55 years suitable for blood donation
 - Sex: NR
 - 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: NR
 - 30-day mortality: reported

Li 2020 (Continued)

- Secondary review outcomes
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): reported
 - Number of participants with SAEs: reported
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: reported at day 7, 15 and 30
 - Time to death: reported
 - 90-day mortality: NR
 - Time to discharge from hospital: reported
 - Admission on the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: yes reported at day 3
 - 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

Libster 2020
Study characteristics

Methods

- Trial design: RCT, double-blinded
- Type of publication: journal publication
- Setting: outpatient (elderly population)
- Recruitment dates: 4 June 2020 and 25 October 2020
- Country: Argentina
- Language: English
- Number of centres: 11
- Trial registration number: NCT04479163
- Date of registration: 21 July 2020

Participants

- Age: 77.1 (SD 8.6) years
- Sex: 37.5% of males in the intervention and control group together
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 165/160 (80 CP, 80 standard treatment)/160
- Severity of condition according to study definition: mild signs and symptoms for < 48 hours at the time of screening for SARS-CoV-2 by reverse transcriptase polymerase chain reaction (RT-PCR)
- Severity of condition according to WHO score: level 4-6
- Comorbidities: arterial hypertension, diabetes, obesity, chronic obstructive pulmonary disease, heart disease, chronic kidney disease, asthma or other respiratory disease, Non-cirrhotic liver disease, cancer (not active), Neurologic disease

Libster 2020 (Continued)

- Inclusion criteria
 - Subjects ≥ 75 years of age irrespective of presenting comorbidities or between 65-74 years of age with at least one comorbidity (hypertension or diabetes under pharmacologic treatment, obesity, chronic renal failure, cardiovascular disease, and COPD)
 - Subjects had experienced at least one of each in the following two categories of signs and symptoms for < 48 hours at the time of screening for SARS-CoV-2 by RT-PCR:
 - temperature $\geq 37.5^{\circ}$ C and/or unexplained sweating and/or chills
 - dry cough, dyspnoea, fatigue, myalgia, anorexia, sore throat, dysgeusia, anosmia, and/or rhinorrhoea
- ◦ Confirmed diagnosis SARS-CoV-2 by RT-PCR
 - Give informed consent
- Exclusion criteria
 - Severe respiratory disease
 - Cardiac insufficiency
 - Chronic renal failure
 - Primary hypogammaglobulinaemias
 - Myelodysplastic syndromes
 - Chronic lymphoproliferative syndromes
 - Monoclonal gammopathies
 - Known hypersensitivity
 - Active cancer
 - HIV, HBV or HCV infection
 - Chronic administration of immunosuppressants
 - Body transplant history
 - Chronic liver disease, Chronic lung disease with oxygen requirement
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
- Donor eligibility criteria
 - Infected with SARS-CoV-2 for a minimum of 10 days
 - Asymptomatic for ≥ 3 days, and with two negative RT-PCR tests
- Donor exclusion criteria: NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy
- Details of CP
 - Type of plasma: plasmapheresis
 - Volume: 250 mL
 - Number of doses: 1
 - Antibody test and antibody-titre: IgG titre against SARS-CoV-2 spike (S) protein $> 1:1000$ (COVIDAR IgG, Instituto Leloir, Argentina)
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors
 - Sex: both
 - HLA and HNA antibody-negative: NR
 - Severity of disease: NR
 - Timing from recovery from disease: infected with SARS-CoV-2 for a minimum of 10 days, asymptomatic for ≥ 3 days
 - RT-PCR tested: two negative RT-PCR tests
- Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage within 72 hours of mild COVID-19 symptoms.
- For studies including a control group: comparator (type): placebo
- Concomitant therapy: NR
- Duration of follow-up: 25 days
- Treatment cross-overs: none

Libster 2020 (Continued)

- Compliance with assigned treatment: one subject voluntarily abandoned the trial on day 11 of follow-up.

Outcomes

- Primary study outcome(s): development of severe respiratory disease defined as a respiratory rate (RR) ≥ 30 and/or an O_2 sat $< 93\%$ when breathing room air determined between 12 h after infusion of the investigational product (IP) and day 15 of study participation
- Primary review outcomes (outpatient)
 - All-cause mortality: yes reported (after 25 days follow-up)
 - Admission to hospital: NR
- Secondary review outcomes (outpatient)
 - Number of participants with grade 1 and grade 2 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 grade 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 for transfusion related events
 - Development of clinical COVID-19 symptoms, assessed with the WHO Clinical Progression Scale (WHO 2020f) up to longest follow-up: NR
 - Time to symptom onset: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Length of hospital stay, for hospitalised patients: NR
 - Admission on the ICU: NR
 - Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
- Additional study outcomes
 - Life-threatening respiratory disease, defined as: need for 100% oxygen supplementation and/or non-invasive ventilation and/or admission to ICU and/or Mechanical ventilation
 - Critical systemic illness, defined as respiratory failure ($PaO_2/FiO_2 \leq 200$ mmHg) and/or shock and/or multi-organ distress syndrome (defined in supplementary material)
 - Death associated with COVID-19 (On 22 July 2020, we amended the protocol to include a fourth secondary endpoint including any of the three endpoints described above, alone or in combination)
 - The distribution of serum titres 24 h after infusion in plasma versus placebo recipients

Notes

- Preprint publication: 21 November 2020
- Sponsor/funding: funded by The Bill and Melinda Gates Foundation and The Fundación INFANT Pandemic Fund. Registered in the Dirección de Sangre y Medicina Transfusional del Ministerio de Salud (PAEPC19), Plataforma PRIISA (1421), and clinicaltrials.gov (NCT04479163).
- COIs: RL, GPM, DW and FPP are investigators in a phase 3 SARS CoV2 trial from Pfizer; no other relationships or activities that could appear to have influenced the submitted work.
- Other: early termination due to slow enrolment pace (enrolled 76% of the target population)

O'Donnell 2021

Study characteristics

Methods

- Trial design: RCT, double-blind
- Type of publication: preprint

O'Donnell 2021 (Continued)

- Setting: inpatient
- Recruitment dates: between 21 April and 27 November 2020
- Country: New York, USA and Brazil
- Language: English
- Number of centres: 5
- Trial registration number: NCT04359810
- Date of trial registration: 24 April 2020

Participants

- Age: median age of participants was 61 years
- Sex: 66% of males in the intervention and control group together
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 630/223/150 (CP) and 73 (SOC)
- Severity of condition according to study definition: adults hospitalised with severe and critical COVID-19
- Severity of condition according to WHO score: moderate and severe, WHO level 5-9, as 57% (126/223) of participants required supplemental oxygen, 25% (55/223) required high-flow oxygen therapy or non-invasive mechanical ventilation, and 13% (28/223) required IMV or ECMO
- Inclusion criteria
 - Hospitalised patients aged ≥ 18 years
 - Evidence of SARS-CoV-2 infection by polymerase chain reaction (PCR) of nasopharyngeal, oropharyngeal swab or tracheal aspirate sample within 14 days of randomisation
 - Infiltrates on chest imaging
 - Oxygen saturation $\leq 94\%$ on room air or requirement for supplemental oxygen (including non-invasive positive pressure ventilation or high flow supplemental oxygen), IMV, or extracorporeal membrane oxygenation (ECMO) at the time of screening
- Exclusion criteria
 - Participation in another clinical trial of anti-viral agent(s) for COVID-19
 - Receipt of any anti-viral agent with possible activity against SARS-CoV-2 within 24 h of randomisation
 - Duration of IMV or ECMO ≥ 5 days at time of screening; severe multi-organ failure
 - A history of prior reactions to transfusion blood products.
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR
- Donor eligibility criteria
 - Recovered from laboratory-confirmed COVID-19
 - Provided informed consent
 - Had a minimum anti-SARS-CoV-2 total IgG antibody titre of $\geq 1:400$ by quantitative enzyme linked immunosorbent assay against the spike protein
 - Were at least 14 days asymptomatic following resolution of COVID-19
 - Had a negative PCR test for SARS-CoV-2 from a nasopharyngeal swab
- Donor exclusion criteria: NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP (anti-SARS-CoV-2 plasma)
- Details of CP
 - Type of plasma: NR
 - Volume: 200-250 mL
 - Number of doses: 1 unit
 - Type of antibody test and antibody-titre: data on neutralising antibody titres were available for 89% (130/150) of convalescent plasma units. Of these, the median titre was 1:160 (IQR 1:80-1:320)
 - Pathogen inactivated: NR
 - RT-PCR tested: NR

O'Donnell 2021 (Continued)

- Details of donors
 - Gender: NR
 - HLA and HNA antibody-negative: NR
 - Severity of disease: NR
 - Timing from recovery from disease: complete recovery of symptoms for at least 2 weeks prior to donation
 - RT-PCR tested: yes (negative)
- For studies including a control group: comparator (type): normal plasma
- Concomitant therapy: during the trial period, 81% (181/223) of participants received corticosteroids and 6% (13/223) received remdesivir, hydroxychloroquine, antibacterial agent
- Duration of follow-up: 28 days
- Treatment cross-overs: no
- Compliance with assigned treatment: four participants were randomised but did not receive their assigned treatment: three participants (two randomised to convalescent plasma and one to control plasma) had improvements in oxygen saturation to > 94% prior to transfusion, and one participant randomised to convalescent plasma developed a maculopapular rash prior to receipt of plasma for which subsequent transfusion was deferred.

Outcomes

- Primary study outcome
 - Clinical status at day 28 following randomisation, measured using a 7-point ordinal scale based on that recommended by the WHO
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: reported for day 28
- 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
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: yes (up to day 28)
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: yes (duration of hospital stay)
 - Admission on the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
- Additional review outcomes
 - Time-to-clinical improvement (defined as improvement in at least one point from baseline on the ordinal scale or alive at discharge from hospital, whichever came first)
 - In-hospital mortality

Notes

- Publication: preprint published 13 March 2021
- Sponsor/Funding: Max R. O'Donnell, Columbia University

Ray 2020

Study characteristics

Methods

- Trial design: RCT, open label

Ray 2020 (Continued)

- Type of publication: preprint publication
- Setting: hospital (inpatient and ICU)
- Recruitment dates: 31 May 2020 to 12 October 2020
- Country: India
- Language: English
- Number of centres: 1
- Trial registration number: CTRI/2020/05/025209
- Date of registration: 15 May 2020

Participants

- Age: female: 61.43 ± 11.33 years; male: 61.36 ± 12.17 years
- Sex: 71% of males in the intervention and control group together
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 80/80/80
- Severity of condition according to study definition: severe COVID-19 patients with mild ARDS (defined as patients having PaO₂/FiO₂ ratio of 200-300 mmHg) or moderate ARDS (defined as PaO₂/FiO₂ 100-200 mmHg) not on mechanical ventilation
- Severity of disease according to WHO score: level 5-6
- Comorbidities: NR
- Inclusion criteria
 - Consenting patients admitted with RT-PCR-proven COVID-19 with severe disease (fever or suspected respiratory infection, plus one of the following:
 - respiratory rate > 30 breaths/min
 - severe respiratory distress
 - SpO₂ < 90% at room air
 - With mild ARDS - defined as patients having partial pressure of oxygen in the arterial blood (PaO₂)/fraction of inspired oxygen (FiO₂) ratio of 200-300 mmHg - or moderate ARDS, defined as PaO₂/FiO₂ 100-200 mmHg, not on mechanical ventilation.
- Exclusion criteria
 - Pregnant or breastfeeding mothers, patients with age less than 18 years, patients participating in any other clinical trial, patients having any clinical condition precluding infusion of blood products
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation)
 - Hydroxychloroquine 400 mg twice daily on first day followed by 400 mg once daily for four days, azithromycin 500mg once daily for 5 days, ivermectin 12 mg once daily for 5 days and doxycycline 100 mg twice daily for 10 days
 - If ARDS: O₂ therapy as per requirement, either intravenous or oral corticosteroids, for patients with D-dimer 1000 ng/ml FEU therapeutic anticoagulation using either low molecular weight heparin or unfractionated heparin, appropriate broad-spectrum antibiotic therapy based on clinical, biochemical and microbiological assessment, appropriate antidiabetic therapy to maintain blood sugar below 200 mg/dL, anti-hypertensive agents, as per requirement, were used to maintain systolic blood pressure 100-140 mmHg, diastolic blood pressure at 70-90 mmHg and mean arterial pressure > 65 mmHg. Awake proning for 6-8 h/day was attempted in all patients with evidence for ARDS
 - Others: tocilizumab in one patient, remdesivir in 24 patients
- Donor eligibility criteria
 - Age > 18 years
 - Males or nulliparous female convalescent volunteers with history of being positive for SARS-CoV-2 on RT-PCR
 - Weight > 55 kg, complete resolution of symptoms at least 28 days prior to donation, and a negative RT-PCR test for SARS-CoV-2 before plasma donation
- Donor exclusion criteria: NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP therapy

Ray 2020 (Continued)

- Details of CP
 - Type of plasma: plasmapheresis
 - Volume: 200 mL
 - Number of doses: 2
 - Antibody test and antibody-titre: anti-SARS-CoV-2 spike protein IgG content via Euroimmun; value of 1.5 for the ratio optical density between the sample and calibrator was taken as a cut-off for inclusion.
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors
 - Sex: males or nulliparous female
 - HLA and HNA antibody-negative: NR
 - Severity of disease: NR
 - Timing from recovery from disease: complete resolution of symptoms at least 28 days prior to donation
 - RT-PCR-tested: one negative RT-PCR test
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severe disease
- For studies including a control group: comparator (type): standard therapy
- Concomitant therapy
 - Hydroxychloroquine 400 mg twice daily on first day followed by 400 mg once daily for four days, azithromycin 500mg once daily for 5 days, ivermectin 12 mg once daily for 5 days and doxycycline 100 mg twice daily for 10 days.
 - If ARDS: O₂ therapy as per requirement, either intravenous or oral corticosteroids, for patients with D-dimer 1000 ng/ml FEU therapeutic anticoagulation using either low molecular weight heparin or unfractionated heparin, appropriate broad-spectrum antibiotic therapy based on clinical, biochemical and microbiological assessment, appropriate antidiabetic therapy to maintain blood sugar below 200 mg/dl, anti-hypertensive agents, as per requirement, were used to maintain systolic blood pressure 100-140 mmHg, diastolic blood pressure at 70-90 mmHg and mean arterial pressure > 65 mmHg. Awake proning for 6-8 h/day was attempted in all patients with evidence for ARDS.
 - Others: tocilizumab in one patient, remdesivir in 24 patients.
- Duration of follow-up: 30 days
- Treatment cross-overs: none
- Compliance with assigned treatment: one patient died before second transfusion of CP.

Outcomes

- Primary study outcome(s): all-cause mortality at 30 days
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: 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 for transfusion-related events
 - Number of participants with SAEs: reported for transfusion-related events
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to death): yes
 - 90-day mortality: NR
 - Time to discharge from hospital: yes (total hospital stay duration of the patients)
 - Admission on the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: reported at day of enrolment only
 - QoL: NR

Ray 2020 (Continued)

- Additional study outcomes
 - To identify the immune correlates/cytokines for response to plasma therapy, characterisation of antibody response in donor plasma

Notes

- Preprint Ray posted: 29 November 2020
- Preprint Bandopadhyay posted: 7 October 2020
- Sponsor/funding: "DG acknowledges funding for the RCT and associated immune monitoring studies from Council of Scientific Industrial Research (CSIR), Govt. of India (MLP-129); RP acknowledges funding from CSIR (MLP-2005) and Fondation Botnar."
- COIs: "Nil"
- Other: "Nil"

Simonovich 2020
Study characteristics

Methods

- Trial design: RCT, double-blinded
- Type of publication: journal publication
- Setting: hospital (inpatient)
- Recruitment dates: (May-September 2020)
- Country: Argentina
- Language: English
- Number of centres: 12
- Trial registration number: NCT04383535
- Date of trial registration: 12 May 2020

Participants

- Age: median age, plasma group: 62.5 (IQR 53-72.5); control group 62 (49-71)
- Sex: 70.6% of males in the intervention group and 61% of males in the control group
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 448/334/333
- Severity of condition according to study definition: mostly moderate disease: all hospitalised; 4.8% in plasma group versus 6.7% in control group receiving high-flow oxygen (WHO = 6), 85.5% versus 81.9% receiving oxygen by mask or nasal prongs (WHO = 5), 9.7% versus 11.4% no oxygen (WHO = 4)
- Severity of condition according to WHO score: WHO 4-5 > 80%
- Comorbidities: BMI > 30, hypertension, diabetes, chronic obstructive pulmonary disease, asthma, chronic renal failure, haematologic cancer, solid tumours, current tobacco use, previous tobacco use, congestive heart failure, thromboembolic disease
- Inclusion criteria
 - At least 18 years of age
 - Hospitalised adults with a RT-PCR assay of a respiratory tract sample that was positive for SARS-CoV-2
 - Radiologically confirmed pneumonia
 - No previous directives rejecting advanced life support
 - At least one of the following severity criteria: oxygen saturation (SaO₂) below 93% while they were at rest and breathing ambient air, a ratio of the partial pressure of oxygen (PaO₂) to the fraction of inspired oxygen (FiO₂) below 300 mm Hg (PaO₂:FiO₂), or a sequential organ failure assessment (SOFA) or modified SOFA (mSOFA) score of two or more points above baseline status (scores range from 0 to 24, with higher scores indicating more severe disease)
 - Provision of informed consent by the participant

Simonovich 2020 (Continued)

- Exclusion criteria
 - Pregnant or lactating, or of reproductive age and not willing to use contraceptive measures for a period of 30 days after enrolment
 - History of blood component allergies, an infectious cause of pneumonia other than SARS-CoV-2, a requirement for mechanical ventilation, multiorgan failure, or any other condition that would impede the provision of informed consent
 - Confirmation of another concomitant microbiological cause of pneumonia other than COVID-19
 - On mechanical ventilation, with multiple organ failure or who for any other reason couldn't voluntarily give their consent.
- Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation)
 - Drugs: ACEI or ARB 2, NSAID, anticoagulation, corticosteroids, immunosuppressants, statins
 - Use of oxygen supplementation devices: low-flow nasal cannula, venturi or nonrebreather mask, high-flow nasal cannula, noninvasive ventilatory support
- Donor eligibility criteria
 - General acceptance criteria for blood donors according to Administrative and Technical Regulations RM 797/13 - 139/14 - 1507/15. Directorate of Blood and Hemoderivatives of the Ministry of Health of the Nation, Argentine Association of Hemotherapy, Immunohematology and Cell Therapy (AAHITC).
 - Age: 18 to 60 years
 - People who had recovered from SARS-CoV-2 infection
 - Previously diagnosed for COVID-19 and subsequently negative or SARS-CoV-2 and for other respiratory viruses
 - Donors had to have completed a period of 28 days for complete resolution of symptoms and return a negative result for COVID-19 (quali PCR swab or viral load in blood) according to FDA recommendations. If the result of this PCR was positive, a new assessment was performed according to the criteria of the treating physician
 - Multiparous donors had to be negative for anti-HLA antibodies. If the determination of anti-HLA antibodies could not be carried out, multiparous donors were not accepted.
 - The specific titre of total antibodies had to be $> 1/1000$
 - Study profile of transfusion transmissible infections (TTI) had to be negative for hepatitis B virus, hepatitis C virus, HIV, syphilis, brucellosis, HTLV and Chagas disease.
 - The donor had to read, understand and voluntarily sign the informed consent for Apheresis Plasma Donation.
- Donor exclusion criteria: NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP
 - Type of plasma: COVID-19 convalescent plasma
 - Volume: the infused volume was defined within the range of 5-10 mL/kg with an inferior limit around 400 mL when body weight was below 70 kg, and a superior limit of 600 mL for those above 70 kg. Median volume of infused convalescent plasma was 500 mL (IQR, 415 to 600).
 - Number of doses: 1
 - Type of antibody test and antibody-titre: end-point IgG titrations of specific antibodies against the SARS-CoV-2 spike and receptor-binding domain were performed with the COVIDAR Argentina Consortium enzyme-linked immunosorbent assay (ELISA) test
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors
 - Sex: NR
 - HLA and HNA antibody-negative: NR
 - Severity of disease: NR
 - Timing from recovery from disease: fully recovered from a clinical perspective and discharged from the hospital for at least 2 weeks
 - RT-PCR tested: yes
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR

Simonovich 2020 (Continued)

- For studies including a control group: comparator (type): placebo (saline)
- Concomitant therapy: antiviral agents, glucocorticoids, or both according to the standard of care
- Duration of follow-up: 30 days
- Treatment cross-overs: NA
- Compliance with assigned treatment: good (according to flow-chart)

Outcomes

- Primary study outcome
 - Clinical status 30 days after intervention, as represented by one of six mutually exclusive ordinal categories on an adapted version of the WHO clinical scale: 1 indicated death, 2 invasive ventilatory support, 3 hospitalised with supplemental oxygen requirement, 4 hospitalised without supplemental oxygen requirement, 5 discharged without full return to baseline physical function, and 6 discharged with full return to baseline physical function.
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: yes
- Secondary review outcomes
 - Participants with grade 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
 - Participants with SAEs: yes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): yes
 - 90-day mortality: NR
 - Time to discharge from hospital: yes
 - Admission on the ICU: NR
 - Length of stay on the ICU: yes
 - Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
- Additional review outcomes: the time to improvement in at least two categories on the ordinal scale and the time to full functional recovery.

Notes

- Journal published: 24 November 2020, at NEJM.org
- Sponsor/funding: Hospital Italiano de Buenos Aires

Abbreviations: 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; C: celsius; CDC: US Centers for Disease Control and Prevention; COI: conflict of interest; COPD: chronic obstructive pulmonary disease; CP: convalescent plasma; CPAP: continuous positive airway pressure; CPK: creatine phosphokinase; CRP: c-reactive protein; CT: computed tomography; DFPP: double-filtration plasmapheresis; DSMB: Data and Safety Monitoring Board; DVT: deep vein thrombosis; ECMO: extracorporeal membrane oxygenation; ED: emergency department; ELISA: enzyme-linked immunosorbent assay; FDA: US Food and Drug Administration; FiO₂: fractional inspired oxygen; GFR: glomerular filtration rate; HBV/HCV: hepatitis B/C; HCPOA: healthcare power of attorney; HLA: human leukocyte antigen; HNA: human neutrophil antigens; ICU: intensive care unit; IgA (B/G/M): immunoglobulin A (B/G/M); IL-6: interleukin-6; IMV: invasive mechanical ventilation; IQR: interquartile range; IV: intravenous; IVIG: intravenous immunoglobulin; LAR: legal authorised representative; LDH: lactate dehydrogenase; NR: not reported; NYHA: New York Heart Association; PaO₂: arterial blood oxygen partial pressure; PCR: polymerase chain reaction; PE: pulmonary embolism; PRNT: plaque reduction neutralisation test; QoL: quality of life; RCT: randomised controlled trial; RCU: respiratory care unit; RNA: ribonucleic acid; RT-PCR: reverse transcription polymerase chain reaction; SAE: serious adverse event; SARS: severe acute respiratory syndrome; SC: subcutaneous; SD: standard deviation; SOC: standard of care; 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; VMNT: viral microneutralisation test; WBC: white blood count; WHO: World Health Organization.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abdullah 2020	Single arm study; fewer than 500 participants received convalescent plasma
Abolghasemi 2020	Single arm study; fewer than 500 participants received convalescent plasma
Ahn 2020	Single-arm study; not pre-registered in a clinical study registry
Anderson 2020	Single-arm study; not pre-registered in a clinical study registry
Baklaushev 2020	Controlled study, probably not truly randomised
Balcells 2020	Performed another intervention comparison (early vs deferred plasma)
Bao 2020b	Single-arm study; not pre-registered in a clinical study registry
Bobek 2020	Single-arm study; not pre-registered in a clinical study registry
Bradfute 2020	Single arm study; fewer than 500 participants received convalescent plasma
Brasil Ministerio 2020	Standard operating procedure
Budhai 2020	Feasibility of plasma collection only
Cantore 2020	Single-arm study compared to published cases; not pre-registered in a clinical study registry
Cao 2020a	Ineligible intervention
Chen 2020b	Ineligible intervention
Chen 2020c	Ineligible intervention
ChiCTR2000029850	Single arm study; fewer than 500 participants will receive convalescent plasma
ChiCTR2000030039	Single arm study; fewer than 500 participants will receive convalescent plasma
ChiCTR2000030312	Study cancelled before starting recruitment
ChiCTR2000030381	Study cancelled before starting recruitment
ChiCTR2000030442	Study cancelled before starting recruitment
ChiCTR2000031501	Single arm study; fewer than 500 participants will receive convalescent plasma
ChiCTR2000033798	Single arm study; fewer than 500 participants will receive convalescent plasma
Clark 2020	Single-arm study; not pre-registered in a clinical study registry
CTRI/2020/04/024804	Single arm study; fewer than 500 participants will receive convalescent plasma
CTRI/2020/08/027285	Single arm study; fewer than 500 participants will receive convalescent plasma
CTRI/2020/10/028547	Ineligible intervention

Study	Reason for exclusion
Çınar 2020	Single-arm study; not pre-registered in a clinical study registry
de Assis 2020	Ineligible indication
Díez 2020	Ineligible intervention
Donato 2020	Single arm study; fewer than 500 participants received convalescent plasma
Duan 2020	Single arm study; fewer than 500 participants received convalescent plasma
Dulipsingh 2020	Single-arm study; fewer than 500 participants received convalescent plasma
Enzmann 2020	Single-arm study; not pre-registered in a clinical study registry
Erkurt 2020	Single-arm study; not pre-registered in a clinical study registry
Fan 2020	Single-arm study; not pre-registered in a clinical study registry
Figlerowicz 2020	Single-arm study; not pre-registered in a clinical study registry
Franchini 2020	Standard operating procedure
Grisolia 2020	Single-arm study; not pre-registered in a clinical study registry
Hashim 2020	Feasibility of plasma collection only
Hu 2020	Ineligible intervention
Ibrahim 2020	Single-arm study; fewer than 500 participants received convalescent plasma
Im 2020	Single-arm study; not pre-registered in a clinical study registry
IRCT20151228025732N53	Single-arm study; fewer than 500 participants will receive convalescent plasma
IRCT20200406046968N2	Single-arm study; fewer than 500 participants will receive convalescent plasma
IRCT20200414047072N1	Single-arm study; fewer than 500 participants will receive convalescent plasma
IRCT20200416047099N1	Single-arm study; fewer than 500 participants will receive convalescent plasma
ISRCTN86534580	Ineligible intervention
Jamous 2020	Single-arm study; not pre-registered in a clinical study registry
Jiang 2020a	Single-arm study; not pre-registered in a clinical study registry
Jiang 2020b	Ineligible intervention
Jin 2020	Single-arm study; fewer than 500 participants received convalescent plasma
Karatat 2020	Single-arm study; not pre-registered in a clinical study registry
Kong 2020	Single-arm study; not pre-registered in a clinical study registry
Lin 2020	Ineligible intervention

Study	Reason for exclusion
Liu 2020	Single-arm study; fewer than 500 participants received convalescent plasma
Liu 2020a	Single-arm study; not pre-registered in a clinical study registry
Madariaga 2020	Single-arm study; fewer than 500 participants received convalescent plasma
Martinez-Resendez 2020	Single-arm study; not pre-registered in a clinical study registry
McCuddy 2020	Single-arm study; not pre-registered in a clinical study registry
Ministerio de Salud 2020	Standard operating procedure
Mira 2020	Single-arm study; not pre-registered in a clinical study registry
NCT04261426	Ineligible intervention
NCT04264858	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04292340	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04321421	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04323800	Ineligible participant population (participants exposed to COVID-19)
NCT04325672	Study cancelled before starting recruitment
NCT04327349	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04332380	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04333355	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04344015	Feasibility of plasma collection only
NCT04344379	Ineligible intervention
NCT04344977	Feasibility of plasma collection only
NCT04345679	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04346589	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04347681	Controlled, non-randomised studies with less than 500 participants receiving convalescent plasma or hyperimmune immunoglobulin
NCT04348877	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04350580	Ineligible intervention
NCT04353206	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04354831	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04355897	Single-arm study; fewer than 500 participants will receive convalescent plasma

Study	Reason for exclusion
NCT04356482	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04360278	Feasibility of plasma collection only
NCT04365439	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04368013	Ineligible intervention
NCT04374565	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04376034	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04377672	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04383548	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04384497	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04384588	Controlled, non-randomised studies with less than 500 participants receiving convalescent plasma or hyperimmune immunoglobulin
NCT04388527	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04389710	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04389944	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04390178	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04392232	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04393727	Terminated in November 2020 (Study was stopped because the sponsor was changed and a new study on convalescent plasma sponsored by the Italian Medicines Agency (AIFA) was started in Italy)
NCT04397523	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04407208	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04408209	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04411602	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04412486	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04418531	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04432103	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04438694	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04458363	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04462848	Single-arm study; fewer than 500 participants will receive convalescent plasma

Study	Reason for exclusion
NCT04467151	Study withdrawn
NCT04471051	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04474340	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04476888	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04502472	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04513158	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04516954	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04535063	Single-arm study; fewer than 500 participants received convalescent plasma
NCT04554992	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04555109	Study of plasma donors
NCT04565197	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04569188	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04570982	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04614012	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04616976	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04622826	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04638634	Study on pharmacokinetics
NCT04644198	Single-arm study; fewer than 500 participants will receive convalescent plasma
NCT04661839	Pharmacokinetics study
NCT04721236	Single-arm hyperimmune immunoglobulin study with fewer than 500 participants
Niu 2020	Single-arm study; not pre-registered in a clinical study registry
Olivares-Gazca 2020	single arm study; less than 500 participants received convalescent plasma
Pei 2020	Single-arm study; not pre-registered in a clinical study registry
Peng 2020	Single-arm study; not pre-registered in a clinical study registry
PER-031-20	Single arm study; less than 500 participants will receive convalescent plasma
Perotti 2020	Single arm study; less than 500 participants received convalescent plasma
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.

Study	Reason for exclusion
	Article translated by Rujan Shrestha and Ya-Ying Wang via Cochrane TaskExchange
Rasheed 2020	Controlled study, probably not truly randomised
RBR-4vm3yy	Single arm study; less than 500 participants will receive convalescent plasma
Robbiani 2020	Ineligible intervention
RPCEC00000323	Single arm study; less than 500 participants will receive convalescent plasma
Salazar 2020a	single arm study; less than 500 participants received convalescent plasma
Salazar 2020b	Single-arm study; not pre-registered in a clinical study registry
Shen 2020	Single-arm study; not pre-registered in a clinical study registry
Shi 2020	Ineligible intervention
Soleimani 2020	Single-arm study; not pre-registered in a clinical study registry
Taher 2020	Single-arm study; not pre-registered in a clinical study registry
Tan 2020	Single-arm study; not pre-registered in a clinical study registry
Tu 2020	No use of convalescent plasma. Reporting on generalised collection of information about COVID-19 infection relating to aetiology, pathology, symptoms, clinical presentation and some generalised pharmacological treatment methods. The papers do not contain patient data that we required. Article translated by Rujan Shrestha and Ya-Ying Wang via Cochrane TaskExchange
Wang 2020	Single-arm study; not pre-registered in a clinical study registry
Wright 2020	Single-arm study; not pre-registered in a clinical study registry
Xia 2020	Single arm study; less than 500 participants received convalescent plasma
Xie 2020	Ineligible intervention
Xu 2020b	Single-arm study; not pre-registered in a clinical study registry
Yang 2020	Single-arm study; not pre-registered in a clinical study registry
Ye 2020	Single-arm study; not pre-registered in a clinical study registry
Zeng 2020	Single arm study; less than 500 participants received convalescent plasma
Zhang 2020a	Single-arm study; not pre-registered in a clinical study registry
Zhang 2020b	Single-arm study; not pre-registered in a clinical study registry
Zhang 2020c	Single-arm study; not pre-registered in a clinical study registry

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

Beltran 2021

Methods	<ul style="list-style-type: none"> • Trial design: single-centre, double-blind, RCT • Type of publication: preprint • Setting: inpatient • Recruitment dates: between 5 May and 17 October 2020 • Country: Mexico • Language English • Number of centres: 1 • Trial registration number: NCT04381858 • Date of trial registration: 11 May 2020
Participants	<ul style="list-style-type: none"> • Age: median age was 58 years (IQR 47-72) • Gender: male 62.6 % • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 193/190/165 • Severity of condition according to study definition: severe <ul style="list-style-type: none"> ◦ 85.2 % (n = 162) required invasive mechanical ventilation ◦ the remaining participants were managed with high-oxygen flow devices • Severity of condition according to WHO score: level > 6 • Inclusion criteria <ul style="list-style-type: none"> ◦ Fulfilled the operational definition of a suspected or confirmed case of COVID-19, and presented with criteria of severe pneumonia according to the ATS/IDSA guidelines ◦ Positive nasopharyngeal and oropharyngeal swab RT-PCR for SARS-CoV-2 ◦ Pneumonia diagnosed by high-resolution CT scan of the chest, and a pattern suggesting coronavirus infection ◦ Recently developed hypoxaemic respiratory failure or acute clinical exacerbation of pre-existing pulmonary or heart disease ◦ Requirement of respiratory support with a high-flow nasal cannula, defined as 60 L with a 90% inspired oxygen fraction or invasive mechanical ventilation with an orotracheal tube • Exclusion criteria: <ul style="list-style-type: none"> ◦ Viral infection other than COVID-19
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP or human immunoglobulin • Details of CP <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: 400 mL ◦ Number of doses: 2 ◦ Antibody-titre: when assay available > 1:640 ◦ Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: human immunoglobulin 0.3 g/kg/day for 5 doses • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: mean hospitalisation time • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: yes ◦ Time to death: yes

Beltran 2021 *(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
 - 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

Notes

- Recruitment status: completed
- Publication date: 31 March 2021
- Published after submission
- Sponsor/funding: Centenario Hospital Miguel Hidalgo

Bennett-Guerrero 2021

Methods

- Trial design: double-blind RCT
- Type of publication: journal publication
- Setting: inpatient
- Recruitment dates:
- Country: USA
- Language: English
- Number of centres: 1
- Trial registration number: NCT04344535
- Date of trial registration: 14 April 2020

Participants

- Age: intervention group mean: 67 (SD 15.8), control group mean: 64 (SD 17.4)
- Sex: intervention group: male 61.0%; control group: male 53.3%
- Number of participants (recruited/allocated/evaluated): 82/74/59 CP, 15 control group
- Severity of condition according to study definition
 - Nasal cannula or mask: intervention group 50.8% and control group 26.7%
 - Intubated: intervention group 18.6% and control group 20.0%
- Severity of condition according to WHO score: level 4, 5 and 6
- Inclusion criteria
 - Adults \geq 18 years
 - Hospitalised with PCR+ COVID-19 infection
 - If female, not pregnant or breastfeeding

Bennett-Guerrero 2021 (Continued)

- Exclusion criteria
 - Contraindication to transfusion or history of prior reactions to transfusion blood products
 - Receipt of pooled (polyclonal) immunoglobulin or any intravenous polyclonal immunoglobulin (IVIg) in past 30 days
 - Females with positive pregnancy test, breastfeeding, or planning to become pregnant/breast-feed during the study period
 - In the treating physician's opinion, unable to tolerate a 450-550 mL infusion of plasma over up to 8 h (4 h max per unit)
 - Unable to be randomised within 14 days of admission to Stony Brook Hospital (or any other hospital if a transfer)

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 remained 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 to 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)

Notes

- Trial status: completed
- Publication date: 16 April 2021
- Published after submission
- Sponsor/funding: Stony Brook University

CTRI/2020/05/025299

Methods

- Trial design: randomised, parallel group trial
- Sample size: 20

CTRI/2020/05/025299 (Continued)

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

Participants

- Inclusion criteria
 - Males or females aged between 18 to 75 years (both inclusive)
 - Hospitalised with RT-PCR confirmed COVID-19 illness and had one of either:
 - $\text{PaO}_2/\text{FiO}_2 < 300$
 - Respiratory rate $> 24/\text{min}$ and $\text{SaO}_2 < 93\%$ on room air
 - Subject or LAR agreed to provide a signed written informed consent prior to any study specific procedures and also agreed to comply with study requirements
- Exclusion criteria
 - Receipt of pooled immunoglobulin in past 30 days
 - Contraindication to transfusion or history of prior reactions to transfusion blood products
 - Critically ill with:
 - $\text{PaO}_2/\text{FiO}_2$ ratio < 200 (moderate - severe ARDS)
 - shock
 - Participating in any other clinical trial
 - Clinical status precluding infusion of blood products
 - Females with positive pregnancy test, breastfeeding, or planning to become pregnant or breastfeed during the study period

Interventions

- Details of CP
 - Type of plasma: NR
 - Volume: NR
 - Number of doses: 1 dose; additional unit will be given only if required based on subject's clinical status
 - 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
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome
 - Avoidance of progression to severe ARDS
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: yes (28 days)

CTRI/2020/05/025299 (Continued)

- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days): NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: length of hospital stay
 - Admission to the ICU: NR
 - Length of stay on the ICU: yes
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes (change and duration of RT-PCR test turning negative)
 - QoL: NR
 - 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 serious adverse events: NR
- Additional study outcomes
 - Improvement in symptoms and radiological findings
 - Change in anti-SARS-CoV-2 titers pre and post plasma transfusion
 - Evaluated duration and type (invasive or non-invasive) of ventilation support needed

Notes

- Recruitment status: completed, no results available
- Prospective completion date: 28 August 2020
- Sponsor/funding: Wockhardt Limited, Wockhardt Towers, 1st Floor, West Wing, Bandra Kurla Complex Mumbai – 400 051, India

CTRI/2020/05/025328

Methods

- Trial design: randomised, parallel group, active controlled trial
- Sample size: 100
- Setting: inpatient
- Country: India
- Language: English
- Number of centres: 5

Participants

- Inclusion criteria
 - Tested positive for COVID-19 by RT-PCR
 - Age > 18 years
 - Written and informed consent
 - Severe disease, defined as one or more of:
 - dyspnoea with oxygen saturation 93%
 - respiratory frequency 30/min and oxygen saturation 93%
 - partial pressure of arterial oxygen to fraction of inspired oxygen ratio
 - infiltrates on chest X-ray > 50% within 24 to 48 h
 - Life-threatening disease, defined as one or more of:
 - respiratory failure needing invasive support
 - sepsis
 - multiple organ dysfunction or failure

CTRI/2020/05/025328 (Continued)

- Exclusion criteria
 - Known hypersensitivity to blood products
 - Receipt of pooled immunoglobulin in last 30 days
 - Participating in any other clinical trial
 - Contraindications to blood products
 - Pregnant or breastfeeding women
 - In the opinion of the site investigator or primary clinical care team, expected to die within 48 h.
 - On mechanical ventilation for more than 7 days
 - Acute or chronic disease/illness that, in the opinion of the site investigator, had an expected life expectancy of less than 28 days unrelated to COVID-19 induced pneumonia (e.g. stage IV malignancy, neurodegenerative disease, anoxic brain injury, etc.)
 - Respiratory failure caused by illness other than SARS-CoV-2
 - Other documented, uncontrolled infection
 - Severe DIC, TTP, or antithrombin III deficiency needing factor replacement, FFP, cryoprecipitate
 - Active intracranial bleeding
 - Clinically significant myocardial ischaemia

 Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP
 - Type of plasma: NR
 - Volume: 200 mL
 - Number of doses: 2 doses
 - 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
- Concomitant therapy: NR
- Treatment cross-overs: none

 Outcomes

- Primary study outcome
 - All-cause mortality at 28 days
 - Improvement of SOFA score post transfusion
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: 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, transfusion-related AEs only
 - 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 (but with WHO scale)
 - 30-day and 90-day mortality: NR (up to 28 days)
 - Admission to the ICU: NR
 - Length of stay on the ICU: NR
 - Time to discharge from hospital: yes (Length of hospital stay)
 - QoL: NR

CTRI/2020/05/025328 (Continued)

- Additional study outcomes
 - Time to symptom resolution - Fever, shortness of breath, fatigue
 - Change in oxygen requirement post-transfusion
 - Decreased duration of respiratory support required:
 - duration of invasive mechanical ventilation
 - duration of non-invasive/HFNC
 - Radiological improvement
 - Adverse events (AE) associated with transfusion
 - Levels of bio-markers (CRP, IL-6, Ferritin) pre- and post-transfusion
 - Need of vasopressor use

Notes

- Recruitment status: completed
- Prospective completion date: 1 December 2020
- Sponsor/funding: Indraprastha Apollo Hospitals (a unit of Apollo Hospitals Enterprise Limited), Mathura Rd, SaritaVihar, New Delhi -110076

CTRI/2020/09/027903

Methods

- Trial design: prospective, open-label, two-arm, parallel-group, randomised, controlled, multi-centric trial
- Sample size: 60
- Setting: inpatient
- Country: India
- Language: English
- Number of centres: 10

Participants

- Inclusion criteria
 - Informed consent
 - 18 to 65 years of age (both inclusive)
 - Documented laboratory-confirmed SARS-CoV-2 infection determined by reverse transcription-polymerase chain reaction (RT-PCR) in any specimen, within 72 h prior to randomisation
 - Moderate or severe active COVID-19 (Clinical Management of COVID-19 Guidelines of MOHFW) at screening and baseline defined as:
 - radiological evidence of pulmonary infiltrates or clinical features such as dyspnoea and/or hypoxia, fever, cough, AND
 - SpO₂ of less than 94 % on room air AND
 - respiratory rate of greater than or equal to 24 per minute
 - Females had to not be pregnant or breastfeeding, with at least one of the following:
 - not of childbearing potential (WOCBP) OR
 - WOCBP and using an acceptable contraceptive method as described in [Appendix 8.4](#) during the intervention period and for a minimum 30 days after the last dose of study intervention
 - WOCBP must have a negative highly sensitive pregnancy test [serum] within 4 days before the first dose of study intervention
 - Male participants had to agree to the following during the intervention period and for at least 90 days after the last dose of study intervention:
 - refrain from sperm donation for the purpose of reproduction PLUS
 - use contraception/barrier
- Exclusion criteria
 - Need for invasive ventilation or having hemodynamic instability (MOHFW guideline) or multiple organ dysfunction/failure or evidence of bacterial superinfection (as defined by procalcitonin level greater than or equal to 0.5 µg/L or other applicable diagnostic parameters as per standard medical care)

CTRI/2020/09/027903 (Continued)

- Documented medical history of known allergies, hypersensitivity, or intolerance to intravenous immunoglobulin or other injectable form of IgG or blood products
- Documented medical history of known IgA deficiency
- History of at least one thrombotic event
- Received any blood products within 30 days prior to randomisation
- More than 5 days of COVID-19-specific hospitalisation prior to the first administration of treatment at baseline
- More than 10 days between the onset of symptoms and the day of first administration of treatment at baseline
- Pregnant or breastfeeding females
- Receiving renal replacement therapy/dialysis OR creatinine clearance < 50 mL/min using the Cockcroft-Gault formula
- Documented medical history of hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tested positive for HBsAg or anti-HCV at screening
- History of human immunodeficiency virus (HIV) antibody positive, or tests positive for HIV at screening
- Receiving or, in the last 14 days had received, experimental immune modulators, and/or monoclonal antibody therapies
- Confirmed diagnosis of bacterial pneumonia or other active/uncontrolled fungal or viral infections at screening/baseline
- Received organ transplantation or major surgery in the past 6 months
- ALT/AST levels 5 times higher than the normal upper limit and total bilirubin 3 times higher than the upper limit of normal
- Comorbid systemic illnesses (which, in the judgment of the investigator, would make the participant inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed treatment)
- Participation in another ongoing interventional clinical trial (with an investigational drug)
- Any other clinical/social/ psychiatric condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (e.g. compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments
- Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site

Interventions

- Details of hyperimmune immunoglobulin therapy
 - Drug name: COVID-19 hyper-immunoglobulin (human) solution
 - Dose: 30 mL as an intravenous injection on days 1 and 2 at the rate of not more than 0.5mL/kg/h
 - Number of doses: 2
 - Route: intravenous injection
 - Source: human
- Treatment details, including time of plasma therapy (e.g. early stage of disease): intervention within first 10 days of symptom onset
- For studies including a control group: comparator (type): standard of care
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome
 - Mean change from Day 1 to Day 8 in clinical outcome of treatment with COVID-19 hyper-immunoglobulin (human) compared to the control arm as assessed by 8-point ordinal scale
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: yes (day 28)

CTRI/2020/09/027903 (Continued)

- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days): NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission to the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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 serious adverse events: NR
- Additional study outcomes
 - Time to symptom resolution based on 5-point ordinal scale for up to 14 days: fever, shortness of breath, fatigue, cough
 - Mean change from Day 1 to Day 3 and Day 14 in clinical outcome of treatment with COVID-19 hyper-immunoglobulin (human) as compared to the control arm as assessed by 8-point ordinal scale
 - Composite clinical outcome assessed by following up to 14 days

Notes

- Recruitment status: completed
- Prospective completion date: 22 January 2021
- Sponsor/funding: Intas Pharmaceuticals Limited, Corporate House, Nr. Sola Bridge, S.G. Highway, Thaltej, Ahmedabad- 380054, Gujarat, India.

IRCT20120215009014N353

Methods

- Trial design: parallel-arm, phase II, randomised controlled trial
- Sample size: 100
- Setting: inpatient and outpatient
- Country: Iran
- Language: English
- Number of centres: 1

Participants

- Inclusion criteria
 - Age of 18 to 65 years
 - Moderate to severe COVID-19 disease
- Exclusion criteria
 - Pregnancy
 - IGA deficiency

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP
 - Type of plasma: NR
 - Volume: 500 IU
 - Number of doses: every week for at least 3 weeks
 - Antibody-titre: NR
 - Pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR

IRCT20120215009014N353 (Continued)

- For studies including a control group: comparator (type): standard of care, medication
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome
 - Dyspnoea
 - Fever
 - Cough
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: NR
 - All-cause mortality: NR
 - Admission to hospital: NR
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time-to-event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission to the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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 serious adverse events: NR
 - Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR
 - Time to symptom onset: NR
 - Length of hospital stay, for hospitalised patients: NR
- Additional study outcomes: none

Notes

- Recruitment status: completed
- Prospective completion date: NR
- Sponsor/funding: Hamedan University of Medical Sciences

IRCT20150808023559N21

Methods

- Trial design: RCT
- Sample size: 60
- Setting: hospitalised patients
- Country: Iran
- Language: English
- Number of centres: 1
- Trial registration: [IRCT20150808023559N21](#)
- Date of registration: 2020-05-09

IRCT20150808023559N21 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Blood oxygenation saturation < 90% ◦ Abnormal lung CT scan ◦ Significant shortness of breath ◦ Fever ◦ Did not improve within 48 h from enrolment ◦ No possibility of discharge in 48 h from enrolment ◦ Patient consent • Exclusion criteria <ul style="list-style-type: none"> ◦ Connected to a ventilator ◦ Did not give consent • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: 500 mL ◦ Number of doses: 1 ◦ Antibody test and antibody-titre: NR ◦ Pathogen inactivated or not: NR ◦ RT-PCR tested: NR • Details of donors <ul style="list-style-type: none"> ◦ Gender: NR ◦ HLA and HNA antibody: NR ◦ Severity of disease: NR ◦ Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients • Comparator (type): standard of care • Concomitant therapy: standard of care • Duration of follow-up: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome <ul style="list-style-type: none"> ◦ Reduction in all-cause mortality • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: yes ◦ Time to death: yes • Secondary review outcomes <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR ◦ WHO ordinal scale: NR ◦ 30-day and 90-day mortality: reported ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: reported ◦ QoL: NR ◦ Virological response: NR

IRCT20150808023559N21 (Continued)

- Additional outcomes: nil

Notes

- Recruitment status: completed
- Prospective completion date: 2020-08-22
- Sponsor/funding: Ardabil University of Medical Sciences

IRCT20200404046948N1

Methods

- Trial design: open-label, RCT
- Sample size: 60
- Setting: hospitalised patients
- Country: Iran
- Language: English
- Number of centres: 4

Participants

Participants

- Inclusion criteria
 - Laboratory-confirmed COVID-19 by PCR
 - Aged 18-70 years
 - Inpatients
 - Clinical severe disease, defined as any of the following:
 - dyspnoea
 - respiratory frequency $\geq 30/\text{min}$
 - blood oxygen saturation $\leq 93\%$ (in resting state)
 - $\text{PaO}_2/\text{FiO}_2 < 300$, and/or lung infiltrates $> 50\%$ within 24-48 h
 - Life-threatening disease defined as:
 - respiratory failure and need for mechanical ventilation
 - septic shock and/or multiple organ dysfunction or failure
 - Patient or legal guardian signed informed consent and participated voluntarily
 - Accepted randomised allocation (allocating into any group)
 - 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 such as multiple organ failure, and estimated survival time < 3 days
 - Severe congestive heart failure, or any other conditions for which plasma transfusion would be contraindicated (decided by study authors)
 - Any risk factor that might 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 believed that the patient was not a suitable participant

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

IRCT20200404046948N1 (Continued)

- For studies including a control group: comparator (type): conventional therapy and CP or conventional therapy only
- Concomitant therapy: conventional therapy
- Treatment cross-overs: NR

Outcomes

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

Notes

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

IRCT20200409047007N1

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
 - 50-75 years old
 - Normal IgA level
 - < 1 week since entry to the ICU
- Exclusion criteria
 - Uncontrolled hypertension
 - Advanced heart failure
 - Systolic blood pressure < 90 mmHg
 - COPD
 - Intubated
 - Chronic renal failure with GFR < 30

IRCT20200409047007N1 (Continued)

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|---------------|--|
| Interventions | <ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP <ul style="list-style-type: none"> ◦ Type of plasma: NR ◦ Volume: 500 cc each time ◦ Number of doses: up to 3 times/day ◦ Antibody-titre: NR ◦ Pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): treatment started as soon as possible after entry to the ICU (within a week) • For studies including a control group: comparator (type): in the control group, patients benefit from all available supportive and specific therapies based on existing standards • Concomitant therapy: NR • Treatment cross-overs: NR |
|---------------|--|

- | | |
|----------|--|
| Outcomes | <ul style="list-style-type: none"> • Primary study outcome: mortality rate in first month from the time of entry into the study • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: yes <ul style="list-style-type: none"> ■ mortality rate in first month from the time of entry into the study ◦ Time to death: NR, first month only • Secondary review outcomes <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR ◦ 30-day and 90-day mortality: yes ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: yes ◦ Time to discharge from hospital: NR ◦ QoL: NR • Additional study outcomes: NR |
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| Notes | <ul style="list-style-type: none"> • Recruitment status: completed • Prospective completion date: 15 August 2020 • Sponsor/funding: Mashhad University of Medical Sciences, Mashhad, Iran |
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IRCT20200413047056N1

- | | |
|---------|---|
| Methods | <ul style="list-style-type: none"> • Trial design: randomised, clinical trial • Sample size: 15 • Setting: hospitalised patients • Country: Iran • Language: English • Number of centres: 1 |
|---------|---|

IRCT20200413047056N1 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ 18-50 years old ◦ RT-PCR ◦ Confirmed infection in throat swab or sputum or lower respiratory tract samples ◦ Signed informed consent form on a voluntary basis ◦ Met any of the following criteria for severe or critical ill conditions: <ul style="list-style-type: none"> ■ respiratory rate \geq 30/min; or ■ rest SpO₂ \leq 90%; or ■ PaO₂/FiO₂ \leq 300 mmHg; or ■ respiratory failure and needs mechanical ventilation; or ■ multiple organ failure and needed ICU monitoring • Exclusion criteria <ul style="list-style-type: none"> ◦ NR
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP <ul style="list-style-type: none"> ◦ Type of plasma: NR ◦ Volume: 200 cc each time ◦ Number of doses: 2 ◦ Antibody-titre: NR ◦ Pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): 3 arms: CP; IV immunoglobulin (400 mg/kg/d); this group received common national protocol • Concomitant therapy: common national protocol • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcomes <ul style="list-style-type: none"> ◦ Lung involvement in X-ray and CT-scan ◦ SpO₂ ◦ LDH enzyme ◦ Viral load ◦ Acute phase protein ◦ White blood cell count ◦ Erythrocyte sedimentation rate ◦ Length of hospital stay ◦ Duration of mechanical ventilation • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ Time to death: NR • Secondary review outcomes <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes ◦ 30-day and 90-day mortality: NR ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: yes ◦ QoL: NR

IRCT20200413047056N1 (Continued)

- 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

Notes

- Recruitment status: completed
- Prospective completion date: 15 August 2020
- Sponsor/funding: Birjand University of Medical Sciences, Birjand, Iran

IRCT20200503047281N1

Methods

- Trial design: RCT
- Sample size: 40
- Setting: inpatient
- Country: Iran
- Language: English
- Number of centres: 1

Participants

- Inclusion criteria
 - Age 20-60 years
 - People with severe coronavirus disease
- Exclusion criteria
 - People with a history of other immune, genetic or infectious diseases other than corona virus
 - Individual suspended, but negative for clinical standard COVID-19 test

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP
 - Type of plasma: NR
 - Volume: 200 mL
 - Number of doses: 2 doses
 - 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
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome
 - Percentage of patients discharged from the intensive care unit and hospital (timing of measurement: "specific intervals, up to 1 year")
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: NR

IRCT20200503047281N1 (Continued)

- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: Length of hospital stay
 - Admission to the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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 serious adverse events: NR
- Additional study outcomes
 - Mortality (12 months)

Notes

- Recruitment status: completed
- Prospective completion date: NR
- Sponsor/funding: Yazd University of Medical Sciences

IRCT20200525047562N1

Methods

- Trial design: RCT
- Sample size: 100
- Setting: hospitalised patients
- Country: Iran
- Language: English
- Number of centres: 4
- Trial registration: [IRCT20200525047562N1](#)
- Date of registration: 6 May 2020

Participants

- Inclusion criteria
 - Hospitalised symptomatic COVID-19 patients scoring > 4 on the WHO Progression Scale
- Exclusion criteria
 - COVID-19 patients scoring < 4 on the WHO Progression Scale > 24 h since hospitalisation, won't enter the study
- Control group: people hospitalised with suspicion of COVID-19 but not randomised or not satisfied with receiving plasma
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP
 - Type of plasma: CP
 - Volume: 500 cc
 - Number of doses: 1-2
 - Antibody test and antibody-titre: NR
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR

IRCT20200525047562N1 (Continued)

- Details of donors
 - Gender: NR
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator (type): no CP
- Concomitant therapy: standard of care
- Duration of follow-up: NR
- Treatment cross-overs: NR

Outcomes

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

Notes

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

IRCT20201004048922N1

Methods

- Trial design: RCT, 3-arm, parallel, single-centre, phase 3 clinical trial
- Sample size: 75
- Setting: inpatient
- Country: Iran
- Language: English
- Number of centres: 1

IRCT20201004048922N1 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Confirmed or suspected COVID-19 pneumonia based on PCR or pulmonary imaging ◦ Presenting clinical symptoms of COVID-19 (fever, cough, dyspnoea) ◦ O₂ saturation equal or less than 93% ◦ Age 18 years and above ◦ Provided written consent to participate in the study ◦ Less than 7 days between the onset of clinical symptoms and the time of enrolment ◦ No participation in another concurrent clinical trial . • Exclusion criteria <ul style="list-style-type: none"> ◦ Advanced renal or liver disease ◦ Active cancer ◦ Known hypersensitivity reaction to plasma-derived drugs ◦ Pregnancy ◦ Lactation ◦ Patients could be excluded from the study during the first 48 h
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: hyperimmune immunoglobulin • Details of hyperimmune immunoglobulin therapy <ul style="list-style-type: none"> ◦ Drug name: routine human COVID-19 hyperimmune plasma ◦ Dose: 500 mL ◦ Number of doses: 1 dose ◦ Route: intravenous infusion ◦ Source: human • 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 • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Length of hospital stay due to COVID-19 • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: yes (day 28) • Secondary review outcomes <ul style="list-style-type: none"> ◦ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: NR ◦ Mortality (time to event): NR ◦ 90-day mortality: NR ◦ Time to discharge from hospital: yes (primary study endpoint) ◦ Admission to the ICU: yes (Requirement rate of receiving ICU care (days 1-7)) ◦ Length of stay on the ICU: NR ◦ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR ◦ QoL: NR ◦ 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), acute transfusion reactions): NR ◦ Number of participants with serious adverse events: NR

IRCT20201004048922N1 (Continued)

- Additional study outcomes
 - Requirement rate of mechanical ventilation (days 1-7)
 - " The 7-point ordinal scale" (no further information or reference to scale) (days 1, 7)
 - National Early Warning Score 2 (NEWS2) changes (days 1, 7)
 - Chest CT-scan score changes (days 1, 28)
 - Side effects (days 1-7)

Notes

- Recruitment status: completed
- Prospective completion date: NR
- Sponsor/funding: Tehran University of Medical Sciences

ISRCTN85216856

Methods

- Trial design: RCT
- Sample size: 200
- Setting: hospitalised patients
- Country: Ecuador
- Language: English
- Number of centres: 1
- Trial registration: [ISRCTN85216856](#)
- Date of registration: 6 May 2020

Participants

- Inclusion criteria
 - Aged ≥ 18 years
 - Clinical, molecular (using IgM/IgG or RT-PCR), or lung imaging diagnosis of COVID-19
 - Deterioration of previously normal lung function defined as SaO₂ of < 90% in 0.5 FiO₂, and/or a higher requirement of O₂ than in the previous 24 h
 - A score of 5-7 on the early warning scale for COVID-19 patients or a SOFA score between 2 and 10
 - Informed consent provided by participants or their representatives
- Exclusion criteria
 - Diagnosis and/or treatment for cancer
 - HIV infection
 - Currently receiving immunosuppressants for a condition other than SARS-CoV-2 infection
 - Superimposed systemic infections
 - Liver or kidney failure
 - COPD, previous pulmonary fibrosis, and/or restrictive lung disease
 - Have received previous transfusions
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP
 - Type of plasma: CP
 - Volume: 5 mL of plasma/kg of body weight IV
 - Number of doses: 1
 - Antibody test and antibody-titre: NR
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR

ISRCTN85216856 (Continued)

- Details of donors
 - Gender: NR
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator (type): standard plasma
- Concomitant therapy: standard of care
- Duration of follow-up: 21 days
- Treatment cross-overs: NR

Outcomes

- Primary study outcome
 - Case fatality rate assessed through data collected from the follow-up instrument and medical records at 21 and 28 days
- Primary review outcomes
 - All-cause mortality at hospital discharge: yes (up to day 21)
 - 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): reported
 - Number of participants with SAEs: reported
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - WHO ordinal scale: reported
 - 30-day and 90-day mortality: NR
 - Admission on the ICU: reported
 - Length of stay on the ICU: reported
 - Time to discharge from hospital: reported
 - QoL: NR
 - Virological response: NR
- Additional outcomes
 - SOFA, thoracic X-ray and/or tomography documented at discharge
 - Demographic information, including age and sex collected using the specific instrument created to screen potential patients at baseline
 - Time of initiation of treatment in relation to the evolution of the disease assessed using the follow-up instrument, completed daily from baseline to 21 days)
 - Sequelae at discharge (liver, kidney functions, pulmonary, cardiac and neurological) assessed by the follow-up instrument at discharge

Notes

- Recruitment status: completed
- Prospective completion date: December 2020
- Sponsor/funding: SalvarVidasEC (Ecuador)

jRCT2031200174

Methods

- Trial design: adaptive, randomised, double-blind, placebo-controlled trial
- Sample size: 10
- Setting: inpatient
- Country: Japan (part of international trial)
- Language: English

jRCT2031200174 (Continued)

Participants	<ul style="list-style-type: none"> • Number of centres: 1 (in Japan) <hr/> <ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Men and women ◦ Age > 18 years ◦ SARS-CoV-2 infection documented by PCR or other nucleic acid test (NAT) within 3 days prior to randomisation OR documented by NAT more than 3 days prior to randomisation AND progressive disease suggestive of ongoing SARS-CoV-2 infection ◦ Symptomatic COVID-19 disease ◦ Duration of symptoms attributable to COVID-19 ≤ 12 days ◦ Requiring inpatient hospital medical care for clinical manifestations of COVID-19 (admission for public health or quarantine only is not included) ◦ Age ≥ 18 years ◦ Willingness to abstain from participation in other COVID-19 treatment trials until after study Day 7 ◦ Provision of informed consent by participant or legally authorised representative • Exclusion criteria <ul style="list-style-type: none"> ◦ Prior receipt of SARS-CoV-2 hyperimmune immunoglobulin (hIVIG) or convalescent plasma from a person who recovered from COVID-19 at any time ◦ Prior receipt of standard IVIG (not hyperimmune to SARS-CoV-2) within 45 days ◦ Current or predicted imminent (within 24 h) requirement for any of the following: <ul style="list-style-type: none"> ■ invasive ventilation ■ non-invasive ventilation ■ extracorporeal membrane oxygenation ■ mechanical circulatory support ■ continuous vasopressor therapy ◦ History of allergy to IVIG or plasma products ◦ History of selective IgA deficiency with documented presence of anti-IgA antibodies ◦ Any medical conditions for which receipt of the required volume of intravenous fluid may be dangerous to the patient, including New York Heart Association Class III or IV stage heart failure ◦ Any of the following thrombotic or procoagulant disorders: <ul style="list-style-type: none"> ■ acute coronary syndromes ■ cerebrovascular syndromes ■ pulmonary or deep venous thrombosis within 28 days of randomisation ■ history of prothrombin gene mutation 20210, homozygous Factor V Leiden mutations, antithrombin III deficiency, protein C deficiency, protein S deficiency or antiphospholipid syndrome ◦ Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments
Interventions	<ul style="list-style-type: none"> • Details of hyperimmune immunoglobulin therapy <ul style="list-style-type: none"> ◦ Drug name: NR (hIVIG) ◦ Dose: 400 mg/kg bodyweight to a maximum dose of 40 g or 400 mL (i.e. capped at a body weight of 100 kg) ◦ Number of doses: 1 dose ◦ Route: infusion ◦ Source: human • 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 and placebo (first control group), standard of care (second control group) • Concomitant therapy: Remdesivir (200 mg IV loading dose (100 mL volume) on the first day of its infusion followed by 100 mg daily) • Treatment cross-overs: NR

jRCT2031200174 (Continued)

Outcomes

- Primary study outcome
 - Ordinal scale on clinical status on day 7 with the following categories:
 - a. no limiting symptoms due to COVID-19
 - b. limiting symptoms due to COVID-19
 - c. moderate end-organ dysfunction
 - d. serious end-organ dysfunction
 - e. life-threatening end-organ dysfunction
 - f. end-organ failure
 - g. death
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: yes (day 28)
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: partially (see primary study outcomes)
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: yes
 - Admission to the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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), acute transfusion reactions): yes
 - Number of participants with serious adverse events: yes
- Additional study outcomes
 - Change in National Early Warning Score (NEWS) from baseline at Day 3.
 - Time to the 3 least favourable categories of the primary outcome measure.
 - Time to the 2 most favourable categories of the primary outcome measure.
 - Hospitalisation status (a binary outcome, alive and discharged from the hospital to home or rehabilitation versus dead or hospitalised) at Days 7, 14 and 28.
 - Days alive outside of a hospital to Day 28
 - Pulmonary only components of the primary outcome measure at Days 3, 5, 7, 14 and 28
 - Thrombotic components of the primary outcome measure (stroke, myocardial infarction, venous and arterial thrombosis or embolism, plus disseminated intravascular coagulation) at Days 3, 5, 7, 14, and 28.
 - Outcomes assessed in other treatment trials of COVID-19 for hospitalised participants in order to facilitate cross trial comparisons and overviews, e.g., 6-, 7- and 8-category ordinal scales at

jRCT2031200174 (Continued)

days 7, 14 and 28; and binary outcomes defined by improvement or worsening based on the primary ordinal outcome and ordinal outcomes used in other trials.

- Clinical organ dysfunction defined by new onset of any one or more of the following conditions (or requirement for the following therapies) through Day 28:
 - extracorporeal membrane oxygenation (ECMO)
 - invasive ventilation
 - non-invasive ventilation or high flow oxygen
 - myocardial infarction
 - myocarditis or pericarditis
 - NYHA Class III/IV congestive cardiac failure
 - vasopressor therapy
 - renal replacement therapy (dialysis)
 - hepatic decompensation
 - cerebrovascular event (stroke)
 - encephalitis, meningitis or myelitis
 - acute delirium
 - disseminated intravascular coagulation
 - new thrombotic events, including pulmonary embolism, deep venous thrombosis, or arterial thrombosis
 - microbiologically-proven severe infection (not including SARS-CoV-2)
- Infusion reactions of any grade severity during the infusion and 2 h post-infusion, and percentage of participants for whom the infusion was interrupted or stopped prior to completion
- Change in immunoglobulin levels (IgG, IgG subclasses, IgM, IgA) and neutralising antibody titers from baseline to Days 1, 2, 3, 7, 28 and 90.
- Duration of symptoms

Notes

- Recruitment status: completed
- Prospective completion date: NR
- Sponsor/funding: Funded by the National Institute of Allergy and Infectious Diseases / National Institutes of Health, Ministry of Health, Labour and Welfare, Japan Agency for Medical Research and Development
- Part of ITAC study, other centres of ITAC study: [NCT04546581](#) and 2020-002542-16

Lopardo 2021

Methods

- Trial design: double-blind, placebo-controlled, multicenter clinical trial
- Type of publication: journal publication
- Setting: inpatient
- Recruitment dates:
- Country: Argentina
- Language: English
- Number of centres: NR

Participants

- Age: intervention group median: 54 (43 to 63) and control group median 54 (45 to 65)
- Sex: male intervention group: 67.8% and male control group: 62.6%
- Number of participants (recruited/allocated/evaluated): 247/245/241

Lopardo 2021 (Continued)

- Severity of condition according to study definition: moderate (partial pressure of oxygen in arterial blood/ fraction of inspired oxygen (PaO₂/FiO₂) ratio between 200 mmHg and 300 mmHg or a respiratory rate of more than 24/min with oxygen saturation 93% or less on room air)
 - Moderate illness: patients who had any of the various signs and symptoms of COVID-19 plus evidence of lower respiratory disease during clinical assessment or imaging and who had oxygen saturation (SpO₂) ≥ 94% on room air at sea level
 - Severe illness: individuals who had SpO₂ < 94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO₂/FiO₂) < 300 mmHg, respiratory frequency > 30 breaths per minute, or lung infiltrates > 50%
- Severity of condition according to WHO score: level 4-6
- Inclusion criteria
 - Men and women aged 18 to 79 years
 - SARS-CoV-2 infection confirmed by PCR for virus detection
 - Moderate or severe disease by NIH definition, which required hospitalisation.
 - Informed consent signed by a participant or relative, if applicable
 - Screening visit within 10 days of the onset of symptoms (case definition from the National Ministry of Health)
 - Females of child-bearing age to have a negative pregnancy test
- Exclusion criteria
 - Received treatment with plasma from COVID-19 convalescents.
 - Participating in other therapeutic clinical trials
 - Required mechanical respiratory assistance or were hospitalised in the ICU at the time of the screening visit.
 - History of anaphylaxis, prior administration of equine serum (for example, anti-tetanus serum or anti-ophidic serum or anti-arachnid toxin serum) or allergic reaction due to contact or exposure to horses.
 - Pregnant or breastfeeding
 - Likely to die within the next 30 days due to a concomitant disease other than the study disease
 - Referral to another institution expected within 72 h of enrolment, thus preventing proper follow-up

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: Anti-SARS-CoV-2 hyperimmune equine immunoglobulin
- Details of hyperimmune immunoglobulin therapy
 - Drug name: INM005
 - Dose: dose of 4 mg/kg
 - Number/frequency of doses: 2
 - Route: intravenous
 - Source (eg human/equine/other): equine
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): Placebo
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome
 - Proportion of participants that showed improvement 28 days after the administration of the first dose of at least two categories based upon the WHO 8-point ordinal clinical scale or hospital discharge
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: yes, up to 4 weeks

Lopardo 2021 (Continued)

- 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): NR
 - Number of participants with serious adverse events: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale ([WHO 2020e](#)), WHO Ordinal Scale for Clinical Improvement ([WHO 2020f](#))) at up to 7 days, 8 to 15 days, 16 to 30 days: yes
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: yes
 - Admission to the ICU: yes
 - Length of stay on the ICU: yes
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes
 - Change in viral load from baseline to 7 and 21 days after the start of the treatment.
 - QoL: NR
- Additional study outcomes
 - Pharmacokinetics evaluation of INM005 (time frame: 1 week)
 - Time to achieve a change in at least 2 categories on the 8-point WHO ordinal scale of clinical status (4 weeks)
 - Proportion of patients discharged at 28 days
 - Proportion of patients who require MVA
 - Measurement of anti SARS-CoV-2 antibodies titre levels; IgG (0, 21 days)
 - Changes in troponin T levels will be evaluated at 7 and 21 days as a measurement of disease progression
 - Changes in D-dimer levels will be evaluated at 7 and 21 days as a measurement of disease progression
 - Changes in ferritin levels
 - Changes in LDH levels
 - Changes in C-reactive protein levels
 - Immunogenicity

Notes

- Recruitment status: completed
- Publication date: April 11, 2021
- Published after submission
- Sponsor: Inmunova S.A.

NCT04315948

Methods

- Trial design: RCT (platform trial)
- Sample size: 3100
- Setting: inpatient
- Country: France
- Language English
- Number of centres: NR

Participants

Inclusion criteria

- Adults \geq 18 years of age

NCT04315948 (Continued)

- Hospitalised with any of the following criteria:
 - pulmonary rales/crackles on clinical exam OR
 - SpO₂ ≤ 94% on room air OR
 - requirement of supplementary oxygen, including high-flow oxygen devices or non-invasive ventilation
- < 9 days between onset of symptoms and randomisation
- Positive SARS-CoV-2 PCR performed on a NP swab within the 5 days preceding randomisation
- Positive SARS-CoV-2 rapid antigen test performed on a NP swab within the 6 h preceding randomisation
- Contraceptive use (by men and women)
 - Male participants: although contraception was not required, to avoid the transfer of any fluids, all male participants were required to use condoms from Day 1 and agree to continue for 90 days following administration of IMP.
 - Female participants: women of child-bearing potential required to agree to use contraception for 365 days following administration of IMP

Exclusion criteria

- Refusal to participate expressed by patient or legally authorised representative
- Need for invasive mechanical ventilation and/or ECMO at the time of enrolment
- Spontaneous blood ALT/AST levels > 5 times the upper limit of normal
- Glomerular filtration rate (GFR) < 15 mL/min or requiring maintenance dialysis
- Pregnant or breastfeeding
- Anticipated transfer to another hospital not included in the study within 72 h of randomisation
- Known history of allergy or reaction to any component of the study drug formulation
- Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of monoclonal or polyclonal antibodies
- Any prior receipt of investigational or licensed vaccine or other mAb/biologic indicated for the prevention of SARS-CoV-2 infection or COVID-19 or expected receipt in the 30 days following hospital discharge, according to current recommendation in each country
- Any medical condition which, in the judgment of the investigator, could interfere with the interpretation of the trial results or that precluded protocol adherence

Interventions

- Intervention(s): NA, there is no convalescent plasma or hyperimmune immunoglobulin arm included yet in this platform trial.
- Details of CP: NA
 - Type of plasma: NA
 - Volume: NA
 - Number of doses: NA
 - Antibody-titre: NA
 - Pathogen inactivated: NA
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NA
- Comparator: standard of care
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome
 - Percentage of subjects reporting each severity rating on a 7-point ordinal scale (time frame: Day 15)
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - Time to death: NR

NCT04315948 (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: NR
 - Length of stay on the ICU: NR
 - Time to discharge from hospital: yes (hospitalisation time)
 - QoL: NR
- Additional outcomes
 - Duration of hospitalisation (days)
 - Percentage of participants reporting each severity rating on a 7-point ordinal scale (time frame: Days 3, 5, 8, 11, 15 and 29)
 - The time to discharge or to a NEWS of ≤ 2 and maintained for 24 h, whichever occurs first (time frame: Days 3, 5, 8, 11, 15 and 29)
 - Number of oxygenation-free days in the first 28 days
 - Duration of new oxygen use, non-invasive ventilation or high flow oxygen devices during the trial
 - Ventilator-free days in the first 28 days
 - Incidence of new mechanical ventilation use during the trial
 - Hospitalisation
 - Number of participants with a discontinuation or temporary suspension of study drugs (for any reason)
 - Changes from baseline in blood white cell count (time frame: 29 days)
 - Changes from baseline in haemoglobin
 - Changes from baseline in platelets
 - Changes from baseline in creatinine
 - Changes from baseline in blood electrolytes (including kalaemia)
 - Changes from baseline in prothrombin time
 - Changes from baseline in international normalised ratio (INR)
 - Changes from baseline in glucose
 - Changes from baseline in total bilirubin
 - Changes from baseline in alanine aminotransferase (ALT)
 - Changes from baseline in aspartate aminotransferase (AST)
 - Percent of subjects with SARS-CoV-2 detectable in nasopharyngeal sample (time frame: Days 3, 5, 8, 11, 15, 29)
 - Quantitative SARS-CoV-2 virus in nasopharyngeal sample (time frame: Days 3, 5, 8, 11, 15, 29)
 - Quantitative SARS-CoV-2 virus in blood (time frame: Days 3, 5, 8 and 11)
 - Plasma concentration of lopinavir (time frame: Days 1, 3, 5, 8 and 11)
 - Plasma concentration of hydroxychloroquine (time frame: Days 1, 3, 5, 8 and 11)

Notes

Recruitment status: active, not recruiting

Prospective completion date: March 2023

Sponsor/funding: Institut National de la Santé et de la Recherche Médicale, France

NCT04332835

Methods

- Trial design: randomised, open-label, parallel-controlled trial

NCT04332835 (Continued)

- 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 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
- 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

NCT04332835 (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 immunoglobulin M COVID-19 antibodies titres
 - Change in immunoglobulin G COVID-19 antibodies titres
 - Clinical status assessed according to the WHO guideline

Notes

- Recruitment status: completed
- 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

NCT04355767

Methods

- Trial design: RCT (terminated early for futility, and the trial stopped recruiting)
- Sample size: 206
- Setting: outpatient (patients presenting to ED)
- Country: USA
- Language: English
- Number of centres: 1

Participants

- Inclusion criteria
 - Age ≥ 18 years
 - People requiring clinical evaluation in the ED but not hospital admission
 - Within 14 days of onset of COVID-19 symptoms
 - COVID-19 confirmed via COVID-19 SARS-CoV-2 RT-PCR testing or rapid RNA assay
 - Agree to storage of specimens for future testing
- Exclusion criteria
 - 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

NCT04355767 (Continued)

- For studies including a control group: comparator (type): normal plasma
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome
 - Number of patients with disease progression (day 15)
- Primary review outcomes
 - All-cause mortality: yes
 - Admission to hospital: NR (but might be requested, see additional study outcomes)
- Secondary review outcome
 - Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR
 - Time to symptom onset: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8 to 15 days, 16 to 30 days: yes (worst severity rating on WHO scale within 30 days)
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Length of hospital stay, for hospitalised patients: NR
 - Admission to ICU: NR (but might be requested, see additional study outcomes)
 - Viral clearance, assessed with RT-PCR test: NR
 - QoL: NR
 - Number of participants with grade 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
- Additional study outcomes
 - Time to disease progression (15 days), on COVID Outpatient Ordinal Outcome Scale:
 - a. patient requires care in the hospital
 - b. patient requires care in the ED or urgent care
 - c. patient at home with symptoms rated as moderate (defined as fever, shortness of breath, abdominal pain)
 - d. patient at home with symptoms rated as mild (defined as afebrile, constitutional symptoms (flu-like illness) without shortness)
 - e. patient in their usual state of health
 - Number of hospital-free days during the 30 days following randomisation (30 days)

Notes

- Recruitment status: recruiting
- Prospective completion date: December 2022
- Sponsor/funding: Stanford University

NCT04358211

Methods

- Trial design: expanded access study
- Sample size: intermediate-size population
- Setting: inpatient
- Country: USA
- Language: English
- Number of centres: single centre

NCT04358211 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ 18 years or older ◦ Hospitalised and intubated in the ICU with COVID-19 respiratory symptoms and confirmation via COVID-19 SARS-CoV-2 RT-PCR testing ◦ Patient or proxy provides written informed consent ◦ Provide consent to storage of specimens for future testing, or consent waived. ◦ Pregnant and breastfeeding women eligible for population 1 (mechanically ventilated intubated COVID-19 patients) • Exclusion criteria <ul style="list-style-type: none"> ◦ 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 ◦ Positive pregnancy test, breastfeeding, or planning to become pregnant or breastfeed during the study period (only an exclusion criterion for population 2: non-intubated patients) ◦ Receipt of pooled immunoglobulin in past 30 days (only exclusion criterion for population 2: non-intubated patients)
Interventions	<ul style="list-style-type: none"> • Details of convalescent plasma <ul style="list-style-type: none"> ◦ Volume: 200-400 mL ◦ Number of doses: 1-2 doses ◦ Antibody-titre: >1:160 ◦ Pathogen inactivated or not: NR • For studies including a control group: comparator (type): NA • Treatment details of control group (e.g dose, route of administration): NA • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcomes <ul style="list-style-type: none"> ◦ NR explicitly, "safety and efficacy of convalescent plasma" • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: NR • Secondary review outcomes <ul style="list-style-type: none"> ◦ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: partially (see primary study outcomes): NR ◦ Mortality (time to event): NR ◦ 90-day mortality: NR ◦ Time to discharge from hospital: NR ◦ Admission to ICU: NR ◦ Length of stay on ICU: NR ◦ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR ◦ QoL: NR ◦ Number of participants with grade 3 and grade 4 adverse events: NR ◦ Number of participants with serious adverse events: NR • Additional study outcomes <ul style="list-style-type: none"> ◦ None reported explicitly
Notes	<ul style="list-style-type: none"> • Expanded access status: no longer available • Prospective completion date: 31 December 2022 • Sponsor/funding: Nakhle Saba, MD, Tulane University School of Medicine

NCT04372368

Methods	<ul style="list-style-type: none"> • Trial design: expanded access study • Sample size: NR • Setting: inpatient • Country: USA • Language: English • Number of centres: 6
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Laboratory confirmed diagnosis of infection with SARS-CoV-2 ◦ Aged at least 18 years ◦ 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, defined as one of the following: <ul style="list-style-type: none"> ■ moderate disease: hospitalised with COVID-19, respiratory rate > 25/min, oxygen saturation < 96%, with or without radiographic evidence of pulmonary involvement ■ severe disease: dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, radiographic evidence of pulmonary disease ■ life-threatening disease: respiratory failure requiring mechanical ventilation or non-re-breather oxygenation in ICU, prone oxygenation, multiple organ dysfunction or failure ◦ Informed consent provided by the patient or healthcare proxy • Exclusion criteria <ul style="list-style-type: none"> ◦ History of transfusion reactions or contraindication to receiving convalescent plasma ◦ Risk of transfusion exceeds potential benefit based on clinician or blood bank determination
Interventions	<ul style="list-style-type: none"> • Details of convalescent plasma <ul style="list-style-type: none"> ◦ Volume: 100-400 mL (administration over 1 to 2 h with a rate of 100 to 200 mL/hr) ◦ Number of doses: 1-2 doses ◦ Antibody-titre: NR ◦ Pathogen inactivated or not: NR • For studies including a control group: comparator (type): NA • Treatment details of control group (e.g dose, route of administration): NA • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome <ul style="list-style-type: none"> ◦ Adverse effects ("incidents of adverse events judged by the treating physician to be potentially related to the administration of COVID-19 convalescent plasma") • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: NR

NCT04372368 (Continued)

- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: partially (see primary study outcomes): NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission to the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - Number of participants with grade 3 and grade 4 adverse events: NR
 - Number of participants with serious adverse events: NR
- Additional study outcomes:
 - Antibody response (change from day one after treatment to hospital discharge)
 - Correlation of level of neutralising antibody titers with clinical outcomes observed

Notes

- Expanded access status: no longer available
- Prospective completion date: NR
- Sponsor/funding: University of Colorado, Denver

NCT04392414

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
 - COVID-19 infection confirmed by PCR testing
 - COVID-19 pneumonia pattern on the chest HRCT with damage to more than 25% of the lung parenchyma
 - Morning fever ≥ 38.0 °C over previous 3 days
 - CRP blood level ≥ 50 mg/mL or ferritin blood level ≥ 600 µg/mL
 - 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
 - Need for home continuous oxygen therapy before the onset of current disease
 - Serum creatinine level > 150 µmol/L
- Pregnant or breastfeeding

Interventions

- Intervention(s): CP therapy

NCT04392414 (Continued)

- 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
 - Number and proportion of participants with normal body temperature (≤ 37.2 C) at days 1, 2, 3, 4, 5, 6, and 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 to ICU: NR
 - Length of stay on ICU: yes
 - Time to discharge from hospital: yes (up to 30 days)
 - QoL: NR
- Additional study outcomes
 - Changes of plasma levels of IL2, IL6, IL10, TNF alpha and INF gamma on days 3 and 7
 - Changes of plasma levels of CRP on days 1, 2, 3, 4, 5, 6, 7

Notes

- Recruitment status: completed
- Prospective completion date: 15 September 2020
- Sponsor/funding: Federal Research Clinical Center of Federal Medical & Biological Agency, Russia

NCT04405310

Methods

- Trial design: RCT
- Sample size: 80
- Setting: inpatient
- Country: Mexico
- Language: English
- Number of centres: 2

NCT04405310 (Continued)

Participants

- Inclusion criteria
 - Adults 18-70 years of age
 - Serious or critically ill patients confirmed with SARS-CoV-2 disease (RT-PCR)
 - Met criteria for phase II (moderate) and phase III (severe) disease with SARS-CoV-2
 - 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
 - Met criteria (plain chest CT or plain chest radiograph) for SARS-CoV-2 disease
 - Require supplemental oxygen through the facial store plus reservoir bag, high-flow nasal tips or advanced airway management and invasive mechanical ventilation support
- Exclusion criteria
 - 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
 - History of autoimmune diseases or selective IgA insufficiency
 - Participating in other trial 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): people with pneumonia due to SARS-COV-2
- Comparator: placebo 20% albumin in Hartman solution
- Concomitant therapy: azithromycin, hydroxychloroquine
- Treatment cross-overs: no

Outcomes

- Primary study outcome
 - All-cause mortality within 15 days
- Primary review outcomes
 - All-cause mortality at hospital discharge: yes, to 15 days
 - 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, to 15 days
 - 30-day and 90-day mortality: NR
 - Admission to ICU: yes, to 15 days
 - Length of stay on ICU: yes, to 15 days
 - Time to discharge from hospital: NR
 - QoL: NR

NCT04405310 (Continued)

- Additional outcomes (time frame: 15 days)
 - Changes in viral load by RT-PCR
 - Changes in pro-inflammatory and anti-inflammatory biomarkers (IL-6, PCR, ferritin, D Dimer, IL-8 IL-10)
 - Changes in SOFA scale

Notes

Recruitment status: completed

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

NCT04433910

Methods

- Trial design: randomised
- Sample size: 106
- Setting: hospitalised patients with severe disease
- Country: Germany
- Language: English
- Number of centres: 3
- Trial registration number: [NCT04433910](#) or EudraCT2020-001310-38
- Date of registration: 16 June 2020

Participants

- Inclusion criteria
 - SARS-CoV-2 infection confirmed by PCR (BAL, sputum, nasal and/or pharyngeal swab)
 - Age \geq 18 years and \leq 75 years
 - Severe disease defined by at least 1 of the following:
 - respiratory rate \geq 30 breaths/minute under ambient air
 - requirement of any type of ventilation support
 - need for ICU treatment
 - Written informed consent by patient or LAR

NCT04433910 (Continued)

- Exclusion criteria
 - Accompanying diseases other than COVID-19 with an expected survival time of < 12 months
 - Previous treatment with any SARS-CoV-2-CP
 - In the opinion of the clinical team, progression to death imminent and inevitable within following 48 h, irrespective of the provision of treatment
 - Interval > 72 h since start of ventilation support
 - Not eligible for ECMO support (even in case of severe ARDS according to Berlin classification with Horovitz-Index < 100 mgHg)
 - COPD, stage 4
 - Lung fibrosis with UIP pattern in CT and severe emphysema
 - Chronic heart failure NYHA ≥ 3 and/or pre-existing reduction of left ventricular ejection fraction to ≤ 30%
 - Shock of any type requiring ≥ 0.5 µg/kg/min noradrenaline (or equivalent) or requiring > 2 types of vasopressor medication for > 8 h
 - Liver cirrhosis Child C
 - Liver failure: bilirubin > 5 x ULN and elevation of ALT/AST (at least one > 10 x ULN)
 - Any history of adverse reactions to plasma proteins
 - Known deficiency of IgA
 - Pregnant or breastfeeding
 - Participation in another clinical trial with an investigational medicinal product
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP
 - Type of plasma: CP
 - Volume: (250-325 mL) on days 1, 3 and 5
 - Number of doses: 3 (transfusion on day 1, 3 and 5)
 - Antibody test and antibody-titre: NR
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors
 - Gender: NR
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients with severe disease
- Comparator: standard of care
- Concomitant therapy: standard of care
- Duration of follow-up: 60 days
- Treatment cross-overs: yes (cross over for participants with progressive disease on day 14 with CP transfusion on day 15, 17 and 19)

Outcomes

- Primary study outcome
 - Composite endpoint of survival and no longer fulfilling criteria of severe COVID-19 (time frame: Day 21)
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - Time to death: NR

NCT04433910 (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 (up to 4 h)
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - WHO ordinal scale: reported
 - 30-day and 90-day mortality: reported
 - Admission on the ICU: reported
 - Length of stay on the ICU: reported
 - Time to discharge from hospital: reported
 - QoL: NR
 - Virological response: reported (time until negative SARS-CoV-2 PCR (nasopharyngeal sample))
- Additional outcomes
 - Laboratory parameters (inflammatory markers, thrombotic markers, anti-SARS-CoV-2-antibody titres correlated with age; sex; severity of COVID-19; interval between resolution of symptoms and plasmapheresis of plasma donors, correlation of antibody titres with:
 - "Survival and no longer fulfilling criteria of severe COVID-19";
 - change in WHO ordinal scale;
 - time to clinical improvement;
 - length of hospital stay;
 - length of ICU stay;
 - length of mechanical ventilation or ECMO support.
 - Percentage of former COVID-19 patients willing to donate qualifying for plasma donation (time frame: through study completion, an average of 8 months)
 - Amount of plasma units that could be collected for the clinical trial (time frame: through study completion, an average of 8 months)
 - Titre of anti-SARS-CoV-2 in transfused plasma units (time frame: any plasmapheresis, through study completion, an average of 8 months)
 - Impact of donor characteristics on anti-SARS-CoV-2 humoral response (time frame: up to 60 days)
 - Course of anti-SARS-CoV-2 titre in both participant groups at different time points related to transfusion of CP (time frame: up to 60 days)

Notes

- Recruitment status: completed
- Prospective completion date: January 2021
- Sponsor/funding: Deutsches Rotes Kreuz DRK-Blutspendedienst Baden-Württemberg-Hessen

NCT04442958

Methods

- Trial design: randomised cross-over
- Sample size: 60
- Setting: severe with ARDS
- Country: Turkey
- Language: English
- Number of centres: 1
- Trial registration number: [NCT04442958](#)
- Date of registration: 23 June 2020

Participants

- Inclusion criteria
 - Clinical diagnosis of COVID-19

NCT04442958 (Continued)

- Exclusion criteria
 - < 18
 - Lower plasma IgA levels
 - PaO₂/FiO₂ > 300 mmHg
 - SpO₂ > 90
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP
 - Type of plasma: CP
 - Volume: 200 mL
 - Number of doses: 1
 - Antibody test and antibody-titre: neutralising antibody titres above 1:640
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors:
 - Gender: NR
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severe patients with ARDS
- Comparator: standard care
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcomes (time frame: 7 days)
 - Plasma ferritin level
 - Lymphocyte count
 - D-dimer level
 - CRP level
 - Plasma procalcitonin level
 - Plasma fibrinogen level
- 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
 - WHO ordinal scale: NR
 - 30-day and 90-day mortality: NR
 - Admission on the ICU: NR
 - Length of stay on the ICU: NR
 - Time to discharge from hospital: NR
 - QoL: NR
 - Virological response: NR

NCT04442958 (Continued)

- Additional outcomes (time frame: 7 days)
 - FiO₂ level
 - PaO₂ level
 - Arterial oxygen level

Notes

- Recruitment status: completed
- Prospective completion date: 17 June 2020
- Sponsor/funding: Bagcilar Training and Research Hospital

NCT04492501

Methods

- Trial design: non-randomised factorial assignment
- Sample size: 600
- Setting: hospitalised patients
- Country: Pakistan
- Language: English
- Number of centres: 1

Participants

- Inclusion criteria
 - PCR-positive-confirmed COVID-19
 - Admitted to hospital
 - Willing to participate in trial
 - Day of illness < 14 days
 - No contraindications to invasive procedure or novel therapies
- Exclusion criteria
 - Comorbidities with life expectancy < 6 months
 - Multi-organ failure
 - Septic shock before initiation of treatment
 - Congestive cardiac failure (ejection fraction < 20%)
 - Receiving immunotherapy, anti-thymocyte globulin or hematopoietic stem cell transplant recently
 - Haematological or solid organ malignancies

Interventions

- Details of CP
 - Volume: 200-400 mL
 - Number of doses: 1
 - Antibody test and antibody-titre: IgG titre of > 1.320
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients, within 14 days of illness
- Comparator: supportive care, procedure: therapeutic plasma exchange, tocilizumab, remdesivir, mesenchymal stem cell therapy
- Concomitant therapy: supportive care
- Duration of follow-up: 90 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome
 - Survival (time frame: 28 days)
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - Time to death: NR

NCT04492501 (Continued)

- Secondary review outcomes
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - Number of participants with SAEs: NR
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR
 - 30-day and 90-day mortality: NR
 - Admission to ICU: NR
 - Length of stay on ICU: NR
 - Time to discharge from hospital: reported
 - QoL: NR
 - Virological response: viral clearance at 45 days
- Additional outcomes:
 - Time to resolution of cytokine release storm (time frame: 28 days)
 - Complications (time frame: 90 days)

Notes

- Recruitment status: completed
- Prospective completion date: 20 July 2020
- Sponsors: UNICEF, Pak Emirates Military Hospital Rawalpindi

NCT04501978

Methods

- Trial design: RCT (platform trial)
- Sample size: 10,000
- Setting: inpatient
- Country: Denmark, USA, India, Poland, Singapore, Spain, Switzerland, UK
- Language: English
- Number of centres: 88

Participants

- Inclusion criteria
 - Signed informed consent
 - Positive test for COVID-19 and progressive disease suggestive of ongoing COVID-19 infection
 - Symptoms of COVID-19 for ≤ 12 days
 - Require admission to hospital for acute medical care (not for purely public health or quarantine purposes)

NCT04501978 (Continued)

- Exclusion criteria
 - Received plasma from a person who recovered from COVID-19 or who has received neutralising monoclonal antibodies at any time prior to hospitalisation.
 - Not willing to abstain from participation in other COVID-19 treatment trials until after Day 5 of the study, although co-enrolment in certain trials that compare recommended Standard of Care treatments allowed, based on the opinion of the study leadership team.
 - Any condition which, in the opinion of the responsible investigator, participation would not be in the best interest of the participant or that could prevent, limit, or confound the protocol-specified assessments.
 - Considered unable to participate in study procedures.
 - Women of child-bearing potential who were not pregnant at study entry and who were unwilling to accept advice to abstain from sexual intercourse with men or practice appropriate contraception during the 18 months of the study.
 - Men who were unwilling to accept advice to abstain from sexual intercourse with women of child-bearing potential or to use barrier contraception during the 18 months of the study.
 - Presence at study enrolment of any of the following:
 - stroke
 - meningitis
 - encephalitis
 - myelitis
 - myocardial ischemia
 - myocarditis
 - pericarditis
 - symptomatic congestive heart failure
 - arterial or deep venous thrombosis or pulmonary embolism
 - Current or imminent requirement for any of the following:
 - invasive mechanical ventilation
 - ECMO (extracorporeal membrane oxygenation)
 - Mechanical circulatory support
 - vasopressor therapy
 - commencement of renal replacement therapy at this admission (i.e. not patients on chronic renal replacement therapy).

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: hyperimmune immunoglobulin therapy
- Details of hyperimmune immunoglobulin therapy
 - Drug name: LY3819253, VIR-7831, BR11-196/BR11-198, AZD7442
 - Dose: one of the ACTIV-3 drug plus SOC (remdesivir)
 - Number/frequency of doses: NR
 - Route: intravenous
 - Source (e.g. human/equine/other): human
- Treatment details, including time of plasma therapy (e.g. early stage of disease): 2 disease severity strata
 - Participants without organ failure (severity stratum 1)
 - Participants with organ failure (severity stratum 2)
- For studies including a control group: comparator (type): placebo (commercially available 0.9% sodium chloride solution) + SOC (remdesivir)
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome
 - Time from randomisation to sustained recovery (time frame: to Day 90)
- Primary review outcomes
 - All-cause mortality at hospital discharge: probably yes
 - 30-day mortality: yes

NCT04501978 (Continued)

- Secondary review outcomes
 - 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): yes
 - Number of participants with serious adverse events: yes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale ([WHO 2020e](#)), WHO Ordinal Scale for Clinical Improvement ([WHO 2020f](#))) at up to 7 days, 8 to 15 days, 16 to 30 days: probably yes
 - Mortality (time to event): NR
 - 90-day mortality: yes
 - Time to discharge from hospital: NR
 - Admission to the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
- Additional study outcomes
 - All-cause mortality (time frame: to Day 90)
 - Composite of time to sustained recovery and mortality (time frame: to Day 90)
 - Days alive outside short-term acute care hospital (time frame: to Day 90)
 - Pulmonary ordinal outcome (time frame: Days 1-7, 14 and 28)
 - Pulmonary+ ordinal outcome (time frame: Days 1-7)
 - Incidence of clinical organ failure (time frame: through Day 28)
 - Composite of death or serious clinical COVID-19 related events (time frame: to Day 90)
 - Composite of cardiovascular events and thromboembolic events (time frame: to Day 90)
 - Composite of grade 3 and 4 clinical adverse events, serious adverse events (SAEs) or death (time frame: to Days 5 and 28)
 - Incidence of infusion reactions (time frame: to Day 0)
 - Composite of SAEs or death (time frame: to 18 months)
 - Change in SARS-CoV-2 neutralising antibody levels (time frame: baseline to Days 1, 3, 5, 28 and 90)
 - Change in overall titres of antibodies (time frame: baseline to Days 1, 3, 5, 28 and 90)
 - Change in neutralising antibody levels (time frame: baseline to Days 1, 3, 5, 28 and 90)
 - Incidence of home use of supplemental oxygen above pre-morbid oxygen use (time frame: 18 months)
 - Incidence of no home use of supplemental oxygen above pre-morbid oxygen use (time frame: 14 days)

Notes

- Recruitment status: recruiting
- Planned completion date: July 2022
- Sponsor: National Institute of Allergy and Infectious Diseases (NIAID)

NCT04521309

Methods

- Trial design: RCT, sequential assignment
- Sample size: 50
- Setting: inpatient
- Country: Pakistan
- Language: English
- Number of centres: NR

NCT04521309 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Over 18 years of age ◦ Positive SARS-CoV-2 PCR on nasopharyngeal and/or oropharyngeal swabs ◦ Admitted in isolation ward and ICU of institutes affiliated with DUHS ◦ Severe or critical COVID-19 as judged by the treating physician ◦ Consent given by the patient or first degree relative • Exclusion criteria <ul style="list-style-type: none"> ◦ Pregnant ◦ Previous allergic reaction to immunoglobulin treatment ◦ Ig A deficiency ◦ Requiring 2 inotropic agents to maintain blood pressures ◦ Known case of any autoimmune disorder ◦ Acute kidney injury or chronic renal failure ◦ Known case of thromboembolic disorder ◦ Aseptic meningitis
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP <ul style="list-style-type: none"> ◦ Type of plasma: Immunoglobulins (IVIg) developed from convalescent plasma ◦ Volume: <ul style="list-style-type: none"> ■ single dose of 0.20 g/Kg anti-COVID-19 IVIg ■ single dose of 0.25 g/Kg anti-COVID19 IVIg ■ single dose of 0.30 g/Kg anti-COVID19 IVIg ■ single dose of 0.35 g/Kg anti-COVID19 IVIg ◦ 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 care only n = 10 patients • Concomitant therapy: airway support, anti-viral medication, antibiotics, fluid resuscitation, haemodynamic support, steroids, painkillers, antipyretics • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcomes (time frame: 28 days) <ul style="list-style-type: none"> ◦ Mortality ◦ Requirement of supplemental oxygen support ◦ Number of days on assisted ventilation ◦ Days to step down ◦ Days to hospital discharge ◦ Adverse events during hospital stay ◦ Change in C-reactive protein (CRP) levels ◦ Change in neutrophil lymphocyte ratio • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: yes, 28-day mortality

NCT04521309 (Continued)

- 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, TRALI reported
 - Number of participants with serious adverse events
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale ([WHO 2020e](#)), WHO Ordinal Scale for Clinical Improvement ([WHO 2020f](#))) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: yes
 - Admission to the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes, time frame: 28 days
 - QoL: NR
- Additional study outcomes
 - Change in ferritin levels
 - Change in lactate dehydrogenase
 - Change in radiological (X-ray) findings
 - Anti-SARS-CoV-2 Antibody
 - Change in sodium levels
 - Change in potassium levels
 - Change in chloride levels
 - Change in bicarbonate levels

Notes

- Recruitment status: completed
- Planned completion date: March 2021
- Sponsors: Dow University of Health Sciences Higher Education Commission (Pakistan)

NCT04542941

Methods

- Trial design: prospective randomised two-arm open-label clinical trial
- Sample size: 136
- Setting: inpatient
- Country: Uganda
- Language: English
- Number of centres: 1

Participants

- Inclusion criteria
 - Adults with documented laboratory RT-PCR confirmed SARS-CoV-2 infection
 - Able to provide informed consent or next of kin or legal surrogate to provide consent
- Exclusion criteria
 - Prior diagnosis of IgA deficiency
 - Inability to return for post discharge follow-up

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP

NCT04542941 (Continued)

- 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): standard of care
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome
 - Time to viral clearance (RT-PCR negativity) (time frame: 28 days)
- Primary review outcomes
 - All-cause mortality: NR
 - Admission to hospital: NR
- Secondary review outcomes
 - Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR
 - Time to symptom onset: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Length of hospital stay, for hospitalised patients: NR
 - Admission to the ICU: NR
 - Viral clearance, assessed with RT-PCR test: probably reported
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: NR
- Additional study outcomes
 - Time to symptom resolution (time frame: 28 days)
 - Time to severe/critical disease (time frame: 28 days)
 - Number of participants reporting an adverse event as evidenced by clinical manifestations (time frame: 28 days)

Notes

- Recruitment status: completed
- Prospective completion date: 31December 2020
- Preprint version not yet posted
- Not yet published
- Sponsor/funding: Makerere University, Uganda Blood Transfusion Services, Joint Clinical Research Center, Uganda Peoples Defence Forces Medical Services, Mulago Hospital, Uganda

NCT04547127
Methods

- Trial design: multi-centre, randomised, open-label, parallel group pilot study
- Sample size: 200
- Setting: inpatient
- Country: Spain

NCT04547127 (Continued)

	<ul style="list-style-type: none"> • Language: English • Number of centres: 12
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Hospitalised men and women \geq 18 years of age ◦ Treated in ICU for COVID-19 for < 48 h or for whom it has been decided that severity of COVID-19 disease warrants ICU admission ◦ Informed consent provided by participant or representative prior to initiation of any study procedures ◦ Laboratory-confirmed novel coronavirus (SARS-CoV-2) infection determined by qualitative RT-PCR, or other commercial or public health assay in any specimen ◦ Illness (symptoms) of any duration, and the following: <ul style="list-style-type: none"> ■ radiographic infiltrates by imaging (chest X-ray, CT scan, etc.), AND ■ requiring mechanical ventilation and/or supplemental oxygen ◦ No limitation of therapeutic effort (decision on the status and future of the subject) ◦ Negative test for pregnancy blood or urine human chorionic gonadotropin (HCG)-based assay at screening/baseline visit for females of child-bearing potential • Exclusion criteria <ul style="list-style-type: none"> ◦ Clinical evidence of any significant acute or chronic disease that, in the opinion of the investigator, may place the subject at undue medical risk ◦ Known serious anaphylactic reaction to blood, any blood-derived or plasma product or methylene blue ◦ Medical condition in which the infusion of additional fluid is contraindicated ◦ Unresponsive to fluid challenge and/or multiple vasopressors and accompanied by multiorgan failure considered by the Principal Investigator not able to be reversed
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP <ul style="list-style-type: none"> ◦ Type of plasma: ABO-compatible convalescent plasma with each unit of plasma, obtained from the same convalescent donor (fresh frozen plasma) ◦ Volume: 200-250 mL ◦ Number of doses: 2 doses ◦ 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 medical treatment • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ All-cause mortality rate (time frame: up to Day 29) • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: probably reported

NCT04547127 (Continued)

- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: probably reported
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: Length of hospital stay
 - Admission to the ICU: NR
 - Length of stay on the ICU: probably reported
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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 serious adverse events: NR
- Additional study outcomes (time frame: Day 1 through Day 29)
 - Change from baseline in National Early Warning Score (NEWS)
 - Time to clinical response as assessed by NEWS ≤ 2 maintained for 24 h
 - Time to hospital discharge
 - Time to ICU discharge
 - Duration of all oxygen use
 - Duration of mechanical ventilation
 - Absolute value change from baseline in ordinal scale
 - Mean change from baseline in ordinal scale
- Additional study outcomes (time frame: Day 15 and Day 29)
 - Percentage of participants in each severity category of the 7-point ordinal scale

Notes

- Recruitment status: completed
- Prospective completion date: March 2021
- Sponsor/funding: Instituto Grifols, S.A.

NCT04547660

Methods

- Trial design: randomised, open-label (single-blinded), phase 3 trial
- Sample size: 160
- Setting: inpatient
- Country: Brazil
- Language: English
- Number of centres: 1

Participants

- Inclusion criteria
 - Age ≥ 18 years
 - Diagnosis of SARS-CoV-2 infection through nasal cavity or oropharynx swab RT-PCR
 - Severe COVID-19 defined by the presence of at least 1 of the following:
 - respiratory rate > 30 breaths per minute in room air
 - oxygen saturation (O_2) $\leq 93\%$ in room air
 - PaO_2/FiO_2 ratio ≤ 300
 - need for supplemental O_2 to maintain O_2 saturation $> 95\%$
 - need for therapy with supplemental O_2 by high flow catheter or non-invasive ventilation or invasive mechanical ventilation
 - Onset of symptoms during previous 14 days

NCT04547660 (Continued)

- Exclusion criteria
 - Failure to perform the first plasma infusion within 14 days of the onset of symptoms
 - Use of immunosuppressants for other underlying diseases, except corticosteroids for the SARS-CoV-2, in the 30 days before enrolment
 - Pregnant
 - History of serious adverse reactions, such as transfusion anaphylaxis
 - Participation in another interventional clinical trial
 - Disagreement of attending physician
 - Decision by patient or legal representative not to participate in the study

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP
 - Type of plasma: frozen convalescent plasma, thawed at 37 degrees Celsius before infusion
 - Volume: 300 mL
 - Number of doses: 2 doses
 - 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): best supportive care, any form of ventilatory support, extracorporeal membrane oxygenation, steroids, antibiotics and other supportive measures except for investigational interventions
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome
 - Clinical improvement (time frame: 28 days)
 - Improvement of 2 points from randomisation in a 6-point ordinal severity scale:
 - a. hospital discharge
 - b. hospitalisation with no supplemental oxygen
 - c. hospitalisation plus supplemental oxygen (not high-flow or noninvasive ventilation)
 - d. hospitalisation plus noninvasive ventilation or high-flow supplemental oxygen
 - e. hospitalisation plus extracorporeal membrane oxygenation (ECMO) or invasive mechanical ventilation
 - f. death
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: probably reported
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: reported
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: Length of hospital stay
 - Admission to the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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): probably reported
 - Number of participants with serious adverse events: probably reported

NCT04547660 (Continued)

- Additional study outcomes
 - 6-point ordinal scale proportion at 14 days (time frame: 14 days from randomisation)
 - 6-point ordinal scale proportion at 28 days (time frame: 28 days from randomisation)
 - Overall mortality (time frame: 14 days)
 - Overall mortality (time frame: 28 days)
 - Days alive and free of respiratory support (DAFOR28) (time frame: 28 days)
 - Mechanical ventilation (time frame: 28 days)
 - PaO₂/FiO₂ ratio (time frame: at 7th day from randomisation)
 - Hospital stay (time frame: 28 days)
 - Lactate dehydrogenase (time frame: Randomisation day, Day 3, Day 7 and Day 14)
 - Troponin I (time frame: randomisation day, Day 3, Day 7 and Day 14)
 - C-reactive protein (time frame: randomisation day, Day 3, Day 7 and Day 14)
 - D-dimers (time frame: randomisation day, Day 3, Day 7 and Day 14)
 - Fibrinogen (time frame: randomisation day, Day 3, Day 7 and Day 14)
 - Prothrombin Time (PT) (time frame: randomisation day, Day 3, Day 7 and Day 14)
 - Activated partial thromboplastin Time (APTT) (time frame: randomisation day, Day 3, Day 7 and Day 14)
 - Tumor necrosis factor alpha (TNF-alpha) (time frame: randomisation day, Day 3, Day 7 and Day 14)
 - Interleukin-6 (IL-6) (time frame: randomisation day, Day 3, Day 7 and Day 14)
 - RT-PCR (time frame: at 7th day from randomisation (or at hospital discharge if earlier than 7 days))
 - Sequential organ failure assessment (SOFA) score (time frame: at 7th day from randomisation)
 - National Early Warning Score 2 (NEWS) 2 (time frame: at 7th and 14th days from randomisation)
 - Safety and adverse events (time frame: 28 days)

Notes

- Recruitment status: completed
- Sponsor/funding: Hospital de Clinicas de Porto Alegre

NCT04610502

Methods

- Trial design: RCT
- Sample size: 26
- Setting: inpatient
- Country: Costa Rica
- Language: English
- Number of centres: 4
- Trial registration number: [NCT04610502](#)
- Date of registration: 30 October 2020

Participants

- Inclusion criteria
 - Adults > 18 years with confirmed diagnosis of COVID-19
 - Onset of symptoms < 10 days
 - Presence of at least 2 documented risk factors
 - Moderate or severe disease

NCT04610502 (Continued)

	<ul style="list-style-type: none"> • Exclusion criteria <ul style="list-style-type: none"> ◦ Critical illness ◦ Previously bitten by a snake and treated with equine hyperimmune serum ◦ Outpatient ◦ Pregnant ◦ Haemodialysis ◦ Previous receipt of convalescent plasma from COVID-19 patient ◦ Reserved prognosis with short lifespan prior to COVID-19 diagnosis • Donor eligibility criteria NR • Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): hyperimmune immunoglobulin therapy • Details of therapy <ul style="list-style-type: none"> ◦ Type of plasma or hyperimmune immunoglobulin therapy: equine immunoglobulin anti SARS-CoV-2 - "S" formulation ◦ Volume: 10 mL ◦ Number of doses: 1 ◦ Antibody-titre: N/R ◦ Pathogen inactivated: N/R • Treatment details, including time of plasma therapy (e.g. early stage of disease): Day 1 • Comparator: equine immunoglobulin anti SARS-CoV-2 - "M" formulation • Concomitant therapy: standard care • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome <ul style="list-style-type: none"> ◦ Evaluation of the efficacy of two formulations of equine anti-SARS-CoV-2 immunoglobulins ("S" and "M") ◦ Evaluation of the safety of two formulations of equine anti-SARS-CoV-2 immunoglobulins ("S" and "M") (time frame: 3 months) • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: yes ◦ Number of participants with SAEs: yes ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes, to 14 days ◦ 30-day and 90-day mortality: up to 24 days ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: yes ◦ QoL: NR ◦ Virological response: yes • Additional outcomes <ul style="list-style-type: none"> ◦ Inflammatory markers ◦ Thrombotic markers ◦ SpFI (Partial saturation oxygen/inspired fraction of oxygen) gain ◦ Lung ultrasound, assessed by POCUS score
Notes	<ul style="list-style-type: none"> • Recruitment status: completed • Sponsor/funding: Caja Costarricense de Seguro Social

Pouladzadeh 2021

Methods	<ul style="list-style-type: none"> • Trial design: hospital-based, parallel-group, single-blind, RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: March-May 2020 • Country: Iran • Language: English • Number of centres: 1 • Trial registration number: IRCT20200310046736N1 • Date of trial registration: 01 April 2020
Participants	<ul style="list-style-type: none"> • Age: intervention group mean age: 53.5 ± 10.3 years; control group mean age: 57.2 ± 17 years • Ethnicity: NR • Number of participants (recruited/allocated/evaluated): 62/62/60 • Severity of condition according to study definition: <ul style="list-style-type: none"> ◦ intervention group: WHO level 5: 66.7%, WHO level 6: 33.3% ◦ control group: WHO level 5: 83.3%, WHO level 6: 16.7% • Severity of condition according to WHO score: level 5 and 6 • Comorbidities: NR • Inclusion criteria <ul style="list-style-type: none"> ◦ COVID-19 patients who had specified COVID-19 symptoms (less than 7 days since the onset of the symptoms) ◦ Positive results for PCR test and CT scan ◦ Severity WHO score > 4 ◦ Blood oxygen saturation (SPO₂) ≤ 93% in room air ◦ No hypersensitivity to plasma intravenous administration ◦ Signed informed consent voluntarily • Exclusion criteria <ul style="list-style-type: none"> ◦ Pregnant (based on WHO protocol) ◦ Lactating (based on WHO protocol) ◦ People with 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 • Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR • Donor eligibility criteria <ul style="list-style-type: none"> ◦ Recovered individuals aged 20–45 years with a recovery asymptomatic period of at least 2 weeks ◦ Negative SARS-CoV-2 RT-qPCR test result ◦ Negative test result for Hepatitis B, C, AIDS, syphilis, HTLV-1, and influenza ◦ No IgA deficiency and or other dangerous underlying diseases ◦ Non-smokers ◦ No pregnant and lactating women ◦ Signed the informed consent ◦ All plasma donors had to show prior strong positive results for SARS-CoV-2 IgG/IgM Quick Test (German) for neutralising IgG antibodies and negative results for IgM antibodies • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP

Pouladzadeh 2021 (Continued)

- Details of CP
 - Type of plasma: obtained from fully recovered patients according to inclusion criteria
 - Volume: 200 mL/day IV administration for 1-4 h
 - Number of doses: for 1-4 days
 - Type of antibody test and antibody-titre: NR
 - Pathogen inactivated or not: NR
 - RT-PCR tested: 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
- Compliance with assigned treatment: yes

Outcomes

- Primary study outcome
 - Improvement in the levels of cytokine storm indices
- 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 (frequency of CP therapy-related side effects)
 - 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 (2-month mortality after admission)
 - Admission on the ICU: NR
 - Length of stay on the ICU: NR
 - Time to discharge from hospital: yes (length of in-hospital stay)
 - 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

Notes

- Recruitment status: completed
- Publication date: 10 April 2021
- Published after submission
- Sponsor/funding: Ahvaz University of Medical Sciences, 61357-15794 Ahvaz, Iran

AE: adverse event; ARDS: acute respiratory distress syndrome; CAP: community-acquired pneumonia; COPD: chronic obstructive pulmonary disease; CP: convalescent plasma; CRP: C-reactive protein; CT: computed tomography; ECMO: extracorporeal membrane oxygenation; ELISA: enzyme-linked immunosorbent assay; FiO₂: fractional inspired oxygen; GFR: glomerular filtration rate; HLA: human leukocyte antigen; HNA: human neutrophil antigens; ICU: intensive care unit; IgA (B/G/M): immunoglobulin A (B/G/M); IL-6: interleukin-6; IQR: interquartile range; IV: intravenous; LDH: lactate dehydrogenase; NR: not reported; PaO₂: arterial blood oxygen partial pressure; PCR: polymerase chain reaction; QoL: quality of life; RCT: randomised controlled trial; RT-PCR: reverse transcription polymerase chain reaction; SAE: serious adverse event; SD: standard deviation; SOFA: sequential organ failure assessment; TACO: transfusion-associated circulatory overload; TAD: transfusion-associated dyspnoea; TRALI: transfusion-related acute lung injury

Characteristics of ongoing studies [ordered by study ID]

ChiCTR2000030010

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

ChiCTR2000030010 (Continued)

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

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

ChiCTR2000030179

Study name	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19)
Methods	<ul style="list-style-type: none"> • Trial design: randomised controlled trial • Sample size: 50 in each arm (100) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Confirmed participant (or legal guardian) agrees to participate in the study and signs the informed consent form ◦ Aged 18-65 years ◦ Real-time fluorescent RT-PCR of respiratory specimens or blood specimens to detect patients positive for novel coronavirus ◦ Patients diagnosed as severe and critically ill and with rapid disease progression according to the "Diagnosis and Treatment Program for Pneumonia of New Coronavirus Infection (Trial Version 6)"

ChiCTR2000030179 (Continued)

	<ul style="list-style-type: none"> • Exclusion criteria <ul style="list-style-type: none"> ◦ Any situation where the solution cannot be carried out safely ◦ Allergic constitution, allergic to plasma or drugs ◦ Being too old, with severe underlying diseases that affect survival, including uncontrolled clinically significant heart, lung, kidney, digestive, haematological, neuropsychiatric, immune, metabolic, or malignant tumours, severe malnutrition, etc ◦ Patients with severe respiratory failure, heart failure, and multiple organ failure ◦ Participants in other clinical trials
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: routine treatment + plasma treatment • Details of CP <ul style="list-style-type: none"> ◦ type of plasma: NR ◦ volume: NR ◦ number of doses: NR ◦ antibody-titre: NR ◦ pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): routine treatment • Concomitant therapy: no • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcomes: cure rate, mortality • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: mortality ◦ Time to death: NR • Secondary review outcomes <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR ◦ 30-day and 90-day mortality: mortality ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: length of stay • Additional study outcomes: cure rate
Starting date	24 February 2020
Contact information	<p>Liu Wei</p> <p>The First Affiliated Hospital of Nanchang University, 17 Yongwai Main Street, Nanchang, Jiangxi, China, 330006, cdyfyliuwei@163.com</p> <p>Le Aiping</p> <p>17 Yongwai Main Street, Nanchang, Jiangxi, China, 330006, leaiping@126.com</p>
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 24 April 2020 • Sponsor/funding: The First Affiliated Hospital of Nanchang University, raised independently

ChiCTR2000030627

Study name	Study on the application of convalescent plasma therapy in severe COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 15 in each arm (30) • Setting: inpatient • Country: China • Language: translated to English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Patients who were diagnosed as COVID-19 by nucleic acid test and were in accordance with the clinical classification of severe or critically illness. (Refer to the clinical classification criteria in the pneumonia diagnosis and treatment program of novel coronavirus infection, General Office of the National Health Commission (trial version 4)) • Exclusion criteria <ul style="list-style-type: none"> ◦ Patients with hypersensitivity to plasma products; patients with severe transfusion reactions in the past; patients with acute pulmonary oedema, congestive heart failure, PE, malignant hypertension, polycythaemia vera, extreme renal failure and other diseases
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: NR <ul style="list-style-type: none"> ◦ type of plasma: NR ◦ volume: NR ◦ number of doses: NR ◦ antibody-titre: NR ◦ pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): routine treatment • Concomitant therapy: no • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcomes: temperature, virus nucleic acid detection • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: mortality rate ◦ Time to death • Secondary review outcomes <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): 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 <ul style="list-style-type: none"> ◦ Laboratory examination
Starting date	1 February 2020
Contact information	Guojun Zhang

ChiCTR2000030627 (Continued)

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

Guojun Zhang

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

Notes

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

ChiCTR2000030702

Study name

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

Methods

- Trial design: open-label, RCT
- Sample size: 25 in each arm (50)
- Setting: inpatient
- Country: China
- 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 \geq 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 \geq 36.7 °C, or oral temperature \geq 38.0 °C, or anal or ear temperature \geq 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 \geq 30 breaths/min; 2) in resting state, oxygen saturation \leq 93%; 3) partial PaO₂/FiO₂ \leq 300 mmHg (1 mmHg = 0.133 kPa); and critically ill patients meet any

ChiCTR2000030702 (Continued)

of the following: 1) respiratory failure and need mechanical ventilation; 2) shock; 3) patients with other organ failure need ICU monitoring treatment

- Diseases that may increase the risk of thrombosis, such as cold globulinaemia, severe refractory hypertriglyceridaemia, clinically defined monoclonal gamma globulinaemia, etc
- Detection of high titre of anti-novel coronavirus antibody RBDIgG (> 1)
- Received any experimental treatment for novel coronavirus infection within 30 days before screening
- Researchers judged that the patients had the following life-threatening conditions, including, but not limited to, Phammer F < 100 mmHg, near-death state or expected survival time < 24 h, severe septic shock or DIC), etc
- Severe congestive heart failure, or other relative contraindications for plasma transfusion determined by study authors

Interventions

- 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
- 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 dyspnoea during infection (existed dyspnoea upon enrolment)
 - Proportion of viral nucleic acid negative

Starting date

15 February 2020

Contact information

Liu Zhong

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ChiCTR2000030702 (Continued)

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

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 IgM- and IgG-positive; IgG-specific against new coronavirus positive conversion or the titre of IgG is 4 times higher in convalescent period than in acute period
 - Adult patients with severe COVID-19 shall meet any of the following:
 - respiratory distress, respiratory rate ≥ 30 times/minute
 - in the resting state, oxygen saturation is $\leq 93\%$
 - for lung radiology, the lesion has obtained $> 50\%$ obvious improvement within 24-48 h
 - $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg (1 mmHg = 0.133 kPa)
 - Patients and/or their legal guardians volunteered to participate in the study and voluntarily signed informed consent.
- Exclusion criteria
 - 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)

ChiCTR2000030929 (Continued)

Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: anti-SARS CoV virus inactivated plasma ◦ volume: NR ◦ number of doses: NR ◦ antibody-titre: NR ◦ pathogen inactivated or not: yes • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type) - ordinary plasma • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: improvement of clinical symptoms (clinical improvement is defined as a reduction of 2 points on the 6-point scale of the patient's admission status or discharge from the hospital) • Primary review outcomes reported: <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: yes (at 14- and 28-day) ◦ Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: Invasive mechanical ventilation during infection; ECMO duration during infection: NR ◦ 30-day and 90-day mortality: 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 <ul style="list-style-type: none"> ◦ Improving time of main clinical symptoms (wheezing, cough, sputum, etc)
Starting date	17 March 2020
Contact information	Lianghao Zhang 11443556@qq.com Sinopharm Wuhan Blood Products Co., Ltd. 1 Golden Industrial Park Road, Zhengdian, Jiangxia District, Wuhan, Hubei, China
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 16 June 2020 • Sponsor/funding: Renmin Hospital of Wuhan University, 99 Zhang-Zhi-Dong Road, Wuchang District, Wuhan, Hubei, China

CTRI/2020/04/024915

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
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CTRI/2020/04/024915 (Continued)

Methods	<ul style="list-style-type: none"> • Trial design: Open-label, phase II, randomised controlled trial • Sample size: 100 • Setting: inpatient • Country: India • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Patients admitted with RT-PCR confirmed COVID-19 illness. ◦ Age > 18 years ◦ Written informed consent ◦ Has any of the two: PaO₂/ FiO₂ 24/min and SaO₂ < 93% on room air • Exclusion criteria <ul style="list-style-type: none"> ◦ Pregnant and lactating 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	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: ABO compatible plasma transfusion ◦ volume: 200 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): Standard care of treatment (guidelines according to The Ministry of Health and Welfare for COVID-19; and ARDSNet and Surviving Sepsis campaign guidelines for ARDS or sepsis) • Concomitant therapy: standard of care for COVID-19 disease • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Progression to severe ARDS (P/F ratio 100) ◦ All-cause mortality at 28 days • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: NR (but 28-day mortality) • Secondary review outcomes <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): no, transfusion-related AEs only (and NR, whether number of participants of events) ◦ 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: assessed, but NR ("Duration of respiratory support required") ◦ 30-day and 90-day mortality: NR (up to 28 days) ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: yes ◦ Time to discharge from hospital: NR ◦ QoL: NR

CTRI/2020/04/024915 (Continued)

- Additional study outcomes
 - Time to symptom resolution: Fever, shortness of breath, fatigue
 - Change in SOFA pre- and post-transfusion
 - Radiological improvement
 - To measure the change in RNA levels (Ct values) of SARS-CoV-2 from RT-PCR [TimeFrame: Days 0, 1, 3, and 7 after transfusion]
 - Levels of bio-markers pre and post transfusion
 - Need of vasopressor use

Starting date 09/05/2020

Contact information Corresponding Author:
 Name: Dr Sangeeta Pathak
 Affiliation: Blood Bank, Max Super Speciality hospital, Saket (A unit of DevkiDevi Foundation)
 Full Address: Max Super Speciality Hospital (Devki Devi Foundation), East Block, Blood Bank, 2, Press enclave Road, Saket New Delhi New Delhi DELHI 110017 India
 Email: sangeeta.pathak@maxhealthcare.com

Notes

- Recruitment status: Not yet recruiting
- Prospective completion date: 09/05/2021
- Sponsor/funding: Max Super Speciality hospital, Saket (A unit of Devki Devi Foundation)

CTRI/2020/05/025346

Study name A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma in severe COVID-19 patients.

Methods

- Trial design: Phase II, open label, randomised controlled trial
- Sample size: 90
- Setting: inpatient
- Country: India
- Language: English
- Number of centres: 1

Participants

- Inclusion criteria
 - Age > 20 years
 - COVID-positive patients who are under treatment in the COVID acute care facility, amongst whom are willing to give consent to participate in this study
 - Should be admitted in the acute care facility for the treatment of COVID-19 infection without complications
 - Clinical symptoms suggestive of COVID infection along with confirmed laboratory diagnosis of infection with COVID-19 as per ICMR/FDA guidelines
 - Patients should be classified under severe COVID-19 infection without complications criteria as judged by the qualified treating physician:
 - Dyspnoea
 - Respiratory rate < 30/min
 - Oxygen saturation < 93%
 - Partial pressure of arterial oxygen to fraction of inspired oxygen ratio
 - Lung infiltrates > 50% within 24 to 48 hours

CTRI/2020/05/025346 (Continued)

- Exclusion criteria
 - Patients with any past history of transfusion reactions to blood products
 - Receipt of Pooled Immunoglobulin in last 30 days
 - Critically ill patients: respiratory failure, sepsis, multi-organ failure, shock (requiring Vasopressor to maintain a MAP > 65mmHg or MAP below 65 mmHg)
 - Participating in any other clinical trial
 - Pregnant and lactating women.
 - Patients infected with COVID-19 not under criteria for severe COVID condition.
 - Patients with any chronic history of coronary artery disease, coronary bypass surgery, acute pulmonary oedema, pulmonary embolism, congestive heart failure, malignant hypertension, polycythaemia vera, severe renal failure, cirrhosis and with any implants

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - type of plasma: ABO compatible convalescent plasma
 - volume: 200 mL
 - number of doses: 2 doses
 - antibody-titre: yes (Titration of anti-covid-19 (both IgG and IgM) antibodies and SARS-CoV-2 neutralizing antibodies may be done depending on availability of facilities at the time of testing. (Desired titers for IgG antibodies >1024 or neutralizing antibodies >40) doubling dilution of donor serum will be done and titration will be done using CLIA. If not done at the time of plasma collection the donor samples will be stored in aliquots at -80° C to be tested at a later date.)
 - pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): severe (see inclusion criteria), initially first dose and subsequent dose after 24 hours of the initial dose
- For studies including a control group: comparator (type): standard acute care
- Concomitant therapy: standard acute care
- Treatment cross-overs: none

Outcomes

- Primary study outcome:
 - prevent progression to severe ARDS (P/F ratio 100)
 - All-cause mortality at 30 days
- Primary review outcomes
 - All-cause mortality at hospital discharge: yes
 - Time to death: no
- 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): unclear whether only transfusion-related AEs are recorded ("After the CCP transfusion, serious adverse events will be noted")
 - 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: 30-day mortality only
 - Admission on the ICU: NA
 - Length of stay on the ICU: NA
 - Time to discharge from hospital: yes (Length of hospital stay)
 - QoL: NR
- Additional study outcomes
 - Duration(days) of ICU stay/hospital stay from symptom onset
 - Duration of mechanical ventilation (Invasive/Non-invasive)
 - Incidence of transfusion reactions, ARDS & sepsis
 - Duration of clinical symptoms and radiological improvement post-transfusion
 - Levels of IgG antibody, neutralizing antibody titers

CTRI/2020/05/025346 (Continued)

Starting date	01/06/2020
Contact information	<p>Corresponding Author</p> <p>Name: Dr S Anbuselvi Mattuvar Kuzhali</p> <p>Affiliation: Madras Medical College</p> <p>Full Address: Institute of Physiology and Experimental Medicine, Madras Medical College, Chennai 4B, third floor, KGEYES HYACINTH, LB road, Kamaraj Nagar, Thiruvanmiyur, Chennai, Chennai, TAMIL NADU 600003 India</p> <p>Email: dranbuselvimk@gmail.com</p>
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 01/06/2022 • Sponsor/funding: Secretariat, Government of Tamilnadu, Namakkal Kavignar Maaligai, Fort St. George, Chennai 600 009

CTRI/2020/06/025803

Study name	Efficacy of convalescent plasma therapy in patients with COVID-19: a randomized control trial
Methods	<ul style="list-style-type: none"> • Trial design: Randomised, parallel group, active controlled trial • Sample size: 400 • Setting: inpatient • Country: India • Language: English • Number of centres: 3
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Age > 18 years ◦ Patients with severe COVID-19 <ul style="list-style-type: none"> ■ Severe COVID -19 defined by WHO Interim Guidance and the Guideline of Diagnosis and Treatment of COVID-19 of National Health Commission of China (version 5.0) ■ along with confirmation by real-time RT-PCR assay with severe disease i.e. meeting any 2 of the following criteria: <ul style="list-style-type: none"> ■ Patients on ventilator (in last 24 hours) ■ Respiratory distress ■ RR greater than or equal to 30 beats/min ■ Oxygen saturation level less than 90 % in resting state ■ Partial pressure of oxygen (PaO₂)/oxygen concentration (FiO₂) less than or equal to 300 mmHg ■ Lung infiltrates > 50% within 24 to 48 hours

CTRI/2020/06/025803 (Continued)

- Exclusion criteria
 - Patient/ family members who do not give consent to participate in the study
 - Patients with age less than 18 years
 - Patients presenting with multi-organ failure
 - Pregnancy
 - Individuals with HIV and viral hepatitis and cancer
 - Extremely moribund patients with an expected life expectancy of less than 24 hours
 - Haemodynamic instability requiring vasopressors
 - Previous history of allergy to plasma
 - Cirrhosis
 - Severe renal impairment with GFR
 - Patients with uncontrolled diabetes mellitus, hypertension, arrhythmias and unstable angina

 Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - type of plasma: NR
 - volume: 250 mL
 - number of doses: 2 doses
 - antibody-titre: NR
 - pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): 2 doses on consecutive days, Start by day 3 of symptom onset (of severe COVID-19 as in inclusion criteria)
- For studies including a control group: comparator (type): standard of care
- Concomitant therapy: NR
- Treatment cross-overs: none

 Outcomes

- Primary study outcome:
 - Time to clinical improvement (Clinical improvement: Reduction of two points in ordinal scale or live discharge from the intensive care unit, whichever is earlier)
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: NR (day 28)
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement, at up to 7 days, 8 to 15 days, 16 to 30 days): NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: yes (duration of hospital stay)
 - Admission to the intensive care unit (ICU): NA
 - Length of stay on the ICU: yes
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes (days 0, 3, 7, 14, 21 & 28)
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: NR

CTRI/2020/06/025803 (Continued)

- Additional study outcomes
 - Duration of oxygen therapy
 - Proportion of patients on mechanical ventilation
 - Mortality in both groups at day 7 and day 28
 - Incidence of adverse effects in both groups
 - Cytokines and acute phase reactants

Starting date	18/06/2020
Contact information	<p>Corresponding Author</p> <p>Name: Dr Meenu Bajpai</p> <p>Affiliation: Institute of Liver and Biliary Sciences</p> <p>Full Address: Room No:16056, Department of Transfusion Medicine, Phasel, Upper Basement, D-1, Vasant Kunj New Delhi-110070 South West DELHI 110070 India</p> <p>Email: meenubajpai@hotmail.com</p>
Notes	<ul style="list-style-type: none"> • Recruitment status: open to recruitment • Prospective completion date: 18/06/2021 • Sponsor/funding: Institute of Liver and Biliary Sciences D-1, Vasant Kunj, New Delhi-110070

CTRI/2020/06/026123

Study name	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma in severe COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: randomised, parallel group, active controlled trial • Sample size: 472 • Setting: inpatient • Country: India • Language: English • Number of centres: 21
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Age > 18 years ◦ Hospitalised COVID-19 patients ◦ Fever, Cough, breathlessness plus one or more of the following: respiratory rate more than 30 per minutes, O₂ saturation less than 90%, PaO₂ by FiO₂ less than 300 ◦ Patients with comorbidities: e.g. diabetes mellitus, chronic obstructive pulmonary disease, hypertension, asthma • Exclusion criteria <ul style="list-style-type: none"> ◦ Pregnant and breastfeeding females ◦ Critically ill patients e.g. with severe ARDS, sepsis, septic shock, multiple organ dysfunction syndrome, coronary artery disease, arrhythmia, heart failure
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP

CTRI/2020/06/026123 (Continued)

- Details of CP:
 - type of plasma: anti-SARS-CoV-2 convalescent plasma viral neutralising antibodies blood product
 - volume: 200 mL
 - number of doses: 2 doses
 - antibody-titre: NR
 - pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): 2 doses, 24 hours apart
- For studies including a control group: comparator (type): standard of care
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome
 - All-cause mortality at 28 days
 - Proportion of patients showing at least 2 points clinical improvement on WHO ordinal scale at 28 days post randomization.
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: NR (28 days)
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: partially (see primary study outcomes)
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: Length of hospital stay
 - Admission to the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: NR
- Additional study outcomes
 - Time to clinical improvement
 - Change in SOFA score
 - Duration of oxygen support
 - Duration of respiratory support required
 - Levels of biomarkers CRP Ferritin, D-dimer pre-and post-transfusion
 - Radiological improvement

Starting date 25/06/2020

Contact information

Corresponding Author

Name: Dr Sushant Meshram

Affiliation: Government Medical College and Hospital, Nagpur

Full Address: Dept of Pulmonary Medicine, 4th floor, Super Specialty Hospital, Government Medical College Hospital, Nagpur, Maharashtra 440009 India

Email: drsushant.in@gmail.com

CTRI/2020/06/026123 (Continued)

Notes	<ul style="list-style-type: none"> Recruitment status: not yet recruiting Prospective completion date: 25/12/2020 Sponsor/funding: Dr Sanjay Mukherjee Secretary Medical Education and Drug Department 9th floor G T Hospital campus, new Mantralaya, Mumbai Government of Maharashtra
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EUCTR2020-001632-10

Study name	A randomized open label phase-II clinical trial with or without infusion of plasma from subjects after convalescence of SARS-CoV-2 infection in high-risk patients with confirmed severe SARS-CoV-2 disease
Methods	<ul style="list-style-type: none"> Trial design: Randomised, open, cross-over, parallel-arm, multi-centre, phase II Sample size: 174 Setting: inpatient Country: Germany Language: English Number of centres: 15
Participants	<ul style="list-style-type: none"> Inclusion criteria <ul style="list-style-type: none"> PCR confirmed SARS-CoV-2 infection in a respiratory tract sample. Oxygen saturation (SaO₂) of 94 % or less while breathing ambient air or a ratio of the partial pressure of oxygen (PaO₂) to the fraction of inspired oxygen (FiO₂) of less than 300 mmHg. High risk due to either pre-existing or concurrent hematologic malignancy and/or active cancer therapy (including chemotherapy, radiotherapy, surgery) within the last 24 months or less (group 1) and/or chronic immunosuppression not meeting the criteria of group 1 (group 2) and/or Age ≥ 50 - 75 years meeting neither the criteria of group 1 nor group 2 (group 3) and at least one of these criteria: <ul style="list-style-type: none"> Lymphopenia < 0.8 x G/l D-dimer > 1µg/mL Age ≥ 75 years meeting neither the criteria of group 1 nor group 2 (group 4). Blood haemoglobin concentration ≥ 8 g/dl. Provision of written informed consent. Patient is able to understand and comply with the protocol for the duration of the study, including treatment and scheduled visits and examinations. Male or female patient aged ≥ 18 years. Postmenopausal or evidence of non-childbearing status. For women of childbearing potential: negative urine or serum pregnancy test within 14 days prior to study treatment. Exclusion criteria <ul style="list-style-type: none"> Dementia, psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principle investigator, would affect subject safety and/or compliance. Contraindication to transfusion or history of prior reactions to transfusion blood products. Patients with known selective IgA deficiency. Patients with mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) at time of initial inclusion into the trial. Participation in another trial with an investigational medicinal product. Treatment with SARS-CoV-2 convalescent plasma in the past.
Interventions	<ul style="list-style-type: none"> CP therapy or hyperimmune immunoglobulin therapy: CP

EUCTR2020-001632-10 (Continued)

- Details of CP:
 - type of plasma: Anti-SARS-CoV-2 convalescent plasma with SARS-CoV-2 antibodies obtained from subjects following recovery of a SARS-CoV-2 infection
 - volume: 238-337 mL
 - number of doses: 2 doses
 - antibody-titre: NR
 - pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): doses given on day 1, 2
- For studies including a control group: comparator (type): standard of care
- Concomitant therapy: NR
- Treatment cross-overs: possible ("A cross over from the standard arm into the experimental arm is possible after day 10 in case of not improving or worsening clinical condition.")

Outcomes

- Primary study outcome:
 - Time from randomisation until improvement (within 84 days), defined as two points on a seven point ordinal scale or live discharge from the hospital
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: NR (28-day mortality)
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: possibly ("Time from randomization until improvement (within 84 days), defined as two points on a seven point ordinal scale or live discharge from the hospital")
 - Mortality (time to event): NR
 - 90-day mortality: NR (84 days)
 - Time to discharge from hospital: yes
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes, but timing of measurement NR ("SARS-CoV-2 viral clearance and load, cytokine changes over time, as well as antiviral antibody titres")
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: NR
- Additional study outcomes
 - overall survival
 - overall survival rate at 28, 56 and 84 days
 - percentage of patients that required mechanical ventilation

Starting date	04 May 2020
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Contact information

Corresponding Author

Name: Prof. Dr. Carsten Müller-Tidow

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EUCTR2020-001632-10 (Continued)

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|-------|---|
| Notes | <ul style="list-style-type: none"> • Trial status: ongoing • Prospective completion date: NR • Sponsor/funding: Ruprecht-Karls-Universität Heidelberg, Medical Faculty, University Hospital Heidelberg • Abbreviation of title: RECOVER |
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EUCTR2020-001936-86

- | | |
|--------------|---|
| Study name | A prospective, randomized, open label phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19 |
| Methods | <ul style="list-style-type: none"> • Trial design: Randomised, open label, parallel arm, phase 2 • Sample size: 340 • Setting: inpatient • Country: Germany • Language: English • Number of centres: 10 |
| Participants | <ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ○ Patients infected with SARS-CoV-2 virus and <ul style="list-style-type: none"> 1. age \geq 18 years and \leq 75 years 2. fulfils RKI case definition including a positive verification of a SARS-CoV-2 infection from any specimen (e.g. respiratory, blood, other bodily fluid) <ul style="list-style-type: none"> ■ confirmed by PCR (BAL, sputum, nasal and/or pharyngeal swap) 3. mild disease defined by the following criteria: <ul style="list-style-type: none"> ■ Hospitalised (score 3 or 4 of WHO R&D Blueprint ordinal scale for clinical improvement) 4. signed written informed consent and willingness to comply with treatment and follow-up procedures ○ men ○ women without childbearing potential defined as follows: <ul style="list-style-type: none"> ■ at least 6 weeks after surgical sterilization by bilateral tubal ligation or bilateral oophorectomy, ■ hysterectomy or uterine agenesis, ■ \geq 50 years and in postmenopausal state $>$ 1 year, or ■ $<$ 50 years and in postmenopausal state $>$ 1 year with serum FSH $>$ 40 IU/l and serum oestrogen $<$ 30 ng/l or a negative oestrogen test, both at screening ○ women with childbearing potential: <ul style="list-style-type: none"> ■ who have sexual relationship with female partners only and/or with sterile male partners, or ■ who are sexually active with fertile male partner, have a negative pregnancy test during screening and agree to use reliable methods of contraception from the time of screening until end of the clinical trial |

EUCTR2020-001936-86 (Continued)

- Exclusion criteria
 - 1. Accompanying diseases other than COVID-19 with an expected survival time of less than 12 months
 - 2. In the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatment
 - 3. Chronic obstructive lung disease (COPD), stage 4
 - 4. Lung fibrosis with UIP pattern in CT and severe emphysema
 - 5. Chronic heart failure NYHA \geq 3 and/or pre-existing reduction of left ventricular ejection fraction to \leq 30%
 - 6. Liver cirrhosis Child C
 - 7. Liver failure: Bilirubin $>$ 5xULN and elevation of ALT /AST (at least one $>$ 10xULN).
 - 8. End stage renal failure requiring haemodialysis
 - 9. Organ or bone marrow transplant in the three month prior to screening
 - 10. History of adverse reactions to plasma proteins
 - 11. Known deficiency of immunoglobulin A
 - 12. Pregnancy and breastfeeding women
 - 13. Volume overload until sufficiently treated
 - 14. Pulmonary oedema
 - 15. Body mass index (BMI) $>$ 40 kg/m²
 - 16. Participation in another clinical trial, especially for treatment of COVID-19
 - 17. Allergy or other contraindication to one of the investigational products
 - 18. Previous treatment with SARS-CoV-2 convalescent plasma

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - type of plasma: Fresh frozen plasma (*Gefrorenes Apherese-COVID-19-RKP Leukozytendepletiert*)
 - volume: 230-270 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): early stage (patients: WHO R&D Blueprint Ordinal Scale for Clinical Improvement = 3 or 4)
- For studies including a control group: comparator (type): standard of care
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome:
 - Proportion of patients with treatment failure on day 14 (defined as progression of COVID-19 disease, defined as score 5, 6, 7 or 8 of WHO R&D Blueprint ordinal scale for clinical improvement)
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: NR (28-day mortality)
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: possibly ("Time to clinical improvement (defined as time from randomization to an improvement of two points on the WHO R&D Blueprint ordinal scale for clinical improvement"))
 - Mortality (time to event): NR
 - 90-day mortality: NR (4 months)
 - Time to discharge from hospital: "Length of hospital stay"
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: NR

EUCTR2020-001936-86 (Continued)

- Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes, but other timing of measurement (day 0, 2, 4 and 6 and every week thereafter up to day 28)
- QoL: NR
- 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): NR in detail (only "adverse events")
- Number of participants with serious adverse events: NR in detail (only "adverse events")
- Additional study outcomes
 - Failure rates at day 7, day 21, day 28
 - All-cause mortality (ACM) on day 7, day 14, day 21, day 28, 4 months
 - Deterioration in health (progressive disease)
 - Need of ventilation support / additional organ support, e.g. ECMO
 - Predictive value of comorbidities and inflammation and coagulation markers on clinical improvement, mortality, length of hospital stay and necessity of transfer to ICU
 - Feasibility of collection of plasma units from donors who recovered from a SARS-CoV-2 infection
 - Level of identity of kinetics of anti-SARS-CoV-2 antibodies in plasma of patients compared to plasma of donors (kinetics of antibodies detectable in the patient after convalescent plasma treatment, pharmacokinetic parameters. The maximum observed anti-SARS-CoV-2 (C_{max}), and the time to C_{max} (t_{max}) will be determined directly from the anti-SARS-CoV-2 versus time data. The observed titre at the end of a dosing interval (C_{trough}) will also be determined directly from the anti-SARS-CoV-2 versus time data. Calculated parameters [apparent terminal phase elimination rate constant (b), terminal phase elimination half-life (t_{1/2}), and the area under the curve (AUC)] will be estimated using non-compartmental analysis with PK-Sim software. Accumulation ratios will be calculated based on the AUC values of the consecutive dosing intervals and the C_{max} values of the consecutive dosing intervals.)
 - Titre of neutralising anti-SARS-CoV-2 in transfused plasma units
 - Impact of donor characteristics on humoral response against anti-SARS-CoV-2 (age; gender; severity of COVID-19; interval between resolution of symptoms and plasmapheresis).
 - Course of anti-SARS-CoV-2 titre in patients (prior to transfusion of convalescent plasma, on day 1 & 2 and after transfusion (day 3 and 7) as well as every week thereafter up to day 28).

Starting date	19 October 2020
Contact information	Corresponding Author/Contact Name: Institute of Transfusion Medicine, Hannover Medical School Affiliation: - Full Address: Carl-Neuberg-Str. 1, Hannover, 30625, Germany Email: NR
Notes	<ul style="list-style-type: none"> • Trial status: ongoing • Prospective completion date: NR • Sponsor/funding: Hannover Medical School, Germany and German Federal Ministry of Health

EUCTR2020-002122-82

Study name	Prospective open-label randomized controlled phase 2b clinical study in parallel groups for the assessment of efficacy and safety of immune therapy with COVID-19 convalescent plasma plus standard treatment vs. standard treatment alone of subjects with severe COVID-19
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EUCTR2020-002122-82 (Continued)

Methods	<ul style="list-style-type: none"> • Trial design: open-label, parallel-arm, multicentre, randomised controlled trial • Sample size: 58 • Setting: inpatient • Country: Germany • Language: English • Number of centres: 4
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Male or female subject aged ≥ 18 years ◦ Estimated BMI $\geq 19\text{kg/m}^2$ to $\leq 40\text{kg/m}^2$ ◦ Florid SARS-CoV-2 infection confirmed by RT-PCR in tracheo-bronchial secretion sample or pharyngeal swab sample ◦ ARDS with Horovitz index < 300 mmHg ◦ Necessity of invasive mechanical ventilation ◦ Written informed consent obtained from the subject's legal representative or under such arrangement as is legally acceptable in Germany ◦ Subject's assent if obtainable • Exclusion criteria <ul style="list-style-type: none"> ◦ Adverse reaction to plasma proteins in medical history ◦ Interval $> 72\text{h}$ since endotracheal intubation ◦ Current or imminent necessity of ECMO treatment ◦ Pre-existing COPD, based on The Global Initiative for Chronic Obstructive Lung Disease definition, stage 4 ◦ Chronic congestive heart failure NYHA ≥ 3 ◦ Pre-existing left ventricular ejection fraction $< 30\%$ ◦ Liver cirrhosis Child-Pugh class C ◦ Acute liver failure with bilirubin $> 5\text{x ULN}$ and either ALT or AST $> 10\text{x ULN}$ ◦ Known deficiency of immunoglobulin A ◦ Cardiovascular resuscitation in the 14 days prior to screening visit [V1] ◦ Organ or bone marrow transplant in the three months prior to screening visit [V1] ◦ Pregnancy ◦ Breastfeeding woman ◦ Previous exposure to COVID-19 convalescent plasma
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: NR ◦ volume: 870 to 910 $\mu\text{l/ml}$ ◦ 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): severe disease/late stage (see inclusion criteria) • For studies including a control group: comparator (type): standard of care • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Change in SOFA score from Baseline Visit [Day 1, Visit 2] to Day 8 [Visit 9] • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: yes (day 29)

EUCTR2020-002122-82 (Continued)

- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days): NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission to the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: NR
- Additional study outcomes
 - SOFA score: mean change from Baseline Visit [Day 1, Visit 2] to all subsequent visits until and including Day 29 [Visit 15] or until extubation, whichever comes first
 - Rescue therapy: number and proportion of subjects without rescue therapy until and including Day 8 [Visit 9]
 - ECMO: mean number of days without ECMO during the period from Baseline Visit [Day 1, Visit 2] until and including Day 8 [Visit 9], Day 15 [Visit 13], and Day 29 [Visit 15], per treatment group and per subject
 - Invasive mechanical ventilation parameters and endotracheal Intubation: mean number of days without invasive mechanical ventilation during the period from Baseline Visit [Day 1, Visit 2] until and including Day 8 [Visit 9], Day 15 [Visit 13], and Day 29 [Visit 15], per treatment group and per subject
 - Safety: cumulated number and proportion of subjects with AE, AR, SAE, serious adverse reaction, and suspected unexpected serious adverse reaction from Baseline Visit [Day 1, Visit 2] until and including Day 11 [Visit 12]

Starting date	12 June 2020
Contact information	Corresponding Author Name: Holger Hackstein Affiliation: Universitätsklinikum Erlangen Full Address: Universitätsklinikum Erlangen, Transfusionsmedizinische Abteilung, Krankenhausstr. 12, Erlangen 91054, Germany Email: holger.hackstein@uk-erlangen.de
Notes	<ul style="list-style-type: none"> • Recruitment status: ongoing • Prospective completion date: NR • Sponsor/funding: Universitätsklinikum Erlangen, Germany

EUCTR2020-005410-18

Study name	Multicentre, randomized, double-blind, placebo-controlled, non-commercial clinical trial to evaluate the efficacy and safety of specific anti-SARS-CoV-2 immunoglobulin in the treatment of COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: multicentre, randomised, double-blind, placebo-controlled, non-commercial clinical trial

EUCTR2020-005410-18 (Continued)

- Sample size: 480
- Setting: inpatient
- Country: Poland
- Language: English
- Number of centres: 5

Participants

- Inclusion criteria
 - Age over 18 years
 - Sign informed consent in order to participate in the study
 - SARS-CoV-2 infection (positive RT-PCR test for SARS-CoV-2)
 - Indication for hospitalisation due to the course of COVID-19
 - The patient's clinical condition is assessed at 3-5 on the ORDINAL scale:
 - 3 - Hospitalisation without oxygen therapy
 - 4 - Hospitalisation with low-flow oxygen support on a nasal mask or moustache
 - 5 - hospitalisation with high flow oxygen therapy > 15L/min without mechanical ventilation
 - There are no contraindications to the use of standard symptomatic treatment in accordance with the guidelines of the Polish Association of Epidemiologists and Infectiologists (Polskie Towarzystwo Epidemiologów i Lekarzy Chorób Zakaźnych)
- Exclusion criteria
 - The patient's inability to comply with the protocol in opinion of the Investigator
 - Intake of any experimental anti-COVID-19 study drugs
 - Intake of any plasma therapy, in particular plasma therapy with COVID-19 convalescents
 - Infection with human immunodeficiency virus (HIV)
 - Pregnancy or breastfeeding
 - All conditions that the doctor qualifying for the study considers harmful to the patient participating in this study, including any clinically significant deviations from normal clinical laboratory values or concurrent medical events or situations that prevent the proper performance of the study (e.g. insufficient knowledge of the Polish language by the patient in the opinion of the researcher)
 - Participation in another interventional clinical trial in the last 30 days

Interventions

- Details of hyperimmune immunoglobulin therapy:
 - drug name: anti SARS-CoV-2 immunoglobulin
 - dose: 60 AU/mL
 - number of doses: NR
 - route: intramuscular
 - source: human
- Treatment details, including time of plasma therapy (e.g. early stage of disease):
- For studies including a control group: comparator (type): placebo
- Concomitant therapy: none
- Treatment cross-overs: none

Outcomes

- Primary study outcome:
 - No oxygen supplementation required on Day 7 and 14 from the start of the therapy
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: NR

EUCTR2020-005410-18 (Continued)

- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: probably yes
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: yes
 - Admission to the ICU: NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: probably yes
 - QoL: NR
 - 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): yes
 - Number of participants with serious adverse events: yes
- Additional study outcomes
 - Occurrence of serious adverse events up to day 28 from the start of study therapy
 - The need for mechanical ventilation in the patient
 - Time of using oxygen therapy
 - The need to use tocilizumab or other anti-cytokine drugs
 - Time to discharge from hospital
 - Time to negative PCR test for SARS-CoV-2 virus RNA
 - Occurrence of any COVID-19 related symptoms on day 28
 - Changes in inflammatory parameters and coagulation parameters at successive time points
 - Presence of lung tissue pathology after completion of therapy
 - Generation of a specific humoral response: Presence and titre of anti-SARS-CoV-2 antibodies during the therapy and after the observation period (on day 28 from the start of study therapy)

Starting date	16/11/2020
Contact information	<p>Samodzielny Publiczny Szpital Kliniczny Nr 1 w Lublinie Samodzielny Publiczny Zakład Opieki Zdrowotnej</p> <p>Krzysztof Tomaszewicz</p> <p>ul. Stanisława Staszica 16</p> <p>Lublin20-081</p> <p>Poland</p> <p>00488153 49 414564</p> <p>00488153 49 410</p> <p>krzysztoftomaszewicz@umlub.pl</p>
Notes	<ul style="list-style-type: none"> • Recruitment status: ongoing • Prospective completion date: NR • Sponsor/funding: Samodzielny Publiczny Szpital Kliniczny Nr 1 w Lublinie Samodzielny Publiczny Zakład Opieki Zdrowotnej

IRCT20200501047258N1

Study name	Investigation of the effects of COVID-19 convalescent plasma in acute respiratory distress syndrome due to COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: RCT (3 arms) • Sample size: 120 (5 samples per patient = 24 patients) • Setting: inpatient • Country: Iran • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Positive PCR test ◦ life-threatening disease (defined as respiratory failure dyspnoea respiratory frequency ≥ 30/min blood oxygen saturation $\leq 93\%$ partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 lung infiltrates $> 50\%$ within 24 to 48 hours) • Exclusion criteria <ul style="list-style-type: none"> ◦ Pregnancy ◦ Hypersensitivity to blood or blood products ◦ Uncontrolled bacterial infection ◦ Disagreement
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: NR ◦ volume: 2-5 mL/kg (first intervention group), 8-10 mL/kg (second intervention group) ◦ number of doses: 3 doses (first intervention group), 1 dose (second intervention group) ◦ antibody-titre: NR ◦ pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): later stage of disease (see inclusion criteria) • For studies including a control group: comparator (type): standard of care • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ hospitalisation time ◦ ICU admission time ◦ mechanical ventilation time ◦ survival rate ◦ <i>all outcomes measured on days 0, 1, 3, 7, 14</i> • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: NR

IRCT20200501047258N1 (Continued)

- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: partially (mechanical ventilation until day 14)
 - Mortality (time to event): yes
 - 90-day mortality: NR
 - Time to discharge from hospital: yes
 - Admission to the intensive care unit (ICU): yes
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes (ELISA on days 0,1,3,7,14)
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: NR
- Additional study outcomes
 - CT scan
 - Haematological markers (flow cytometry)
 - Clinical findings
 - *all outcomes measured on days 0, 1, 3, 7, 14*

Starting date	04 May 2020
Contact information	Corresponding Author Name: Rahim Asghari Affiliation: Oroumia University of Medical Sciences Full Address: Resalat st, UMSU, Urmia, West Azarbaijan Email: rahimasghari@gmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: NR • Sponsor/funding: Oroumia University of Medical Sciences

IRCT20200508047346N1

Study name	Evaluation of the effectiveness of rabbit antibody against coronavirus in patients.
Methods	<ul style="list-style-type: none"> • Trial design: Open-label, parallel-arm, phase III, randomised controlled trial • Sample size: 124 • Setting: inpatient • Country: Iran • Language: English • Number of centres: 1

IRCT20200508047346N1 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Clinical symptoms of COVID 19 ◦ Signed conscious consent ◦ Age > 18 years ◦ Hospitalised at beginning and end of study ◦ One of the moderate to severe clinical symptoms of COVID-19 <ul style="list-style-type: none"> ■ Shortness of breath ■ Respiratory rate more than 30 times per minute ■ Oxygen saturation of blood less than 93% (at rest) ■ Ratio of arterial oxygen pressure to inhaled oxygen less than 300 ■ Pulmonary infiltration more than 50% over 24 to 48 hours • Exclusion criteria <ul style="list-style-type: none"> ◦ History of allergies to blood products such as IVIG or albumin ◦ Critical conditions such as multiple organ failure ◦ Pregnant women ◦ Breastfeeding mothers ◦ Receiving treatment and medication outside the standard COVID-19 treatment protocol ◦ Physician believes that the patient is not suitable to participate in this trial ◦ Known sensitivity to rabbit proteins
Interventions	<ul style="list-style-type: none"> • Details of hyperimmune immunoglobulin therapy: <ul style="list-style-type: none"> ◦ drug name: CoviGlobulin (rabbit polyclonal antibody) ◦ dose: 1-3 mg per kg body weight Body (1-3 mg / kg / d) for 2-4 days ◦ number of doses: 2-4 ◦ route: NR ◦ source: rabbit • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients • For studies including a control group: comparator (type): standard of care • Concomitant therapy: none • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Clinical improvement (14 days), 6-point scale includes: <ul style="list-style-type: none"> ■ Score 6: death ■ Score 5: hospitalization for ECMO and (or) mechanical ventilation ■ Score 4: non-invasive ventilation or high-current oxygen therapy ■ Score 3: hospitalization for oxygen therapy (not high current and mechanical ventilation) Not required) ■ Score 2: Hospitalization ■ Score 1: Clearance ◦ Mortality (14 days) • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: NR

IRCT20200508047346N1 (Continued)

- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: partially (see primary study outcomes)
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: Hospitalization , , Duration
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: yes
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes (Proportion of PCR negative (3 AND 7 days after transfusion))
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: NR
- Additional study outcomes
 - Invasive mechanical ventilation
 - ECMO duration
 - Clinical characteristics including, Fever, Respiratory frequency(RF) and PaO₂/FIO₂

Starting date	21 May 2020
Contact information	Corresponding Author Name: Prof. Mostafa Ghanei Affiliation: Bagheiat-allah University of Medical Sciences Full Address: Mulla Sadra, Sheikh Baha'i, Baqiyatallah Al-Azam Hospital, Teheran, 1435915371 Email: mghaneister@gmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: n.r. • Sponsor/funding: Kowsar Biotechnology Co., Sirous Zeinali, No. 41, Kosar Complex, 3rd Floor, Majlesi St., Valiasr St., Above Fatemi St., Tehran, Tehran

NCT02735707

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

NCT02735707 (Continued)

Participants

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

Interventions

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

NCT02735707 (Continued)

Outcomes

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

Starting date	11 April 2016
Contact information	Cameron Green: info@remapcap.org
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: December 2023 • Sponsor/funding: MJM Bonten

NCT04333251

Study name	Evaluating convalescent plasma to decrease coronavirus associated complications. A phase I study comparing the efficacy and safety of high-titer anti-SARS-CoV-2 plasma versus best supportive care in hospitalized patients with interstitial pneumonia due to COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: open-label, phase I, parallel-RCT

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

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NCT04333251 (Continued)

- 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
- 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

NCT04333251 (Continued)

	<ul style="list-style-type: none"> Additional outcomes: NR
Starting date	1 April 2020
Contact information	NR
Notes	<ul style="list-style-type: none"> Recruitment status: not yet recruiting Prospective completion date: 31 December 2022 Sponsor/funding: NR

NCT04338360

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

NCT04338360 (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
 - QoL: NR
- Additional outcomes: NR

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

NCT04345289

Study name	Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia (CCAP)
Methods	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ ≥ 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

NCT04345289 (Continued)

- 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 10⁹ /L); ALT > 5 x ULN; platelet count < 50,000 per mm³ (= 50 x 10⁹ /L)
 - Immunosuppression, defined as following: treatment with immunosuppressive agents, chemotherapy or immunomodulatory drugs within 30 days prior to inclusion; use of chronic oral corticosteroids for a non-COVID-19-related condition in a dose > prednisolone 20 mg or equivalent per day for 4 weeks; ongoing chemotherapy
 - Any serious medical condition or abnormality of clinical laboratory tests that, in the study author's judgment, precludes the patient's safe participation in and completion of the study

Interventions

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

Outcomes

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

NCT04345289 (Continued)

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

NCT04345991

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

NCT04345991 (Continued)

- 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: yes
 - Admission to hospital: NR
- Secondary review outcomes
 - Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR
 - Time to symptom onset: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: partially (until day 14)
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Length of hospital stay, for hospitalised patients: yes
 - Admission to the intensive care unit (ICU): NR
 - Viral clearance, assessed with RT-PCR test: NR
 - QoL: NR
 - Number of participants with grade 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
- 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: karine.lacombe2@aphp.fr

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

NCT04348656

Study name Convalescent plasma for hospitalized adults with 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

NCT04348656 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ ≥ 16 years old ◦ Admitted to hospital with confirmed COVID-19 respiratory illness ◦ Receiving supplemental oxygen ◦ 500 mL of ABO-compatible CP is available • Exclusion criteria <ul style="list-style-type: none"> ◦ Onset of symptoms > 12 days prior to randomisation ◦ Intubated or plan in place for intubation ◦ Plasma is contraindicated (e.g. history of anaphylaxis from transfusion) ◦ Decision in place for no active treatment
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ volume: 500 mL of CP (from 1 single-donor unit of 500 mL or 2 units of 250 mL from 1-2 donations) collected by apheresis from donors who have recovered from COVID-19 and frozen (1 year expiration date from date of collection) ◦ number of doses: when administering 2 units of 250 mL, the 2nd unit will be administered after the first, and no longer than 12 h later ◦ antibody-titre: NR ◦ pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • For studies including a control group: comparator (type): randomised 1:1 to CP and standard care • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: endpoint of the need for intubation or patient death in hospital • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: yes <ul style="list-style-type: none"> ■ intubation or death in hospital (time frame: day 30) ◦ Time to death: yes • Secondary review outcomes <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes ◦ Number of participants with SAEs: yes ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes ◦ 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 <ul style="list-style-type: none"> ◦ Need for renal replacement therapy (time frame: day 30) ◦ Development of myocarditis (time frame: day 30)
Starting date	27 April 2020
Contact information	Donald M Arnold, MD, McMaster University, Hamilton, Canada: arnold@mcmaster.ca
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 31 December 2020 • Sponsor/funding: Hamilton Health Sciences Corporation, Canada

NCT04352751

Study name	Experimental use of convalescent plasma for passive immunization in current COVID-19 pandemic in Pakistan in 2020
Methods	<ul style="list-style-type: none"> • Trial design: single-arm, interventional • Sample size: 2000 • Setting: moderate-severe cases • Country: Pakistan • Language: English • Number of centres: 1 reported
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Informed consent must have been obtained ◦ Confirmed COVID-19 cases confirmed by RT-PCR laboratory tests ◦ Moderately severe or severe life-threatening COVID-19 related features: <ul style="list-style-type: none"> ■ moderately severe disease as defined by the following features: shortness of breath; respiratory rate \geq 30/min; arterial blood oxygen saturation \leq 92%; and/or lung infiltrates $>$ 25% within 24-48 h ■ severe life-threatening disease as defined by the presence of any of the following features: respiratory failure; shock; multiple organ dysfunction • Exclusion criteria <ul style="list-style-type: none"> ◦ Allergy history of plasma, sodium citrate and methylene blue ◦ For patients with history of autoimmune system diseases or selective IgA deficiency, the application of CP should be evaluated cautiously by clinicians ◦ Patients having evidence of uncontrolled cytokine release syndrome leading to end-stage multiorgan failure
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune globulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: standard apheresis plasma collection protocol using Haemonetics MCS+ intermittent blood flow system or Terumo Optia, Cobe-Spectra, Trima or Fresenius continuous flow system to be used. 900-1000 mL collected each time ◦ volume <ul style="list-style-type: none"> ■ 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	<ul style="list-style-type: none"> • Primary study outcome: change in COVID-19 severity status (for categories: see additional outcomes) • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ Time to death: NR

NCT04352751 (Continued)

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

Starting date	April 2020
Contact information	Dr. Arshi Naz, PhD: labarshi@yahoo.com
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: April 2021 • Sponsor/funding: Hilton Pharma

NCT04358783

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

NCT04358783 (Continued)

Participants

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

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

Interventions

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

Outcomes

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

NCT04358783 (Continued)

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

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

NCT04360486

Study name	Treatment of COVID-19 with anti-SARS-CoV-2 convalescent plasma (ASCoV2CP)
Methods	<ul style="list-style-type: none"> • Trial design: expanded access open-label, single-arm treatment protocol • Sample size: NR • Setting: Military Treatment Facilities (MTFs) (e.g. hospital ships, field hospitals deployed for the COVID-19 response) • Country: USA • Language: English • Number of centres: initially 1 with capacity to expand to multiple sites (number not specified)
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> ◦ Child, adult, older adult ◦ All sexes ◦ Department of Defense (DoD) personnel covered by the Force Health Protection (FHP) program under the Department of Defence Instruction (DoDI) 6200.02 (active duty service members OCONUS and CONUS) and non-DoD personnel who may be treated for COVID-19 at Military Treatment Facilities (MTFs) under the authority of DoDI 6200.03, including Military Health System (MHS) beneficiaries, patients admitted to MTFs, and patients cared for under defence support for civilian authorities (e.g. hospital ships, field hospitals deployed for the COVID-19 response) ◦ Laboratory-confirmed COVID-19 diagnosis ◦ Severe or life-threatening COVID-19 disease, or judged by the subinvestigator (treating physician) to be at high risk for progression to severe or life-threatening disease

NCT04360486 (Continued)

- 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: FFP, plasma frozen for 24 h (PF-24) or liquid plasma
 - Volume: NR
 - Number of doses: NR
 - Antibody-titre: NR
 - Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease):
 - 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 $\leq 93\%$
 - 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
- 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

NCT04360486 (Continued)

- | | |
|-------|--|
| Notes | <ul style="list-style-type: none"> • Recruitment status: expanded access, available • Prospective completion date: NR • Sponsor/Funding: U.S. Army Medical Research and Development Command |
|-------|--|

NCT04361253

- | | |
|---------------|---|
| Study name | A prospective, randomized, double-masked, placebo-controlled trial of high-titer COVID-19 convalescent plasma (HT-CCP) for the treatment of hospitalized patients with COVID-19 of moderate severity |
| Methods | <ul style="list-style-type: none"> • Trial design: phase 3 RCT, double-blind (participant, investigator) parallel assignment • Sample size: 110 in each arm (n = 220) • Setting: e.g. inpatient • Country: USA • Language: English • Number of centres: NR |
| Participants | <ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Age > 1 year ◦ Active COVID-19 infection confirmed by positive SARS-CoV-2 PCR ◦ Meets institutional criteria for admission to hospital for COVID-19 ◦ Admitted to ICU or non-ICU floor within 5 days of enrolment ◦ PaO₂/FiO₂ > 200 mmHg if intubated ◦ Patient or LAR able to provide informed consent • Exclusion criteria: <ul style="list-style-type: none"> ◦ Previous treatment with convalescent plasma for COVID-19 ◦ Current use of investigational antiviral therapy targeting SARS-CoV-2 ◦ History of anaphylactic transfusion reaction ◦ Clinical diagnosis of acute decompensated heart failure ◦ Objection to blood transfusion |
| Interventions | <ul style="list-style-type: none"> • Intervention(s): e.g. COVID-19 CP (HT-CCP) • Details of CP: <ul style="list-style-type: none"> ◦ 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 <ul style="list-style-type: none"> ◦ 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 | <ul style="list-style-type: none"> • Primary study outcome(s): modified WHO Ordinal Scale score • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: yes, using MOS up to 14 days ◦ Time to death: yes, up to 14 days |

NCT04361253 (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: 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: +1-617-732-5232; rmkaufman@bwh.harvard.edu
Notes	<ul style="list-style-type: none"> • 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
Methods	<ul style="list-style-type: none"> • Trial design: phase 3 RCT, parallel assignment (1:1). Randomisation completed in permuted blocks and stratified by site, gender, and age. Triple blinding (participant, care provider, outcomes assessor). Study personnel will not be blinded to the study group assignment • Sample size: 250 in each arm (500) • Setting: inpatient (hospital or ED) • Country: USA • Language: English • Number of centres: NR
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ All sexes ◦ Age ≥ 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

NCT04362176 (Continued)

- 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 lactated Ringer's solution 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)
- 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

NCT04362176 (Continued)

- 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 +1-615-875-8531; amanda.j.bistran-hall@vumc.org
Notes	<ul style="list-style-type: none"> • 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
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NCT04363034 (Continued)

Methods	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ 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 <ul style="list-style-type: none"> ■ Severe disease, defined as ≥ 1 of the following: <ul style="list-style-type: none"> □ 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: <ul style="list-style-type: none"> □ respiratory failure □ septic shock, and/or □ multiple organ dysfunction or failure ◦ Informed consent from patients/LAR • Exclusion criteria <ul style="list-style-type: none"> ◦ 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	<ul style="list-style-type: none"> • Intervention(s): COVID-19 CP • Details of CP: <ul style="list-style-type: none"> ◦ 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
Outcomes	<ul style="list-style-type: none"> • Primary study outcome(s): NR • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: (give details e.g. 28-day mortality) ◦ Time to death: NR

NCT04363034 (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):
 - 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: +1-501-526-7906; DEvans@uams.edu
Notes	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Trial design: phase 2 RCT, double-blind (participant, investigator) 1:1 ratio, parallel assignment • Sample size: 1000 • Setting: inpatient • Country: USA • Language: English • Number of centres: 2
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> ◦ 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 • Exclusion criteria <ul style="list-style-type: none"> ◦ Receipt of pooled immunoglobulin in past 30 days ◦ Contraindication to transfusion or history of prior reactions to transfusion blood products ◦ Invasive mechanical ventilation or ECMO ◦ Volume overload secondary to congestive heart failure or renal failure ◦ Intracranial bleed
Interventions	<ul style="list-style-type: none"> • Intervention(s): SARS-CoV-2 donor CP

NCT04364737 (Continued)

- 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
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting (NYU Langone Health) <ul style="list-style-type: none"> ◦ Montefiore Medical Center Active- Not recruiting • Prospective completion date: 30 April 2023 • Sponsor/Funding: NYU Langone Health; Albert Einstein Medical Center

NCT04366245

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

NCT04366245 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> ◦ 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: <ul style="list-style-type: none"> ■ O_2 saturation $\leq 94\%$ in ambient air, or $PaO_2/FiO_2 \leq 300$ 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: <ul style="list-style-type: none"> ◦ 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 (i.e. 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	<ul style="list-style-type: none"> • Intervention(s): COVID-19 hyperimmune CP • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: NR ◦ Volume: NR ◦ Number of doses: NR ◦ Antibody-titre: NR ◦ Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): 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
Outcomes	<ul style="list-style-type: none"> • Primary study outcome(s): <ul style="list-style-type: none"> ◦ 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).

NCT04366245 (Continued)

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

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	<ul style="list-style-type: none"> • Trial design: triple-blinded, parallel, clinical RCT

NCT04372979 (Continued)

- Sample size: 80
- Setting: inpatient
- Country: France
- 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

NCT04372979 (Continued)

Interventions	<ul style="list-style-type: none"> • Intervention(s): transfusion of SARS-CoV-2 CP <ul style="list-style-type: none"> ◦ 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 • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: standard plasma • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: survival time without need of a ventilator (time frame: day 30) • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: 30-day mortality without need of a ventilator ◦ Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR ◦ 30-day and 90-day mortality: NR ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: yes (length of stay (time frame: day 30) ◦ QoL: NR • Additional study outcomes <ul style="list-style-type: none"> ◦ Morbidity (time frame: Day 15) ◦ Morbidity (time frame: Day 30) ◦ Effect on viral pharyngeal specimen clearance (time frame: at inclusion and Day 7) ◦ Effect on viral blood specimen clearance (time frame: at inclusion and Day 7) ◦ Effect on haemostasis disorders (time frame: at inclusion, Day 1 and every 48 h) ◦ Kinetics of appearance of neutralising antibodies (time frame: at inclusion, Day 7) ◦ Transfusion endotheliopathy effect (time frame: at inclusion, Day 1, Day 7) ◦ Transfusion biological inflammation effect (time frame: at inclusion, Day 1, Day 7) ◦ Transfusion haemovigilance (time frame: 30 days) ◦ Decrease in the consumption of antibiotics (time frame: 30 days)
Starting date	May 2020
Contact information	<ul style="list-style-type: none"> • Contact: Christophe MARTINAUD, PU PH: +33 141467241; christophe.martinaud@intradef.gouv.fr • Contact: Christophe RENARD: +33 140514103; christophe1.renard@intradef.gouv.fr
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: May 2021 • 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 VERRETSservice 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 Themais

NCT04373460

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

NCT04373460 (Continued)

- Primary review outcomes reported
 - All-cause mortality: possibly (two measures: prior to hospitalisation (incidence), death in hospital (time to event), both measures are combined with other measures, see primary and additional study outcomes)
 - Admission to hospital: yes
- Secondary review outcomes reported
 - Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR
 - Time to symptom onset: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): yes (time to death in hospital only)
 - 90-day mortality: yes (two measures: death prior to hospitalisation, death in hospital)
 - Length of hospital stay, for hospitalised patients: NR
 - Admission to the intensive care unit (ICU): yes (time to event, combined endpoint, see additional study outcomes)
 - Viral clearance, assessed with RT-PCR test: yes
 - QoL: NR
 - Number of participants with grade 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): yes
 - Number of participants with SAEs: yes
- 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 ICU admission, invasive mechanical ventilation or death in hospital (90 days)
 - 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	4 May 2020
Contact information	<ul style="list-style-type: none"> • David J Sullivan, MD: 410-502-2522; dsulliv7@jhmi.edu • David Sullivan, MD: 410-502-2522; dsulliv7@jhmi.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: 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 (SARS-CoV-2) convalescent plasma (CP) expanded access protocol (EAP)
Methods	<ul style="list-style-type: none"> • Trial design: intermediate-size population, expanded access • Sample size: NR • Setting: inpatient • Country: USA • Language: English • Number of centres: NR
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Ages \geq 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 \geq 18 years of age); or willing and able to provide assent as required per Institutional Review Board (IRB) prior to performing study procedures • Must have laboratory-confirmed COVID-19-positive test • Must have severe or immediately life-threatening COVID-19 <p>Severe disease is defined as:</p> <ul style="list-style-type: none"> • dyspnoea • respiratory frequency \geq 30/min • blood oxygen saturation \leq 93% • partial pressure of arterial oxygen to fraction of inspired oxygen ratio $<$ 300, and/or • lung infiltrates $>$ 50% within 24-48 h <p>Life-threatening disease is defined as:</p> <ul style="list-style-type: none"> • respiratory failure • septic shock, and/or • multiple organ dysfunction or failure <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Known contraindication to transfusion or history of prior reactions to transfusion of blood products
Interventions	<ul style="list-style-type: none"> • Intervention(s): SARS-CoV-2 CP • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: SARS-CoV-2 CP ◦ Volume: NR ◦ Number of doses: NR ◦ Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: NR • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: NR • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ Time to death: NR

NCT04374370 (Continued)

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

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

NCT04374487

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

NCT04374487 (Continued)

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

Exclusion criteria:

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

Interventions

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

Outcomes

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

NCT04374487 (Continued)

- Additional study outcomes
 - Progression to severe ARDS (P/F ratio 100)
 - Time to symptom resolution - fever, shortness of breath, fatigue (time frame: 1 year)
 - Change in SOFA pre- and post-transfusion (time frame: 1 year)
 - Radiological improvement (time frame: 1 year)
 - AEs associated with transfusion (time frame: 1 year)
 - To measure the change in RNA levels (Ct values) of SARS-CoV-2 from RT-PCR (time frame: days 0, 1, 3, and 7 after transfusion) (time frame: 1 year)
 - Levels of bio-markers pre- and post-transfusion (time frame: 1 year)
 - Need of vasopressor use (time frame: 1 year)

Starting date	9 May 2020
Contact information	<ul style="list-style-type: none"> • Principal Investigator: Sangeeta Pathak, MBBS, Diploma; Max Super Speciality Hospital, Saket (DDF), New Delhi, India
Notes	<ul style="list-style-type: none"> • Recruitment status: Active, not recruiting • Prospective completion date: 9 August 2021 • Sponsor/funding: Max Healthcare Institute Limited

NCT04374526

Study name	Early transfusion of COVID-19 convalescent plasma in elderly COVID-19 patients to prevent disease progression
Methods	<ul style="list-style-type: none"> • Trial design: randomised phase 2/3 • Sample size: 182 • Setting: inpatient • Country: Italy • Language: translated to English • Number of centres: 3
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Age \geq 65 • pneumonia at CT scan • PaO₂/FiO₂ \geq 300 mmHg • Presence of \geq 1 comorbidities (consider the list provided in Appendix A) • Signed informed consent <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Age < 65 • PaO₂/FiO₂ < 300 mmHg • pending cardiopulmonary arrest • refusal to blood product transfusions • Severe IgA deficiency • any life-threatening comorbidity or any other medical condition which, in the opinion of the investigator, makes the patient unsuitable for inclusion
Interventions	<ul style="list-style-type: none"> • Intervention(s): COVID-19 CP

NCT04374526 (Continued)

- Details of CP:
 - Type of plasma: ABO-matched pathogen-inactivated CCP
 - Volume: 200 mL/day
 - Number of doses: 3 (days 1, 2, and 3)
 - Antibody-titre: NR
 - Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: standard therapy
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

- Primary study outcome:
 - Proportion of patients without progression in severity of pulmonary disease, defined as worsening of 2 points in the ordinal scale of WHO by day 14
- Primary review outcomes reported
 - All-cause mortality: yes (day 28)
 - Admission to hospital: NR
- Secondary review outcomes reported
 - Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR
 - Time to symptom onset: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8 to 15 days, 16 to 30 days: yes (until day 14)
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Length of hospital stay, for hospitalised patients: yes
 - Admission to the intensive care unit (ICU): NR
 - Viral clearance, assessed with RT-PCR test: NR
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: yes
- Additional study outcomes:
 - Decreased viral load on nasopharyngeal swab at days 6, 9 and 14
 - Decreased viraemia at days 6 and 9
 - Increased antibody titre against SARS-CoV-2 at days 30 and 60
 - Proportion of patients with negative of SARS-CoV-2 nasopharyngeal swab at day 30
 - Total plasma related adverse event (day 60)
 - Total non-plasma related adverse events (day 60)

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

- (19 January 2021) Register entry is not up to date, latest information extracted from published protocol
- Recruitment status: recruiting
- Prospective completion date: 30 June 2021
- Sponsor/funding: Fondazione Policlinico Universitario Agostino Gemelli IRCCS

NCT04376788

Study name	Exchange transfusion versus plasma from convalescent patients with methylene blue in patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: randomised, parallel-assigned, open-label, phase 2 • Sample size: 15 (5 each group) • Setting: inpatient • Country: Egypt • Language: translated to English • Number of centres: 1
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Adult patients are ≥ 18 years • Inpatients diagnosed as severe COVID-19 disease according to WHO criteria • CT chest with extensive lung disease (ground-glass and consolidative pulmonary opacities) • O₂ saturation $< 93\%$ resting • Respiratory rate ≥ 30/min <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Patients with pregnancy and lactation • Renal failure and heart failure • Contraindication for plasma or blood transfusion
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP • Details of CP (group I) <ul style="list-style-type: none"> ◦ Type of plasma: will receive exchange transfusion by venesection of 500 cc blood with good replacement of one unit packed washed red blood cells daily for 3 days according to daily clinical and investigational follow-up ◦ Volume: 500 cc blood ◦ Number of doses: ◦ Antibody-titre: NR ◦ Pathogen inactivated: NR ◦ Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Details of CP (group II) <ul style="list-style-type: none"> ◦ Type of plasma: will receive IV methylene blue 1 mg/kg IV over 30 min with 200 cc plasma from convalescent matching single patient by plasma extractor machine for 3 days according to daily clinical and investigational follow-up. ◦ Volume: IV methylene blue 1 mg/kg IV over 30 min with 200 cc plasma ◦ Number of doses: ◦ Antibody-titre: NR ◦ Pathogen inactivated: NR ◦ Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Details of CP (group III) <ul style="list-style-type: none"> ◦ Type of plasma: will receive exchange transfusion by venesection of 500 cc blood with good replacement of 1 unit packed washed red blood cells 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

NCT04376788 (Continued)

	<ul style="list-style-type: none"> Concomitant therapy: NR Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> Primary study outcome <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> All-cause mortality at hospital discharge: NR Time to death: NR Secondary review outcomes reported <ul style="list-style-type: none"> Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR Number of participants with SAEs: NR Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR 30-day and 90-day mortality: NR Admission to the ICU: NR Length of stay on the ICU: NR Time to discharge from hospital: NR QoL: NR Additional study outcomes <ul style="list-style-type: none"> 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 progression-free survival and overall survival (time frame: 1 month) change in the liver, kidney function and change in ferritin level with normal D Dimer
Starting date	6 May 2020
Contact information	<ul style="list-style-type: none"> Contact: Mohamed M Moussa, MD: +201001553744; drmohamed_metwali1@med.asu.edu.eg Contact: Essam A Hassan, MD: +201001839394; essam.abdelwahed@yahoo.com
Notes	<ul style="list-style-type: none"> Recruitment status: recruiting Prospective completion date: 1 July 2020 Sponsor/funding: Ain Shams University 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	<ul style="list-style-type: none"> Trial design: open-label, phase 2, RCT Sample size: 100 Setting: inpatient children Country: Canada Language: English Number of centres: 12
Participants	Inclusion criteria:

NCT04377568 (Continued)

- Age 0 to < 19 years old
- hospitalised with symptoms compatible with COVID-19 illness
- Laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen prior to randomisation
- ABO-compatible CP available

Exclusion criteria:

- Onset of symptoms began > 12 days before screening
- History of adverse reactions to blood products or other contraindication to transfusion
- Refusal of plasma for religious or other reasons
- Acute heart failure with fluid overload
- Any condition or diagnosis, that could in the opinion of the Site Principal Investigator interfere with the participant's ability to comply with study instructions, or put the participant at risk
- Anticipated discharge within 24 h

Interventions

- Intervention(s): CP
- Details of CP:
 - Type of plasma: NR
 - Volume: proportional to their weight (10 mL/kg), up to a maximum of 500 mL
 - Number of doses: 1
 - Antibody-titre: NR
 - Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: standard of care
- Concomitant therapy: NR
- Treatment cross-overs: no

Outcomes

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

NCT04377568 (Continued)

- Additional outcomes
 - Clinical recovery (time frame: at day 30) defined in the last 24 h as normal respiratory and heart rate (or return to baseline, absence of fever, absence of low blood pressure, oxygen saturation > 94% or room air (or return to baseline), no need for intravenous fluids (or return to baseline)
 - Combined mortality/intubation at day 30
 - Time to intubation
 - Mean number of ventilator-free days in 30 days
 - Mean number of ventilator days in 30 days
 - The number of oxygen-free days in the first 30 days or the incidence and duration of new oxygen use during the trial, defined as oxygen use that was not present at time of randomisation but occurs subsequently
 - The proportion of participants needing ECMO in 30 days
 - The proportion of participants needing renal replacement therapy
 - The proportion of participants developing myocarditis
 - Proportion of participants with negative virology (time frame: at day 3, 5, 10 and 15)
 - Modulation of biomarkers (time frame: up to 365 days)
 - Resolution of fever (time frame: h)
 - Levels of IgG, IgA antibodies and neutralising antibody titres (time frame: at 30 days)
 - Efficacy of COVID-19 CP on respiratory measures using pediatric-validated dyspnoea (breathlessness) scales
 - Evaluate the efficacy of COVID-19 CP on rehospitalisation after discharge

Starting date	6 May 2020
Contact information	Julia Upton: 416 813 7654 ext 208634, julia.upton@sickkids.ca Christoph Licht, christoph.licht@sickkids.ca
Notes	<ul style="list-style-type: none"> • Recruitment status: • Prospective completion date: 1 December 2021 • Sponsor/funding: The Hospital for Sick Children, C17 Council (regulatory sponsor)

NCT04380935

Study name	Effectiveness and safety of convalescent plasma therapy on COVID-19 patients with acute respiratory distress syndrome
Methods	<ul style="list-style-type: none"> • Trial design: multicentre, open-label RCT • Sample size: 60 • Setting: inpatients • Country: Indonesia • Language English • Number of centres: 3
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patients aged ≥ 18 years • COVID-19 confirmed by RT-PCR • Having severe pneumonia • $PAO_2 / FIO_2 < 300$ • Using mechanical ventilation <p>Exclusion criteria:</p>

NCT04380935 (Continued)

- Contraindication to blood transfusions (fluid overload, history of anaphylaxis of blood products)
- Multiple and severe organ failure, haemodynamically unstable
- Other uncontrolled infections
- DIC, which requires a replacement factor/FFP
- Haemodialysis patients or CRRT (continuous renal replacement therapy)
- Active intracranial bleeding
- Significant myocardial ischaemia
- 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

8 May 2020

Contact information

 Robert Sinto, MD: +628158835432, rsinto@yahoo.com

Notes

- Recruitment status: recruiting
- Prospective completion date: 31 Oktober 2020
- Sponsor/funding: Indonesia University/NR

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

NCT04385043 (Continued)

Methods	<ul style="list-style-type: none"> • 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
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • inclusion criteria for donors: null-gravid, with a negative history of transfusion of blood components; possibility to sign the informed consent • inclusion criteria for COVID-19 infected patients: serious COVID-19 infection, possibility to sign the informed consent (also through the legal tutor) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • exclusion criteria for donors: presence of pregnancy, recent history of transfusion of blood components, < 18 years • exclusion criteria for COVID-19-infected patients: non-serious COVID-19 infection, impossibility to sign the informed consent (also through the legal tutor)
Interventions	<ul style="list-style-type: none"> • Intervention(s): plasma-hyperimmune add on to the standard therapy • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: NR ◦ Volume: NR ◦ Number of doses: NR ◦ Antibody-titre: NR ◦ Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: standard therapy • Concomitant therapy: NR • Treatment cross-overs: no
Outcomes	<ul style="list-style-type: none"> • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: 30-day mortality ◦ Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: invasive mechanical ventilation during infection; ECMO duration during infection: NR ◦ 30-day and 90-day mortality: yes (30-day mortality) ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: NR ◦ QoL: NR

NCT04385043 (Continued)

- 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	Gabriella Talarico, MD0961883111, trasfusionale@aocz.it
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 15 October 2020 (primary), 15 May 2021 (study) • Sponsor/funding: University of Catanzaro; Azienda Ospedaliera Policlinico "Mater Domini", Azienda Sanitaria Provinciale Di Catanzaro, Annunziata Hospital, Cosenza, Italy, Azienda Ospedaliera Bianchi-Melacrino-Morelli

NCT04385186

Study name	Inactivated convalescent plasma as a therapeutic alternative in hospitalized patients COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: multicentre, single-blind, clinical RCT • Sample size: 60 • Setting: inpatient • Country: Colombia • Language: translated to English • Number of centres: 10
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • > 18 years • Confirmed laboratory diagnosis for qRT-PCR to SARS-CoV-2 • Meet any of the following medical criteria (defined by WHO): be currently hospitalised with: pneumonia, severe pneumonia, ARDS (moderate or severe), sepsis or septic shock • The patient, or his representative, must sign an informed consent <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Participate in another clinical trial for COVID-19 • History of acute allergic transfusion reactions due to transfusion of blood or other components, especially plasma components (FFP, cryoprecipitate and platelets), • History of allergic reaction due to IgA deficiency • Allergic reaction to sodium citrate or riboflavin (vitamin B2) • History of immunosuppression
Interventions	<ul style="list-style-type: none"> • Intervention(s): inactivated CP SARS-CoV-2 + support treatment under medical decision (day 0) • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: ABO-Rh compatible inactivated CP SARS-CoV-2 ◦ Volume: 200 mL ◦ Number of doses: 2, day 0 and day 1 ◦ Antibody-titre: NR ◦ Pathogen inactivated: NR

NCT04385186 (Continued)

- 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
- 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

NCT04385186 (Continued)

- 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

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

NCT04385199 (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: 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
Contact information	<ul style="list-style-type: none"> • Geneva Tatem, MD: 313-587-6775, gtatem1@hfhs.org
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 1 August 2020 • Sponsor/funding: Henry Ford Health System

NCT04388410

Study name	Phase 2b/3 trial to evaluate the safety and efficacy of plasma transfusion from convalescent patients with SARS-CoV-2 infection on severity and mortality of COVID-19 in hospitalized patients.
Methods	<ul style="list-style-type: none"> • Trial design: RCT, double-blinded, multicentre, placebo-controlled • Sample size: 410 • Setting: inpatient • Country: Mexico • Language: English • Number of centres: at least 6
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Adults \geq 18 years ◦ Confirmed SARS-CoV-2 infection ◦ Hospitalised for COVID-19 ◦ Severe disease or risk for severe disease ◦ Informed consent from patient or responsible person • Exclusion criteria <ul style="list-style-type: none"> ◦ History of allergic reactions to blood products ◦ SOFA scale $>$ 12 points ◦ Absolute contraindication for administration of plasma ◦ Participation in other blinded clinical trial ◦ Projected life expectancy $<$ 3 months ◦ Any condition perceived by the investigator as not appropriate for participation of the patient in the trial
Interventions	<ul style="list-style-type: none"> • Intervention(s): normal saline and CP therapy

NCT04388410 (Continued)

- 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)
- 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 • Juan G Sierra-Madero, MD+52556559675, jsmadero@yahoo.com

 Notes • Recruitment status: Recruiting
 • Prospective completion date: November 30, 2020
 • Sponsor/funding: Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran

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: 150
 • Setting: outpatient, close contacts of COVID-19 cases
 • Country: USA

NCT04390503 (Continued)

- Language: English
- Number of centres: 1

 Participants

- Inclusion criteria
 - Subjects must be 18 years of age or older
 - Recent close contact with a person with COVID-19, i.e. last close contact occurred within 7 days of anticipated infusion of study product. It is anticipated that most contacts will be household contacts with extensive interaction. All must meet the CDC criteria for close contacts. This includes healthcare workers at higher risk of developing severe disease.
 - OR
 - Recent self-reported or documented evidence of infection by nasal swab PCR that is positive for SARS-CoV-2, i.e., nasal sample was collected within 7 days or 10 days of anticipated infusion of study product for those who are asymptomatic or symptomatic, respectively.
 - Evidence of infection by nasal swab PCR that is positive for SARS-CoV-2 at screening visit.
 - May or may not be hospitalised.
 - No symptoms or no more than 5 days of mild symptoms at the time of screening. Mild symptoms (rated by participant as mild and not interfering with normal daily activities) may include:
 - Mild rhinorrhea
 - Mild sore throat or throat irritation
 - Mild nonproductive cough
 - Mild fatigue (able to perform Activities of Daily Living (ADLs))
 - Risk for severe COVID-19 based on a risk score of ≥ 1 Calculated Risk Score of ≥ 1 point, with risk factors based on Centers 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.
- Exclusion criteria:
 - 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 subject safety and/or compliance.
 - Confirmed or self-reported presumed COVID-19, with symptoms that began more than 5 days prior to enrolment, and SARS-CoV-2 PCR-positive sample that was collected more than 7 days prior to anticipated infusion for an asymptomatic participant or more than 10 days prior to anticipated infusion for a patient with mild symptoms at screening.
 - Symptoms consistent with COVID-19 infection that are more than mild (as defined above) at time of screening.
 - Symptoms consistent with COVID-19 infection that are more than mild at time of screening.
 - History of allergic reaction to transfusion blood products
 - Inability to complete infusion of the product within 48 hours after randomization.
 - 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
 - On supplemental oxygen at time of enrolment
 - Participation in another clinical trial of anti-viral agent(s) for COVID-19
 - Receipt of any COVID-19 vaccine, either as part of a clinical research trial or through routine service delivery.

NCT04390503 (Continued)

Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: NR ◦ Volume: 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	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Efficacy of treatment, determined by rating disease severity on day 28, on 7-category severity scale • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality: NR ◦ Admission to hospital: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR ◦ Time to symptom onset: NR ◦ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8 to 15 days, 16 to 30 days: NR ◦ Mortality (time to event): NR ◦ 90-day mortality: NR ◦ Length of hospital stay, for hospitalised patients: NR ◦ Admission to the intensive care unit (ICU): NR ◦ Viral clearance, assessed with RT-PCR test: NR ◦ QoL: NR ◦ 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): NR ◦ Number of participants with serious adverse events: NR • Additional study outcomes: <ul style="list-style-type: none"> ◦ 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	March 2021 (estimated)
Contact information	<ul style="list-style-type: none"> • Jessica Justman, MD 212-342-0537, jj2158@cumc.columbia.edu • Jennifer Zech, MSc 212-304-5506, jz2973@cumc.columbia.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: April 2022 • Sponsor/funding: Columbia University

NCT04391101

Study name	Efficacy of convalescent plasma for the treatment of severe SARS-CoV-2 infection: a randomized, open label clinical trial
Methods	<ul style="list-style-type: none"> • Trial design: open-label, RCT • Sample size: 231 • Setting: ICU • Country: Colombia • Language: English • Number of centres: 8
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ > 18 years of age ◦ SARS-CoV-2 infection confirmed by PCR in any sample ◦ Hospitalised in the ICU due to shock or respiratory failure, with < 24 h after entering the ICU • Exclusion criteria <ul style="list-style-type: none"> ◦ Serious volume overload or other condition that contraindicates plasma transfusion ◦ History of anaphylaxis or serious adverse reaction to plasma ◦ Previous diagnosis of immunoglobulin A deficiency • Donor eligibility criteria <ul style="list-style-type: none"> ◦ > 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 <ul style="list-style-type: none"> ◦ 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	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> ◦ 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	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ In-hospital mortality from any cause (up to 28 days) • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: 28-day mortality ◦ Time to death: NR

NCT04391101 (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 (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	<ul style="list-style-type: none"> • Oliver G Perilla Suarez, Hematologist +573136395608 gerardoperilla@gmail.com • Fabian A Jaimes Barragan, Epidemiologist +5742192420 fabian.jaimes@udea.edu.co
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: December 2021 • 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

NCT04395170

Study name	A multicenter randomized clinical trial to evaluate the efficacy and safety of the use of convalescent plasma (PC) compared to anti-COVID-19 human immunoglobulin and standard treatment in hospitalized patients
Methods	<ul style="list-style-type: none"> • Trial design: open-label RCT • Sample size: 75 • Setting: inpatient • Country: Colombia • Language: English • Number of centres: 1

NCT04395170 (Continued)

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 $\leq 94\%$ in ambient air requiring supplemental oxygen
 - Patient with no more than 72 h (3 days) of hospitalisation prior to the administration of CP treatment (except the days after initial hospital admission for other reasons and prior to COVID-19 infection).
 - Patients who do not have more than 10 days between the onset of symptoms (fever or cough) and the day of administration of treatment or the demonstration of the absence of anti-SARS-CoV-2 antibodies (patients with more than 10 days of symptoms they can only be included if a negative antibody result has been confirmed).
- Exclusion criteria
 - 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:

- 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

NCT04395170 (Continued)

- 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: December 2020
- Sponsor/funding: Lifefactors Zona Franca, SAS

NCT04397757

Study name

COVID-19 convalescent plasma for the treatment of hospitalized patients with pneumonia caused by SARS-CoV-2

Methods

- Trial design: open-label RCT
- Sample size: 80
- Setting: inpatient
- Country: USA
- Language: English
- Number of centres: 1

Participants

- Inclusion criteria
 - Adult \geq 18 years of age
 - Laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other authorised or approved assay in any specimen collected within 72 h prior to enrolment

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

- - Hospitalised in participating facility
 - Documentation of pneumonia with radiographic evidence of infiltrates by imaging (e.g., chest X-ray or CT scan)

NCT04397757 (Continued)

- 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
 - Tachypnoea with respiratory rate ≥ 30
- Patient or proxy is willing and able to provide written informed consent and comply with all protocol requirements
- Exclusion criteria
 - Contraindication to transfusion (e.g. severe volume overload, history of severe allergic reaction to blood products), as judged by the investigator
 - Clinical suspicion that the aetiology of acute illness (acute decompensation) is primarily due to a condition other than COVID-19
 - Receipt of other investigational therapy as a part of another clinical trial. Note: investigational therapies used as part of clinical care, (e.g., remdesivir, hydroxychloroquine) are permissible.

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - Type of plasma: NR
 - Volume: NR
 - Number of doses: 2
 - Antibody-titre: NR
 - Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients (severe)
- Comparator: standard care
- Concomitant therapy: NR
- Treatment cross-overs: not applicable

Outcomes

- Primary study outcome:
 - Participants with SAEs (at day 29)
 - Comparison of clinical severity score between patients on the experimental versus control arms (at day 29)
- Primary review outcomes reported
 - All-cause mortality at hospital discharge: 29-day mortality
 - Time to death: NR
- Secondary review outcomes reported
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): yes
 - Number of participants with SAEs: yes
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: yes
 - 30-day and 90-day mortality: yes (28-day mortality)
 - Admission on the ICU: yes
 - Length of stay on the ICU: NR
 - Time to discharge from hospital: yes (up to 29 days)
 - QoL: NR
- Additional study outcomes: time to recovery (defined as clinical severity score 1-3), clinical status assessment using the National Early Warning Score (NEWS) of CP administration, WBC, hemoglobin, platelet counts, creatinine, glucose, bilirubin, ALT, AST, PT

Starting date

13 March 2020

Contact information

- Katharine J. Bar, MD (215) 349-8092 BarK@pennmedicine.upenn.edu

NCT04397757 (Continued)

- Julie Starr 215-349-8527 jstarr@penmedicine.upenn.edu

Notes

- Recruitment status: Active, not recruiting
- Prospective completion date: April 30, 2021
- 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)
- 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

NCT04403477 (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
 - 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	<ul style="list-style-type: none"> • Contact: Mohammad S Rahman, MPhil,FCPS+88 01971840757, srkhasru@gmail.com • Contact: Fazle R Chowdhury, FCPS; PhD+88 01916578699, mastershakil@hotmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 20 July 2020 • Sponsor/funding: Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; Dhaka Medical College

NCT04408040

Study name	Use of convalescent plasma collected from donors recovered from COVID-19 virus disease for transfusion, as an empirical and preemptive treatment during viral pandemic outbreak
Methods	<ul style="list-style-type: none"> • Trial design: non-randomised • Sample size: 700 • Setting: inpatient and healthcare providers • Country: USA • Language: English • Number of centres: 1

NCT04408040 (Continued)

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, O_2 sats $\leq 93\%$ at rest, PaO_2/FiO_2 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

Interventions

- 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
- 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

NCT04408040 (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: 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	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: June 2022 • Sponsor/funding: Northside Hospital Inc.

NCT04415086

Study name	Treatment of patients with COVID-19 with convalescent plasma transfusion: a multicenter, open-labeled, randomized and controlled study
Methods	<ul style="list-style-type: none"> • Trial design: randomised • Sample size: 120 • Setting: hospitalised patients • Country: Brazil • Language: English • Number of centres: 1 • Trial registration number: NCT04415086 • Date of registration: 4 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> ◦ Age ≥ 18 years ◦ Laboratory-proven COVID-19 infection by RT-PCR in any clinical sample ◦ Time since symptom onset < 10 days at the time of screening ◦ Presence of COVID-19 pneumonia, with a typical, indeterminate or atypical compatible image in a chest tomography exam (see definition below) ◦ Presence of one of the following criteria: <ul style="list-style-type: none"> ■ Need for > 3L of O₂ in the catheter/mask or > 25% in the Venturi mask to maintain O₂ saturation > 92% ■ presence of respiratory distress syndrome with PaO₂/FiO₂ < 300 mmHg If intubated, within 48 h of orotracheal intubation ■ Absence of a history of serious adverse reactions to transfusion, for example, anaphylaxis ■ Participation approval by the research clinician

NCT04415086 (Continued)

- Exclusion criteria:
 - Already enrolled in another clinical trial evaluating antiviral or immunobiological therapy for the treatment of COVID-19
 - IgA deficiency
 - Presence of a clinical condition that does not allow infusion of 400 mL of volume at clinical discretion
 - Pregnancy or breastfeeding
 - Receipt of immunoglobulin in the last 30 days
 - Presence of significant risk of death within the next 48 h at clinical discretion
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy (3 arms, randomised 1:1:1 into 3 treatment groups: A- standard (control); B- standard and CP in a volume of 200 mL (150-300 mL); C- standard and CP in a volume of 400 mL (300-600 mL)
- Details of CP:
 - Type of plasma: CP
 - Volume: 200 mL or 400 mL
 - Number of doses: NR
 - Antibody test and antibody-titre: NR
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors:
 - Gender: NR
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator: nil
- Concomitant therapy: standard of care
- Duration of follow-up: 28 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - Time elapsed until clinical improvement or hospital discharge
- Primary review outcomes reported
 - All-cause mortality at hospital discharge: reported
 - Time to death: reported

NCT04415086 (Continued)

- Secondary review outcomes reported
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - Number of participants with SAEs: reported
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - WHO ordinal scale: reported
 - 30-day and 90-day mortality: reported
 - Admission on the ICU: NR
 - Length of stay on the ICU: NR
 - Time to discharge from hospital: reported
 - QoL: NR
 - Virological response:
 - SARS-CoV-2 in nasopharyngeal swab (time frame: Days 0, 1, 3, 7, 14 and 28 after transfusion and control groups)
 - IgG, IgM and IgA titres for SARS-CoV-2 (time frame: Days 0, 1, 3, 5, 7, 14 and 28 after transfusion and control groups)
 - Neutralising antibodies (time frame: 0,1,7 14 and 28 days after transfusion and control groups)
- Additional outcomes: nil

Starting date	1 June 2020
Contact information	<ul style="list-style-type: none"> • Contact: Zelinda B Nakagawa, MsC55-11-2661-7214, zelinda.bartolomei@gmail.com • Contact: Natália B Cerqueira55-112661-2277, natalia.b.cerqueira@gmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: April 20, 2022 • Sponsor/funding: University of Sao Paulo General Hospital

NCT04418518

Study name	CONCOR-1: a randomized open-label trial of convalescent plasma for hospitalized adults with acute COVID-19 respiratory illness
Methods	<ul style="list-style-type: none"> • Trial design: randomised • Sample size: 1200 • Setting: hospitalised patients • Country: USA • Language: English • Number of centres: 3 • Trial registration number: NCT04418518 • Date of registration: 5 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> ◦ ≥ 18 years old ◦ Admitted to hospital with confirmed COVID-19 respiratory illness ◦ Receiving supplemental oxygen ◦ 500 mL of ABO compatible convalescent plasma is available

NCT04418518 (Continued)

- Exclusion criteria:
 - Onset of symptoms > 12 days prior to randomisation
 - Intubated or plan for intubation in place
 - Plasma is contraindicated (e.g. history of anaphylaxis from transfusion)
 - Decision in place for no active treatment
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - Type of plasma: CP
 - Volume: 500 mL
 - Number of doses: 1 (or 2 x 250 ml)
 - Antibody test and antibody-titre: NR
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors:
 - Gender: NR
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator: nil
- Concomitant therapy: standard of care
- Duration of follow-up: 90 days
- Treatment cross-overs: nil

Outcomes

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

Starting date

24 June 2020

Contact information

Celine Arar: 212-746-4177; cea4002@med.cornell.edu

NCT04418518 (Continued)

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|-------|--|
| Notes | <ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: December 2021 • Sponsor/funding: Weill Medical College of Cornell University |
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NCT04420988

- | | |
|---------------|--|
| Study name | Investigational COVID-19 convalescent plasma infusion for severely or life-threateningly ill COVID-19 patients |
| Methods | <ul style="list-style-type: none"> • Trial design: expanded access scheme • Sample size: NR • Setting: hospitalised patients, with severely or life-threateningly ill COVID-19 • Country: USA • Language: English • Number of centres: 2 |
| Participants | <ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> ○ Laboratory-confirmed COVID-19 ○ Severe or life-threatening COVID-19 ○ Severe disease is defined as one or more of the following <ul style="list-style-type: none"> ■ dyspnoea ■ respiratory frequency $\geq 30/\text{min}$ ■ blood oxygen saturation $\leq 93\%$ ■ $\text{PaO}_2:\text{FiO}_2$ ratio < 300 ■ lung infiltrates $> 50\%$ within 24-48 h ○ Life-threatening disease is defined as one or more of the following <ul style="list-style-type: none"> ■ respiratory failure ■ septic shock ■ multiple organ dysfunction or failure • Exclusion criteria: <ul style="list-style-type: none"> ○ Contraindication to transfusion (severe volume overload, history of anaphylaxis to blood products) ○ Severe multi-organ failure and haemodynamic instability requiring high doses of pressor agents ○ Other documented uncontrolled infection ○ Severe DIC needing factor replacement, FFP, cryoprecipitate ○ Acute renal failure requiring dialysis ○ Active intracranial bleeding ○ Clinically significant myocardial ischaemia |
| Interventions | <ul style="list-style-type: none"> • Details of CP: <ul style="list-style-type: none"> ○ Type of plasma: CP ○ Volume: NR ○ Number of doses: NR ○ Antibody test and antibody-titre: NR ○ Pathogen inactivated or not: NR ○ RT-PCR tested: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): severe/critically ill patients • Comparator: nil • Concomitant therapy: NR |

NCT04420988 (Continued)

	<ul style="list-style-type: none"> • Duration of follow-up: NR • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: NR • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR ◦ WHO ordinal scale: NR ◦ 30-day and 90-day mortality: NR ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: NR ◦ QoL: NR ◦ Virological response: NR • Additional outcomes: nil
Starting date	NR
Contact information	<ul style="list-style-type: none"> • Marc Klapholz, MD, MBA973-972-4595; klapholz@njms.rutgers.edu • Khyati Mehta, MPH973-972-6794; mehtakp@njms.rutgers.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting (expanded access scheme available) • Prospective completion date: NR • Sponsor/funding: Rutgers, The State University of New Jersey

NCT04421404

Study name	A randomized controlled adaptive study comparing COVID-19 convalescent plasma (CCP) to non-immune plasma to limit coronavirus-associated complications in hospitalized patients
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 50 • Setting: hospitalised patients • Country: USA • Language: English • Number of centres: 3 • Trial registration number: NCT04421404 • Date of registration: 9 June 2020

NCT04421404 (Continued)

Participants

- Inclusion criteria:
 - Patients ≥ 18 years of age
 - Hospitalised with COVID-19
 - Enrolled within 72 h of hospitalisation OR within day 14 from first signs of illness
 - Pulmonary infiltrates on chest imaging
 - Oxygenation of < 95% on room air
 - Laboratory-confirmed COVID-19
- Exclusion criteria:
 - Contraindication to transfusion due to inability to tolerate additional fluid, such as due to de-compensated congestive heart failure
 - Baseline requirement for oxygen supplementation prior to COVID-19 infection or use of positive pressure therapy for sleep-disordered breathing
 - Currently experiencing severe hypoxaemic failure, as defined in study endpoints
 - Prior receipt of plasma products, IVIG, or hyperimmune globulin within past 3 months
 - Not currently enrolled another interventional clinical trial of COVID-19 treatment
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - Type of plasma: CP
 - Volume: NR
 - Number of doses: NR
 - Antibody test and antibody-titre: NR
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors:
 - Gender: NR
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): enrolled within 72 h of hospitalisation OR within day 14 from first signs of illness
- Comparator: standard plasma
- Concomitant therapy: standard of care
- Duration of follow-up: 29 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - Mechanical ventilation or death endpoint
- Primary review outcomes reported
 - All-cause mortality at hospital discharge: reported
 - Time to death: reported

NCT04421404 (Continued)

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

Starting date	9 June 2020
Contact information	<ul style="list-style-type: none"> • Priscilla Hsue, MD, Professor of Medicine, University of California, San Francisco
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: April 30, 2021 • Sponsor/funding: Priscilla Hsue, MD

NCT04425837

Study name	Effectiveness and safety of convalescent plasma in patients with high-risk COVID-19: a randomized, controlled study CRI-CP (Coronavirus Investigation - Convalescent Plasma)
Methods	<ul style="list-style-type: none"> • Trial design: randomised • Sample size: 236 • Setting: critically ill or high risk of progression • Country: Colombia • Language: English • Number of centres: 1 • Trial registration number: NCT04425837 • Date of registration: 11 June 2020

NCT04425837 (Continued)

Participants

- Inclusion criteria:
 - Patients diagnosed with COVID-19 infection by RT-PCR technique
 - Patients ≥ 18 years of age
 - Patients in standard care according to the national guide
 - Onset of symptoms ≤ 14 days
 - Signature of informed consent report
 - Patients at high risk of progression, defined by all of the following:
 - score > 9 on the CALL scale
 - $\text{PaO}_2/\text{FiO}_2 \leq 200$ (parameters adjusted to the elevation of Bogotá, Colombia)
 - X-ray or CT compatible with pneumonia
 - Hospitalised patients
 - Critically ill patients, defined by any of the following:
 - mechanical ventilation requirement
 - patients in ICU or Intermediate Care Unit
 - ventilatory failure, septic shock, dysfunction or multi-organ failure
- Exclusion criteria:
 - Negative RT-PCR result from secretion 48 h prior to study recruitment
 - History of allergic reaction to blood or plasma in patients with a known history of IgA deficiency
 - Patients participating in other clinical trial
 - History of allergy to blood products
 - History of confirmed infection and that required antibiotic or antifungal treatment 30 days prior to recruitment
 - Pregnant women
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - Type of plasma: CP
 - Volume: 400 mL
 - Number of doses: 2
 - Antibody test and antibody-titre: titre $\geq 1:160$
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors:
 - Gender: NR
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): critically ill/high risk of progression
- Comparator: standard of care
- Concomitant therapy: standard of care
- Duration of follow-up: 30 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - Mortality
 - Safety: presence of adverse events
 - ICU admission
 - Mechanical ventilation

NCT04425837 (Continued)

- Primary review outcomes reported
 - All-cause mortality at hospital discharge: reported
 - Time to death: reported
- Secondary review outcomes reported
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - Number of participants with SAEs: reported
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - WHO ordinal scale: reported
 - 30-day and 90-day mortality: reported
 - Admission on the ICU: reported
 - Length of stay on the ICU: reported
 - Time to discharge from hospital: NR
 - QoL: NR
 - Virological response:
- Additional outcomes: laboratory parameters (CRP, ferritin, procalcitonin, lymphocyte count, LDH), SOFA score, Increase in PaO₂/FiO₂, lung infiltration

Starting date	July 2020
Contact information	<ul style="list-style-type: none"> • Contact: Guillermo E Quintero, Hematologist, 5716030303 ext 1221, quiquequintero@yahoo.com.mx • Contact: José A De la Hoz, Epidemiologist, 5716030303 ext 1127, jose.delahoz@fsfb.org.co
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: February 2021 • Sponsor/funding: Fundación Santa Fe de Bogota

NCT04425915

Study name	Efficacy of convalescent plasma therapy in patients with COVID-19: a randomized control trial
Methods	<ul style="list-style-type: none"> • Trial design: randomised parallel-assignment • Sample size: 400 • Setting: severe disease • Country: India • Language: English • Number of centres: 3 • Trial registration number: NCT04425915 • Date of registration: 11 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> ◦ Patients with severe COVID-19 will be considered for randomisation and will be transfused CP within 3 days of symptom onset (severe COVID-19). Severe COVID-19 defined by WHO Interim Guidance and the Guideline of Diagnosis and Treatment of COVID-19 of National Health Commission of China (version 5.0) along with confirmation by real-time RT-PCR assay with severe disease i.e. meeting any 2 of the following criteria: <ul style="list-style-type: none"> ■ Patients on ventilator (in last 24 h) ■ Respiratory distress, respiratory rate ≥ 30 breaths/min ■ Oxygen saturation level $< 90\%$ in resting state ■ PaO₂/FiO₂ ≤ 300 mmHg

NCT04425915 (Continued)

- Lung infiltrates > 50% within 24-48 h
- Exclusion criteria:
 - Patient/family members who do not give consent to participate in the study
 - Patients with age < 18 years
 - Patients presenting with multi-organ failure
 - Pregnancy
 - Individuals with HIV and viral hepatitis and cancer
 - Extremely moribund patients with an expected life expectancy of < 24 h
 - Hemodynamic instability requiring vasopressors
 - Previous history of allergy to plasma
 - Cirrhosis
 - Severe renal impairment with GFR < 30 mL/min or recipients of RRT, peritoneal dialysis
 - Patients with uncontrolled diabetes mellitus, hypertension, arrhythmias and unstable angina
- Donor eligibility criteria:
 - Virologically documented (PCR-positive by nasopharyngeal swab) who is recovered and free of symptoms for 14 days
 - Has tested negative for SARS-CoV-2 on 2 consecutive tests 24 h apart.
 - Fulfill all criteria of donor eligibility for donor plasmapheresis under the Drugs & Cosmetics Act 1940 and Rules 1945, amended 11 March 2020
 - Women who have been pregnant may be tested for anti-HLA antibodies and eligible if negative for the same
- Donor exclusion criteria:
 - Do not fulfil all criteria of donor eligibility for donor plasmapheresis under the Drugs & Cosmetics Act 1940 and Rules 1945, amended 11 March 2020
 - Females who have been pregnant and have not been tested for HLA antibodies or are HLA antibody positive if tested and previously transfused donors (to prevent TRALI)
 - Donors who have taken steroids during treatment for COVID-19

 Interventions

- Intervention(s): CP therapy
- Details of CP:
 - Type of plasma: CP
 - Volume: 250 mL
 - Number of doses: 2
 - Antibody test and antibody-titre: NR
 - Pathogen inactivated or not: NR
 - RT-PCR tested: yes
- Details of donors:
 - Gender: both, exclude women with previous pregnancy without previous testing for HLA antibodies or HLA antibody-positive
 - HLA and HNA antibody: HLA tested in females with previous pregnancy
 - Severity of disease: NR
 - Timing from recovery from disease: 14 days asymptomatic since last negative test
- Treatment details, including time of plasma therapy (e.g. early stage of disease): within 3 days of severe disease
- Comparator: standard of care
- Concomitant therapy: standard of care
- Duration of follow-up: 28 days
- Treatment cross-overs: nil

 Outcomes

- Primary study outcome:
 - Efficacy of CP in severe COVID-19 patients in time to clinical improvement
- Primary review outcomes reported
 - All-cause mortality at hospital discharge: reported
 - Time to death: reported

NCT04425915 (Continued)

- Secondary review outcomes reported
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - Number of participants with SAEs: reported
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - WHO ordinal scale: reported
 - 30-day and 90-day mortality: NR
 - Admission on the ICU: reported
 - Length of stay on the ICU: reported
 - Time to discharge from hospital: NR
 - QoL: NR
 - Virological response: presence of antibodies against SARS-CoV-2 in serum after plasma administration (Days 3, 7, 14, 21, 28)
- Additional outcomes: changes in acute phase reactants, cytokines, correlation of the titres in COVID-19 CP donors with duration of illness, the severity of symptoms, duration of hospital stay, drugs used in therapy, duration between recovery, and donation

Starting date	9 June 2020
Contact information	<ul style="list-style-type: none"> • Contact: Dr Meenu Bajpai, MD01146300000, mbajpai@ilbs.in • Contact: Dr Ankit Bhardwaj, Masters-CT011463000000, abhardwaj@ilbs.in
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 30 May 2021 • Sponsor/funding: Institute of Liver and Biliary Sciences, India

NCT04428021

Study name	Effectiveness of adding standard plasma or COVID-19 convalescent plasma to standard treatment, versus standard treatment alone, in patients with recent onset of COVID-19 respiratory failure. A randomized, three-arms, phase 2 trial
Methods	<ul style="list-style-type: none"> • Trial design: randomised • Sample size: 180 • Setting: hospitalised patients within 5 days of respiratory failure • Country: Italy • Language: English • Number of centres: 1 • Trial registration number: NCT04428021 • Date of registration: 11 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> ◦ Confirmed SARS-CoV-2 diagnosis by RT-PCR on nasopharyngeal swab or on BAL ◦ Respiratory failure onset or progression within 5 days ◦ Signed informed consent • Exclusion criteria: <ul style="list-style-type: none"> ◦ Pregnancy ◦ Previous severe reactions to plasma transfusion ◦ Unavailability of blood group-compatible COVID-19 CP • Donor eligibility criteria: NR

NCT04428021 (Continued)

	<ul style="list-style-type: none"> • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy <ul style="list-style-type: none"> ◦ Enrolled patients will be stratified according to severity of respiratory failure and randomised in 3 arms: 1) Standard Therapy Protocol (STP), 2) Standard Therapy Protocol + 170-350 mL standard plasma (SP) on day 1-3-5 after randomisation, 3) Standard Therapy Protocol + 170-350 mL COVID-19 CP on day 1-3-5 after randomisation. • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: 170-300 mL ◦ Number of doses: 3 ◦ Antibody test and antibody-titre: NR ◦ Pathogen inactivated or not: yes (virus inactivated with riboflavin and ultraviolet light illumination technology) ◦ RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> ◦ Gender: NR ◦ HLA and HNA antibody: NR ◦ Severity of disease: NR ◦ Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): within 5 days of respiratory failure • Comparator: standard of care, standard plasma • Concomitant therapy: standard of care • Duration of follow-up: 12 months • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ 30-day survival • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: reported ◦ Time to death: reported • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported ◦ WHO ordinal scale: reported ◦ 30-day and 90-day mortality: NR ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: NR ◦ QoL: NR ◦ Virological response: proportion of participants showing seroconversion to IgG anti-SARS-CoV-2, proportion of participants showing viral clearance by RT-PCR on plasma and respiratory tract samples • Additional outcomes: SOFA score, variation from standard therapy protocol, Incidence of complications, 6-month survival, ventilator-free survival
Starting date	15 June 2020

NCT04428021 (Continued)

Contact information Paola Maria Manzini, Principal Investigator, Azienda Ospedaliera Città della Salute e della Scienza di Torino

- Notes
- Recruitment status: recruiting
 - Prospective completion date: 15 December 2021
 - Sponsor/funding: Azienda Ospedaliera Città della Salute e della Scienza di Torino

NCT04429854

Study name A randomized, open-label, adaptive, proof-of-concept clinical trial of donated antibodies working against with COVID-19: DAWN-PLASMA

- Methods
- Trial design: randomised
 - Sample size: 483 (483 patients with 2:1 randomisation. 322 participants receiving CP - 161 participants receiving standard of care)
 - Setting: without non-invasive/invasive ventilation
 - Country: Belgium
 - Language: English
 - Number of centres: 14
 - Trial registration number: [NCT04429854](#)
 - Date of registration: 12 June 2020

- Participants
- Inclusion criteria:
 - Participant (≥ 18 years old) or LAR provides informed consent prior to initiation of any study procedures
 - Participant (or LAR) understands and agrees to comply with planned study procedures
 - Male or non-pregnant female adult ≥ 18 years of age at time of enrolment
 - Patient should be hospitalised
 - Has a confirmed diagnosis of SARS-CoV-2 infection, defined as either:
 - laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen as diagnosed within 60 h prior to randomisation or
 - the combination of upper or lower respiratory infection symptoms (fever, cough, dyspnoea, desaturation) and typical findings on chest CT scan and absence of other plausible diagnoses
 - Illness of any duration, and at least 1 of the following:
 - radiographic infiltrates by imaging (chest X-ray, CT scan, etc.), or
 - clinical assessment (evidence of rales/crackles on exam) AND SpO₂ ≤ 94% on room air, or
 - requiring supplemental oxygen
 - ABO D typing of the participant should be done at least once and the result should be known
 - Exclusion criteria:
 - Receiving invasive (any mode where a patient has been intubated endotracheally, or via tracheostomy) or non-invasive (for instance, but not restricted to CPAP, PSV, PCV, SiMV) mechanical ventilation before or upon randomisation
 - Pregnancy or breastfeeding
 - Any medical condition that would impose an unacceptable safety hazard by participation to the study
 - Patients with a documented grade 3 allergic reaction after the administration of FFP (i.e. systemic reaction with cardiovascular and/or respiratory involvement)
 - Patients that have treatment restriction that excludes mechanical ventilation and/or endotracheal intubation
 - Donor eligibility criteria: NR
 - Donor exclusion criteria: NR

NCT04429854 (Continued)

Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy randomised 2:1 to standard care • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: NR ◦ Number of doses: 4 ◦ Antibody test and antibody-titre: NR ◦ Pathogen inactivated or not: NR ◦ RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> ◦ Gender: NR ◦ HLA and HNA antibody: NR ◦ Severity of disease: NR ◦ Timing from recovery from disease: 21 days without symptoms from negative PCR test • Treatment details, including time of plasma therapy (e.g. early stage of disease): without non-invasive/invasive ventilation • Comparator: nil • Concomitant therapy: standard of care • Duration of follow-up: 30 days • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Participants requiring mechanical ventilation or death • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: reported ◦ Time to death: reported • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported ◦ WHO ordinal scale: reported ◦ 30-day and 90-day mortality: reported ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: NR ◦ QoL: NR ◦ Virological response: NR • Additional outcomes: nil
Starting date	2 May 2020
Contact information	Geert Meyfroidt, MD, PhD: geert.meyfroidt@uzleuven.be
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 2 November 2021 • Sponsor/funding: Universitaire Ziekenhuizen Leuven

NCT04432272

Study name	Antibody-level based analysis of COVID-19 convalescent serum (ABACCuS)
Methods	<ul style="list-style-type: none"> • Trial design: controlled trial, non-randomised with 2 arms, both receiving CP • Sample size: 500 • Setting: hospitalised patients • Country: USA • Language: English • Number of centres: 8 • Trial registration number: NCT04432272 • Date of registration: 16 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> ◦ Participants must be ≥ 18 years ◦ Hospitalised with confirmed COVID-19 infection via COVID-19 SARS-CoV-2 RT-PCR testing ◦ Symptoms consistent with COVID-19 infection (fever, acute onset cough, shortness of breath) at time of screening ◦ Patient requires > 6 L nasal cannula oxygen (Group A) or intubated (Group B) ◦ Patient (or their LAR) is willing and able to provide written informed consent and comply with all protocol requirements • Exclusion criteria: <ul style="list-style-type: none"> ◦ For participants in Group A admitted for > 14 days ◦ Female participants with positive pregnancy test, breastfeeding, or planning to become pregnant or breastfeed during the study period ◦ Receipt of pooled immunoglobulin in past 30 days ◦ Contraindication to transfusion or history of prior reactions to transfusion blood products ◦ Patients currently undergoing cancer treatment or those who are presently immunocompromised ◦ Patient who in the opinion of the investigator will not be a good study candidate • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy <ul style="list-style-type: none"> ◦ Participants will be assigned to a study group depending on how sick they are ◦ Group A: those who require > 6 L of supplemental oxygen but are not on a ventilator ◦ Group B: those who require a ventilator to preserve their life • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: 200 mL ◦ Number of doses: 1 ◦ Antibody test and antibody-titre: NR ◦ Pathogen inactivated or not: NR ◦ RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> ◦ Gender: NR ◦ HLA and HNA antibody: NR ◦ Severity of disease: variable ◦ Timing from recovery from disease: variable <ul style="list-style-type: none"> ■ donors either: 1) been symptom-free for 14 days and screen negative via nasopharyngeal swab or 2) symptom-free for at least 28 days or 3) individuals who have never had symptoms of COVID-19 but were found to have elevated anti-SARS-CoV-2 IgG by a serology test deemed to be of acceptable quality and fitting the current guidance by the FDA • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients • Comparator: nil

NCT04432272 (Continued)

- Concomitant therapy: standard of care
- Duration of follow-up: 28 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - Avoidance of intubation at 28 days (group A) (time frame: 28 days)
 - Mortality (group B) (time frame: 28 days)
- Primary review outcomes reported
 - All-cause mortality at hospital discharge: reported
 - Time to death: reported
- Secondary review outcomes reported
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - Number of participants with SAEs: NR
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - WHO ordinal scale: reported
 - 30-day and 90-day mortality: reported
 - Admission on the ICU: reported
 - Length of stay on the ICU: reported
 - Time to discharge from hospital: reported
 - QoL: NR
 - Virological response: reported (count of participants with presence of SARS-CoV-2 RNA detected by RT-PCR-tested nasopharyngeal swabs)
- Additional outcomes: renal failure, liver failure, presence of ARDS, ventilator-free days

Starting date 14 July 2020

Contact information Maureen Cooney, RN, BSN: Maureen.Cooney@beaumont.org

- Notes
- Recruitment status: not yet recruiting
 - Prospective completion date: August 2021
 - Sponsor/funding: William Beaumont Hospitals

NCT04438057

Study name Evaluating the efficacy of convalescent plasma in symptomatic outpatients infected with COVID-19

- Methods
- Trial design: randomised 2:1 (CP:standard of care)
 - Sample size: 150
 - Setting: mild to moderate symptoms
 - Country: USA
 - Language: English
 - Number of centres: 1
 - Trial registration number: [NCT04438057](#)
 - Date of registration: 18 June 2020

NCT04438057 (Continued)

Participants

- Inclusion criteria:
 - Laboratory-confirmed diagnosis of infection with SARS-CoV-2
 - Symptoms of COVID -19 - cough, fever, sore throat, shortness of breath, anosmia, diarrhoea, myalgia
 - Symptoms < 14 days
 - ID physician determination that the patient does not need hospitalisation
 - O2 saturation of > 93%
 - Informed consent provided by the patient or healthcare proxy
 - Age ≥ 18 years
 - Ambulatory outpatient when informed consent obtained and study drug is administered
- Exclusion criteria:
 - Age < 18 years
 - Patients currently receiving intravenous immunoglobulin
 - Hypercoagulable state - neoplasia, collagen vascular disease, myelodysplastic syndrome, chronic anticoagulation treatment, etc
 - Need to be hospitalised
 - O2 sat < 93%
 - D-Dimer > 2 x normal
 - Chronic oxygen therapy
 - Renal insufficiency with Creatinine clearance < 30
 - Long-term care or assisted living facility resident
 - Ongoing usage of hydroxychloroquine for any indication
 - History of blood or plasma transfusion-related complications
 - Enrolment into any other investigational drug or device study within the previous 30 days
 - Any drug, chemical or alcohol dependency as determined by the investigator through history that may affect study procedures and follow-up
 - Pregnant or breastfeeding
 - Any acute or chronic medical comorbidity, psychiatric, social or other circumstance that, in the opinion of the investigator, may interfere with study compliance, completion, or accurate assessment of the study outcomes/safety
 - Admitted to or expected to be admitted to a medical facility
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy (arm 1: 1 dose, arm 2: 2 doses)
- Details of CP:
 - Type of plasma: CP
 - Volume: NR
 - Number of doses: 1
 - Antibody test and antibody-titre: NR
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors:
 - Gender: NR
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): mild to moderate symptoms
- Comparator: standard of care
- Concomitant therapy: standard of care
- Duration of follow-up: 28 days

NCT04438057 (Continued)

	<ul style="list-style-type: none"> Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> Primary study outcome: <ul style="list-style-type: none"> Time to resolution of symptoms (time frame: 28 days) SAEs within 24 h of plasma infusion (time frame: 28 days) Primary review outcomes reported <ul style="list-style-type: none"> All-cause mortality: NR Admission to hospital: yes (28 days) Secondary review outcomes reported <ul style="list-style-type: none"> Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR Time to symptom onset: NR Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8 to 15 days, 16 to 30 days: NR Mortality (time to event): NR 90-day mortality: NR Length of hospital stay, for hospitalised patients: NR Admission to the intensive care unit (ICU): NR Viral clearance, assessed with RT-PCR test: NR QoL: NR 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): NR Number of participants with serious adverse events: NR (severe adverse effects of CP only, 24 hours after infusion) Additional outcomes: <ul style="list-style-type: none"> Laboratory parameters (CRP, D-dimer, LDH, Ferritin, Lactate Dehydrogenase)
Starting date	6 July 2020
Contact information	<ul style="list-style-type: none"> Contact: Nicholas Van Hise, PharmD 630-655-6952 nvanhise@midcusa.com Contact: Nathan Skorodin, PharmD nskorodin@midcusa.com
Notes	<ul style="list-style-type: none"> Recruitment status: recruiting Prospective completion date: August 12, 2021 Sponsor/funding: Metro Infectious Disease Consultants

NCT04442191

Study name	Infusion of convalescent plasma for the treatment of patients infected with severe acute respiratory syndrome-coronavirus-2 (COVID-19): a double-blinded, placebo-controlled, proof-of-concept study
Methods	<ul style="list-style-type: none"> Trial design: randomised Sample size: 50 Setting: hospitalised patients requiring supplemental oxygen Country: USA Language: English Number of centres: 1 Trial registration number: NCT04442191 Date of registration: 22 June 2020

NCT04442191 (Continued)

Participants

- Inclusion criteria:
 - Patients \geq 40 years who are admitted to the University of Illinois Hospital (UIC) due to COVID-19
 - Positive oropharyngeal and/or nasopharyngeal swab test for SARS-CoV-2 by RT-PCR within the preceding 72 h (performed by University of Illinois Hospital Laboratories or, if performed elsewhere, documented in the patient's UIC medical record)
 - Symptomatic infection with any of the following: fever, cough, dyspnoea, or tachypnoea $>$ 22 breaths/min
 - Need for supplemental oxygen, between 1-5 L/minute by nasal canula, to maintain O₂ saturations $>$ 92%
 - Consents to comply with all protocol requirements
 - Agrees to storage of specimens for future testing
- Exclusion criteria:
 - Patients with known IgA deficiency (high risk of severe or fatal anaphylactic reactions)
 - Patients who are on a ventilator
 - Patients with past history of severe transfusion reaction including transfusion-related acute lung injury (TRALI) or anaphylaxis
 - Patients with a baseline requirement for supplemental oxygen due to chronic lung disease or with known history of either moderate-to-severe asthma or emphysema
 - Women who report that they are pregnant or breastfeeding
 - Receipt of pooled immunoglobulin in the past 30 days
 - Patients must be willing to not take any another alternative experimental treatment for COVID-19 from the time they undergo enrolment until the 28-day follow-up phone call
 - Participants who are being treated with remdesivir and have had their first dose of remdesivir $>$ 24 h prior to the time they will receive their first dose of CP
 - Patients with severe disease due to COVID-19, as manifested by a need for vasopressors, and/or diagnosis of ARDS
- Donor eligibility criteria: NR
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - Type of plasma: CP
 - Volume: NR
 - Number of doses: NR
 - Antibody test and antibody-titre: neutralising antibody titres $>$ 1:64
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors:
 - Gender: NR
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients requiring supplemental oxygen
- Comparator: standard FFP
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome:
 - The primary endpoint will be clinical response at 8 days, defined as no need for oxygen supplementation for the previous 24 h

NCT04442191 (Continued)

- Primary review outcomes reported
 - All-cause mortality at hospital discharge: NR (up to 28 days)
 - Time to death: NR
- Secondary review outcomes reported
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - Number of participants with SAEs: reported
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - WHO ordinal scale: NR
 - 30-day and 90-day mortality: NR
 - Admission on the ICU: reported
 - Length of stay on the ICU: NR
 - Time to discharge from hospital: reported
 - QoL: NR
 - Virological response: NR
- Additional outcomes:
 - CRP (time frame: 28 days)
 - Lymphocyte count (time frame: 28 days)
 - Change in LDH following treatment
 - LDH (time frame: 28 days)
 - Ferritin (time frame: 28 days)
 - D-Dimer (time frame: 28 days)
 - WBC Count (time frame: 28 days)

Starting date	5 May 2020
Contact information	Jessica Herrick, Assistant Professor of Clinical Medicine, University of Illinois at Chicago
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 5 May 2021 • Sponsor/funding: University of Illinois at Chicago

NCT04445207

Study name	Experimental expanded access treatment with convalescent plasma for the treatment of patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: expanded access • Sample size: NR • Setting: NR • Country: USA • Language: English • Number of centres: 1

NCT04445207 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> ○ At least 12 years of age ○ COVID-19 CP (CCP) treatment is in line with the patient's current goals of care (i.e. recipient cannot be DNI status) ○ Laboratory-confirmed diagnosis of infection with SARS-CoV-2 that is severe or life-threatening OR the individual is judged by the treating provider to be at a high risk of progression to severe or life-threatening disease ○ Severe COVID-19 is defined by one or more of the following: <ul style="list-style-type: none"> ■ Dyspnoea ■ Respiratory frequency ≥ 30/min ■ Blood oxygen saturation $\leq 93\%$ ■ PaO₂/FiO₂ ratio < 300 ■ Lung infiltrates $> 50\%$ within 24-48 h ○ Life-threatening COVID-19 is defined as one or more of the following: <ul style="list-style-type: none"> ■ Respiratory failure ■ Septic shock ■ Multiple organ dysfunction or failure • Exclusion criteria: <ul style="list-style-type: none"> ○ History of prior life-threatening reactions to transfusion of blood products ○ Not receiving other therapies that would preclude plasma transfusion
Interventions	<ul style="list-style-type: none"> • Details of CP: <ul style="list-style-type: none"> ○ Type of plasma: CP ○ Volume: 200 mL ○ Number of doses: 1-6 ○ Antibody test and antibody-titre: NR ○ Pathogen inactivated or not: NR ○ RT-PCR tested: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: nil • Concomitant therapy: NR • Duration of follow-up: NR • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: NR • Primary review outcomes reported <ul style="list-style-type: none"> ○ All-cause mortality at hospital discharge: NR ○ Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ○ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): NR ○ Number of participants with SAEs: NR ○ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR ○ WHO ordinal scale: NR ○ 30-day and 90-day mortality: NR ○ Admission on the ICU: NR ○ Length of stay on the ICU: NR ○ Time to discharge from hospital: NR ○ QoL: NR ○ Virological response: NR • Additional outcomes: NR

NCT04445207 (Continued)

Starting date	NR
Contact information	<ul style="list-style-type: none"> Contact: Jonathan Gerber, MD508-856-3216 cancerresearch@umassmed.edu Contact: Cara Gregoire 774-455-4458 Cara.Gregoire@umassmed.edu
Notes	<ul style="list-style-type: none"> Recruitment status: available Prospective completion date: NR Sponsor/funding: Jonathan Gerber

NCT04452812

Study name	Pilot clinical, statistical and epidemiological study on efficacy and safety of convalescent plasma for the management of patients with COVID-19
Methods	<ul style="list-style-type: none"> Trial design: pilot, experimental, randomised, prospective, longitudinal, clinical study Sample size: 15 Setting: hospitalised patients in ICU Country: Mexico Language: English Number of centres: 1 Trial registration number: NCT04452812 Date of registration: 30 June 2020
Participants	<ul style="list-style-type: none"> Inclusion criteria: <ul style="list-style-type: none"> Signed informed consent provided by the patient, legal guardian or the health provider if not available Patients hospitalised in an ICU dedicated to the treatment of COVID-19 patients At least positive for 1 q-PCR test for SARS-CoV-2 Patients with COVID-19 defined as severe or critically ill: <ul style="list-style-type: none"> Severe: RF > 30 breaths/min, oxygen saturation < 94%, Pa/FiO₂ < 301, bilateral lung infiltrates that extends in > 50% (by chest radiograph or CT scan) in 24-48 h Critically ill: RF (PaO₂ < 60 mmHg or SatO₂ < 90% with FiO₂ > 60%) and septic shock (MAP < 65 mmHg with vasoactive requirement, lactate > 2 mmol/L and SOFA score > 1) Exclusion criteria: <ul style="list-style-type: none"> Positive pregnancy test Patients in lactation Informed consent not signed Patients involved in other treatment protocols Patients on immunomodulatory drugs (DMARDs, monoclonal antibodies or small molecule drugs) Donor eligibility criteria: <ul style="list-style-type: none"> Signed informed consent At least positive for 1 q-PCR test for SARS-CoV-2 14 days of COVID-19 clinical remission Positive serologic test for SARS-CoV-2 Requirements to donate according to NOM-253-SSA1-2012 To accept sample storing for future study Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> Intervention(s): CP therapy

NCT04452812 (Continued)

- Details of CP:
 - Type of plasma: CP
 - Volume: 200 mL
 - Number of doses: 2
 - Antibody test and antibody-titre: yes
 - Pathogen inactivated or not: NR
 - RT-PCR tested: yes
- Details of donors:
 - Gender: NR
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: at least 14 days from resolution of COVID-19-associated symptoms including fevers
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients in ICU
- Comparator: placebo
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - All-cause mortality (time frame: 30 days)
 - Side effects (time frame: 30 days)
- Primary review outcomes reported
 - All-cause mortality at hospital discharge: reported
 - Time to death: reported
- Secondary review outcomes reported
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - Number of participants with SAEs: reported
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - WHO ordinal scale: NR
 - 30-day and 90-day mortality: reported (30 days)
 - Admission on the ICU: reported (inclusion criteria)
 - Length of stay on the ICU: reported
 - Time to discharge from hospital: reported
 - QoL: NR
 - Virological response: NR
- Additional outcomes:
 - Inflammatory biomarkers (d-dimer) (time frame: 21 days)
 - Inflammatory biomarkers (CRP) (time frame: 21 days)
 - Inflammatory biomarkers (LDH) (time frame: 21 days)
 - Inflammatory biomarkers (ferritin) (time frame: 21 days)

Starting date

6 July 2020

Contact information

- Contact: Julio César Martínez Gallegos, MD, MMSc8113852249, juliomartinez.18@hotmail.com

Notes

- Recruitment status: Not yet recruiting
- Prospective completion date: 1 March 2021
- Sponsor/funding: Universidad Autonoma de Coahuila

NCT04453384

Study name	Study to evaluate the safety and efficacy of XAV-19 in patients with COVID-19 induced moderate pneumonia (POLYCOR)
Methods	<ul style="list-style-type: none"> • Trial design: randomised double-blind, placebo-controlled study (clinical trial) • Sample size: 414 • Setting: hospital • Country: France • Language: English • Number of centres: NR
Participants	<ul style="list-style-type: none"> • Inclusion criteria: Phase 2a <ul style="list-style-type: none"> ◦ Willing and able to provide written informed consent prior to performing study procedures ◦ Male or female ≥ 18 years and ≤ 85 years ◦ Hospitalized for COVID-19 ◦ Positive SARS-CoV-2 RT-PCR in any body specimen (nasopharynx, saliva, sputum) ≤ 10 days before enrolment ◦ Evidence of pulmonary involvement (on lung examination [rales/crackles] and/or chest-imaging [Chest X-ray or computed tomography]) ◦ Requiring O₂ supplement ≤ 6L/min at screening ◦ Requiring O₂ supplementation with SpO₂ $\geq 94\%$ on O₂ therapy at screening ◦ First onset of COVID-19 symptoms ≤ 10 days, among fever and/or chills, headache, myalgias, cough, shortness of breath, whichever as occurred first ◦ WOCBP must have a negative urinary pregnancy test the day of inclusion ◦ All sexually active male subjects must agree to use an adequate method of contraception throughout the study period and for 90 days after the last dose of study drug and agree to no sperm donation until the end of the study, or for 90 days after the last dose of XAV-19, whichever is longer ◦ Patients with French social security • Exclusion criteria: phase 2a <ul style="list-style-type: none"> ◦ Evidence of multiorgan failure (severe COVID-19) ◦ Mechanically ventilated (including ECMO) ◦ Receipt of immunoglobulins or any blood products in the past 30 days ◦ Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the investigator, would affect subject safety and/or compliance ◦ End-stage renal disease (eGFR < 15 ml/min/1,73 m²) ◦ Child-Pugh C stage liver cirrhosis ◦ Decompensated cardiac insufficiency ◦ History of active drug abuse ◦ Known allergy, hypersensitivity, or intolerance to the study drug, or to any of its components ◦ Females of childbearing potential without contraceptive method, or with positive pregnancy test, breastfeeding, or planning to become pregnant during the study period ◦ Current documented and uncontrolled bacterial infection. ◦ Prior severe (grade 3) allergic reactions to plasma transfusion ◦ Patient participating in another interventional clinical trial ◦ Life expectancy estimated to be less than 6 months ◦ Patient under guardianship or trusteeship

NCT04453384 (Continued)

- Inclusion criteria: phase 2b
 - Willing and able to provide written informed consent prior to performing study procedures
 - Male or female ≥ 18 years and ≤ 85 years
 - Hospitalised for COVID-19
 - Positive SARS-CoV-2 RT-PCR in any body specimen (nasopharynx, saliva, sputum) ≤ 10 days before enrolment
 - Evidence of pulmonary involvement (on lung examination (rales/crackles) and/or chest-imaging (chest X-ray or computed tomography))
 - Requiring O₂ supplement ≤ 6 L/min at screening
 - Requiring O₂ supplementation with SpO₂ $\geq 92\%$ on O₂ therapy at screening (or $\geq 90\%$ if chronic obstructive pulmonary disease)
 - First onset of COVID-19 symptoms ≤ 10 days, among fever and/or chills, headache, myalgias, cough, shortness of breath, whichever as occurred first (other symptoms such as asthenia not to be considered in this list)
 - WOCBP must have a negative urinary pregnancy test the day of inclusion
 - All sexually active male subjects must agree to use an adequate method of contraception throughout the study period and for 90 days after the last dose of study drug and agree to no sperm donation until the end of the study, or for 90 days after the last dose of XAV-19, whichever is longer
 - Patients with French social security
- Exclusion criteria: phase 2b
 - Evidence of multiorgan failure (severe COVID-19)
 - Mechanically ventilated (including ECMO)
 - Receipt of immunoglobulins or any blood products in the past 30 days
 - Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the investigator, would affect subject safety and/or compliance
 - End-stage renal disease (eGFR < 15 ml/min/1.73 m²)
 - Child-Pugh C stage liver cirrhosis
 - Decompensated cardiac insufficiency
 - History of active drug abuse
 - Known allergy, hypersensitivity, or intolerance to the study drug, or to any of its components
 - Females of childbearing potential without contraceptive method, or with positive pregnancy test, breastfeeding, or planning to become pregnant during the study period
 - Current documented and uncontrolled bacterial infection.
 - Prior severe (grade 3) allergic reactions to plasma transfusion
 - Patient participating in another interventional clinical trial
 - Life expectancy estimated to be less than 6 months
 - Patient under guardianship or trusteeship

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: hyperimmune immunoglobulin therapy
 - Details:
 - type: XAV-19
 - volume: XAV-19 at 0.5 mg/kg (Group 1) or at 2 mg/kg (Group 2)
 - 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): Placebo
 - Concomitant therapy: NR
 - Treatment cross-overs: none
-

NCT04453384 (Continued)

Outcomes

- Primary study outcome:
 - Phase 2a: XAV-19 antibody titers [Time Frame: Day 8]
 - Phase 2a: Adverse events of XAV-19 [Time Frame: Day 29]
 - Phase 2b: Time to weaning of supplemental oxygen. [Time Frame: Day 15]
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: yes, all cause mortality day 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. transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions): Adverse events of XAV-19 between the two groups of treated patients and vs. placebo over 29 days
 - Number of participants with serious adverse events: reported as Occurrence of all suspected XAV-19 related adverse effects or Incidence of serious adverse events
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale ([WHO 2020e](#)), WHO Ordinal Scale for Clinical Improvement ([WHO 2020f](#))) at up to 7 days, 8 to 15 days, 16 to 30 days: reported as Clinical status using the 8-point ordinal scale assessed and difference between baseline and D3, D5, D8, D15, and D29
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: yes
 - Admission to the intensive care unit (ICU): reported as Evaluation of Transfer to intensive care
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days:
 - QoL: NR
- Additional study outcomes
 - Phase 2a: Pharmacokinetic analysis [Time Frame: Day 1 (pre-dose, post-dose), at Day 5 (pre-dose, post-dose), Day 8, Day 15, and Day 29]
 - Phase 2a: Antibody titre between the two groups [Time Frame: day 15]
 - Phase 2a: Duration Supplemental oxygen [Time Frame: Day 1 to Day 29]
 - Phase 2a: Normalization of Fever [Time Frame: Day 1 to Day 29]
 - Biomarkers: CRP, Ferritin
 - Phase 2b: National Early Warning Score (NEWS) [Time Frame: Day 8, Day 15 and Day 29]
 - Proportion of patients who die, develop respiratory failure (requiring noninvasive ventilation, high-flow oxygen devices or invasive mechanical ventilation) between baseline and Day 8, then between baseline and D29
 - Time to improvement of one category from admission using the 8-point ordinal scale. This scale is rated 0 to 8 with score 0 being the better score (no clinical impact) and 8 being the worst score (death)
 - Phase 2b: fever normalization [Time Frame: 29 Days]
 - Phase 2b: Duration of oxygen therapy
 - Phase 2b: oxygen requirement
 - Phase 2b: Time to weaning
 - Phase 2b: Ventilation

 Starting date September 1, 2020

 Contact information • Contact: Benjamin GABORIT+33 (0)2 44 76 82 92, benjamin.GABORIT@chu-nantes.fr
 • Contact: François RAFFI, francois.raffi@chu-nantes.fr

 Notes • Recruitment status: recruiting

NCT04453384 (Continued)

- Prospective completion date:
 - Estimated Primary Completion Date: December 2020
 - Estimated Study Completion Date: December 2021
- Sponsor/funding: Nantes University Hospital
- BPIfrance
- Xenothera
- SAS

NCT04456413

Study name	Phase II randomized study of convalescent plasma from recovered COVID-19 donors collected by plasmapheresis as treatment for subjects with early COVID-19 infection
Methods	<ul style="list-style-type: none"> • Trial design: randomised • Sample size: 306 • Setting: outpatient, early stage, high-risk for hospitalisation • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04456413 • Date of registration: 2 July 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> ◦ Patient age > 30 years old, newly diagnosed with a COVID-19 infection with onset of first symptoms < 96 h ◦ And least one other high-risk feature: <ul style="list-style-type: none"> ■ Age > 65 ■ BMI ≥ 3 ■ Hypertension, defined as SBP > 140 or DBP > 90, or requiring medication for control ■ Coronary artery disease (history, not ECG changes only) ■ Congestive heart failure ■ Peripheral vascular disease (includes aortic aneurysm ≥ 6 cm) ■ Cerebrovascular disease ■ Dementia ■ Chronic pulmonary disease ■ Liver disease (such as portal hypertension, chronic hepatitis) ■ Diabetes (excludes diet-controlled alone) ■ Moderate or severe renal disease defined as having a GFR < 60 mL/min ■ Cancer (exclude if > 5 years in remission) ■ AIDS (not just HIV-positive) • Exclusion criteria: <ul style="list-style-type: none"> ◦ History of severe transfusion reaction to plasma products ◦ Need for oxygen supplementation ◦ Positive test for COVID-19 antibodies ◦ Chemotherapy-induced neutropenia (ANC < 0.5 x 10³/mCL) ◦ Immunosuppressive medications except for prednisone (or steroid equivalent) > 10 mg daily ◦ Performance status < 50 by KPS scale ◦ Pneumonia by radiographic evaluation

NCT04456413 (Continued)

- Donor eligibility criteria:
 - Age 18-60
 - A history of a positive nasopharyngeal swab for COVID-19 or a history of positive antibody titre test
 - At least 14 days from resolution of COVID-19-associated symptoms including fevers
 - A negative nasopharyngeal swab (or similar test) for COVID-19
 - Anti-SARS-CoV2 titres > 1:500
 - Adequate venous access for apheresis
 - Meets donor eligibility criteria in accordance to Hackensack University Medical Center (HUMC) Collection Facility at the John Theurer Cancer Center (JTCC) if collecting at the JTCC, and all regulatory agencies as described in SOP 800 01
 - Required testing of the donor and product must be performed in accordance to FDA regulations (21 CFR 610.40), and the donation must be found suitable (21 CFR 630.30)
- Donor exclusion criteria: NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - Type of plasma: CP
 - Volume: NR
 - Number of doses: NR
 - Antibody test and antibody-titre: > 1:500
 - Pathogen inactivated or not: NR
 - RT-PCR tested: yes
- Details of donors:
 - Gender: both
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: at least 14 days from resolution of COVID-19-associated symptoms including fevers
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients
- Comparator: nil
- Concomitant therapy: NR
- Duration of follow-up: NR
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - Hospitalisation rate (up to 10 days)
- Primary review outcomes reported
 - All-cause mortality: yes (60 days)
 - Admission to hospital: yes

NCT04456413 (Continued)

- Secondary review outcomes reported
 - Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR
 - Time to symptom onset: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Length of hospital stay, for hospitalised patients: NR
 - Admission to the intensive care unit (ICU): NR
 - Viral clearance, assessed with RT-PCR test: yes (day 14, 28)
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: NR
- Additional outcomes:
 - Time to symptoms resolution
 - Rate of nasopharyngeal swab positivity in donors
 - Rate of donor titres level
 - Impact of donor titres level on efficacy
 - Participants' anti-SARS-CoV2 titre assessment pre-infusion for the treatment group, at 2 weeks, 4 weeks and 2 months
 - Patients' cytokines levels assessment at +2 and +4 weeks post-randomisation (time frame: 2 weeks and 4 weeks)
 - Patients' chemokines levels assessment at +2 and +4 weeks post-randomisation (time frame: 2 weeks and 4 weeks)
 - Rates of adverse events (adverse effects) associated with convalescent plasma infusion (days 3, 7, 14, 28)

Starting date	November 6, 2020
Contact information	<ul style="list-style-type: none"> • Contact: Mariefel Vendivil: 551-996-5828; Mariefel.Vendivil@HackensackMeridian.org • Contact: Marlo Kemp: 551-996-4464; Marlo.Kemp@HackensackMeridian.org
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: November 2021 • Sponsor/funding: University of California, Los Angeles

NCT04463823

Study name	"NORPLASMA" COVID-19 convalescent plasma treatment monitoring study
Methods	<ul style="list-style-type: none"> • Trial design: observational prospective • Sample size: 500 • Setting: hospitalised patients • Country: Norway • Language: English • Number of centres: 1

NCT04463823 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ patients treated with COVID-19 CP ◦ patients who provided informed consent or where nearest relative gave consent • Exclusion criteria <ul style="list-style-type: none"> ◦ patients included in other clinical studies of COVID-19 treatment ◦ consent not given
Interventions	<ul style="list-style-type: none"> • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: NR ◦ Number of doses: NR ◦ Antibody test and antibody-titre: NR ◦ Pathogen inactivated or not: NR ◦ RT-PCR tested: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients • Comparator: nil • Concomitant therapy: NR • Duration of follow-up: NR • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome <ul style="list-style-type: none"> ◦ observation (time frame: up to 2 years) clinical data and lab results from participants who receive COVID-19 CP on a clinical indication, are being collected for later analysis • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: NR ◦ WHO ordinal scale: NR ◦ 30-day and 90-day mortality: NR ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: NR ◦ QoL: NR ◦ Virological response: NR • Additional outcomes: NR
Starting date	6 July 2020
Contact information	<ul style="list-style-type: none"> • Contact: Lise Sofie Haug Nissen-Meyer, Ph.D: +47 22117828; lisoha@ous-hf.no • Contact: Tor Audun Hervig, Ph.D: tor.audun.hervig@helse-fonna.no
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Estimated Primary Completion Date: May 2022 • Sponsor/funding: Oslo University Hospital

NCT04468009

Study name	Treatment of critically ill patients with COVID-19 with convalescent plasma
Methods	<ul style="list-style-type: none"> • Trial design: randomised sequential assignment • Sample size: 36 • Setting: critically ill requiring mechanical ventilation • Country: Argentina • Language: English • Number of centres: 1 • Trial registration number: NCT04468009 • Date of registration: 13 July 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Age: ≥ 18 years ◦ Patient with COVID-19 confirmed with nuclear acid testing ◦ Critically ill patients with COVID-19 on mechanical ventilation. Potentially critically ill patients (with ARDS, septic shock and/or multiple organ failure) with COVID-19 ◦ Diagnosed with ARDS ◦ Informed consent • Exclusion criteria: <ul style="list-style-type: none"> ◦ No consent ◦ Symptoms for a period > 20 days ◦ Not detectable by acid nuclear testing within 48 h prior to eligibility ◦ Descompensated congestive heart failure, in which receiving 500 mL of IV volume signifies a life risk ◦ History of severe adverse events or anaphylaxis to plasma components • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: NR ◦ Number of doses: NR ◦ Antibody test and antibody-titre: NR ◦ Pathogen inactivated or not: NR ◦ RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> ◦ Gender: NR ◦ HLA and HNA antibody: NR ◦ Severity of disease: NR ◦ Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): critically ill, requiring mechanical ventilation • Comparator: standard care • Concomitant therapy: NR • Duration of follow-up: NR • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ ICU mortality (time frame: mortality at 30, 90 days)

NCT04468009 (Continued)

- Primary review outcomes reported
 - All-cause mortality at hospital discharge: reported
 - Time to death: reported
- Secondary review outcomes reported
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR
 - Number of participants with SAEs: NR
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - WHO ordinal scale: NR
 - 30-day and 90-day mortality: reported
 - Admission on the ICU: reported
 - Length of stay on the ICU: reported
 - Time to discharge from hospital: reported
 - QoL: NR
 - Virological response: NR
- Additional outcomes:
 - SOFA score of study days 1, 3, 5, 7, 14 and 28 (time frame: study days 1, 3, 5, 7, 14 and 28)
 - Need for supportive therapy after enrolment (time frame: duration of supportive therapy through study completion, an average of 3 months)
 - Days without vasopressors after enrolment (time frame: days without vasopressors through study completion, an average of 3 months)
 - Changes in chest X-ray (time frame: changes in chest X-ray through study completion, an average of 3 months)

Starting date	25 June 2020
Contact information	• Contact: Carlos A Gonzalez, MD+54 9 1157233801, carlosgonzalez@buenosaires.gob.ar
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: January 19, 2021 • Sponsor/funding: Hospital de Infecciosas Francisco Javier Muniz

NCT04468958

Study name	Safety, tolerability, and pharmacokinetics of SAB-185 in healthy participants
Methods	<ul style="list-style-type: none"> • Trial design: RCT, sequential assignment • Sample size: 28 • Setting: Outpatient • Country: US • Language: English • Number of centres: NR

NCT04468958 (Continued)

Participants

- Inclusion criteria
 - 18-60 years of age
 - Able to understand the study and comply with all study procedures
 - Agrees not to participate in any other trial of an investigational product during the study period
 - Willing and able to provide written informed consent prior to the start of any study related activities
 - In good health in the opinion of the site principal investigator as determined by vital signs, medical history, physical examination and clinical laboratory tests
 - If female, meets at least one of the following reproductive risk criteria
 - Post-menopausal for at least 12 months
 - Use of one or more of the following highly effective contraceptive methods for at least 90 days following the last dose of study product: combined oestrogen and progestogen containing or progestogen-only hormonal contraception, intrauterine device (IUD), intrauterine hormone-releasing system, surgical bilateral tubal occlusion
 - Vasectomized sole sexual partner who has received medical assessment of the surgical success
 - Subjects agree to sexual abstinence (refraining from heterosexual intercourse for at least 90 days following the last dose of study product) if not using birth control or condoms for males.
- Exclusion criteria
 - Female subjects with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period.
 - Treatment or participation in another clinical trial of any other investigational agent within 30 days prior to enrolment.
 - Use of other drugs that, in the opinion of the investigator, could complicate analysis of SAB-185.
 - Subjects with the following risk factors:
 - Compromised immune system including confirmed diagnosis of current cancer under treatment, inherited deficiencies of the immune system, immune suppressing medication, or other conditions causing leukopenia or neutropenia
 - Known autoimmune condition requiring therapy more intensive than intermittent non-steroidal anti-inflammatories in the prior 6 months (for example: rheumatoid arthritis, lupus, inflammatory bowel disease)
 - Chronic respiratory disease including COPD, emphysema, cystic fibrosis, pulmonary hypertension, or other chronic condition that requires the routine use of supplemental oxygen
 - Chronic asthma requiring the use of oral steroids or hospitalisation in the last six months
 - Renal failure or renal insufficiency requiring dialysis
 - Congestive heart failure or significant atherosclerotic disease (coronary artery disease or peripheral vascular disease)
 - Hypertension, diabetes, those currently vaping or smoking or with a history of chronic smoking, and those with BMI > 35 kg/m²
 - Receipt of pooled immunoglobulin or plasma in past 30 days
 - Any other underlying medical (cardiac, liver, renal, neurological, respiratory) or psychiatric condition that in the view of the investigator would preclude use of SAB-185
 - Known IgA deficiency or previous allergic reaction to intravenous immunoglobulin (IVIG)/subcutaneous immunoglobulin (SCIG)
 - Positive screening test for hepatitis B virus surface antigen, hepatitis C virus antibody, or HIV antibody
 - Positive screening test for rheumatoid factor
 - History of COVID-19
 - Positive FDA-authorized screening test for serum SARS-CoV-2 antibody or presence of SARS-CoV-2 on nasopharyngeal or oropharyngeal swab by FDA-authorized RT-PCR
 - History of allergy, anaphylaxis, or severe reaction to beef products (including milk and gelatin).

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: SAB-185 a purified human immunoglobulin G (hIgG)

NCT04468958 (Continued)

- Details:
 - type of plasma: Anti-SARS-CoV-2 Human Immunoglobulin Intravenous (Tc bovine-derived)
 - volume: 10mg/kg SAB-185 in normal (0.9%) saline; concentration 4mg/mL (0.4%)
 - 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): Placebo (Normal (0.9%) saline)
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome:
 - Number of participants having adverse events [Time Frame: 29 Days]
 - Number of participants having transfusion-related adverse events [Time Frame: 29 Days]
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: NR
- Secondary review outcomes
 - 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): reported
 - Number of participants with serious adverse events: reported
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale ([WHO 2020e](#)), WHO Ordinal Scale for Clinical Improvement ([WHO 2020f](#))) at up to 7 days, 8 to 15 days, 16 to 30 days:NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission to the intensive care unit (ICU):NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
- Additional study outcomes
 - Pharmacokinetics from screening to day 90 [Time Frame: 90 Days]

Starting date August 5, 2020

Contact information • Principal Investigator:David Hoover, MD

Notes • Recruitment status: Active, not recruiting
 • Prospective completion date: February 23, 2021
 • Sponsor/funding: SAb Biotherapeutics, Inc.
 ◦ Department of Health and Human Services Joint Program Executive Office (JPEO) Chemical, Biological, Radiological, and Nuclear Defense (CBRND) Enabling Biotechnologies (EB)

NCT04469179

Study name Safety, tolerability, and pharmacokinetics of SAB-185 in ambulatory participants with COVID-19

Methods • Trial design: phase 1B, randomised, double-blind, placebo-controlled, single ascending dose study
 • Sample size: 21

NCT04469179 (Continued)

- Setting: outpatient
- Country: United States
- Language: English
- Number of centres: 3

Participants

- Inclusion criteria
 - 18-60 years of age
 - Positive for presence of SARS-CoV-2 on NP or OP swab by FDA-authorized RT-PCR test within seven days prior to infusion
 - At least one current symptom of COVID-19, onset within seven days prior to infusion:
 - Fever or chills, Cough, Shortness of breath or difficulty breathing, Fatigue, Muscle or body aches, Headache, New loss of taste or smell, Sore throat, Congestion or runny nose, Nausea or vomiting, Diarrhoea
 - Able to understand the study and comply with all study procedures
 - Agrees not to participate in any other trial of an investigational product during the study period
 - Willing and able to provide written informed consent prior to the start of any study related activities
 - If female, meets at least one of the following reproductive risk criteria
 - Post-menopausal for at least 12 months
 - Use of one or more of the following highly effective contraceptive methods for at least 90 days following the last dose of study product: combined oestrogen and progestogen containing or progestogen-only hormonal contraception, intrauterine device (IUD), intrauterine hormone-releasing system, surgical bilateral tubal occlusion
 - Vasectomized sole sexual partner who has received medical assessment of the surgical success
 - Male and female subjects agree to sexual abstinence (refraining from heterosexual intercourse for at least 90 days following the last dose of study product) if not using birth control or condoms for males.

NCT04469179 (Continued)

- Exclusion criteria
 - Dyspnoea at rest
 - Respiratory rate > 30 breaths per minute
 - SpO₂ ≤ 93% on room air
 - Heart rate ≥ 125 beats per minute
 - Respiratory distress or respiratory failure.
 - Evidence of critical illness
 - Female subjects with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period.
 - Hospitalisation or need for hospitalisation for any cause
 - Treatment or participation in another clinical trial of any other investigational agent within 30 days prior to enrolment.
 - Use of other drugs that, in the opinion of the investigator, could complicate analysis of SAB-185.
 - Subjects with the following risk factors:
 - Compromised immune system including confirmed diagnosis of current cancer under treatment, inherited deficiencies of the immune system, immune suppressing medication, or other conditions causing leukopenia or neutropenia
 - Known autoimmune condition requiring therapy more intensive than intermittent non-steroidal anti-inflammatories in the prior 6 months (for example: rheumatoid arthritis, lupus, inflammatory bowel disease)
 - Chronic respiratory disease including COPD, emphysema, cystic fibrosis, pulmonary hypertension, or other chronic condition that requires the routine use of supplemental oxygen
 - Chronic asthma requiring the use of oral steroids or hospitalisation in the last six months
 - Renal failure or renal insufficiency requiring dialysis
 - Congestive heart failure or significant atherosclerotic disease (coronary artery disease or peripheral vascular disease)
 - Receipt of pooled immunoglobulin or plasma in past 30 days
 - Any other underlying medical (cardiac, liver, renal, neurological, respiratory) or psychiatric condition that in the view of the investigator would preclude use of SAB-185
 - Known IgA deficiency or previous allergic reaction to intravenous immunoglobulin (IVIG)/ subcutaneous immunoglobulin (SCIG)
 - Positive for hepatitis B virus surface antigen, hepatitis C virus antibody, or HIV antibody by medical history
 - History of allergy, anaphylaxis, or severe reaction to beef products (including milk and gelatin)

Interventions

- Details of hyperimmune immunoglobulin therapy:
 - drug name: SAB-185
 - dose:
 - Group 1: 10mg/kg SAB-185 in normal (0.9%) saline; concentration 4mg/mL (0.4%)
 - Group 2: 25mg/kg SAB-185 in normal (0.9%) saline; concentration 20mg/mL (2%)
 - Group 3: 50mg/kg SAB-185 in normal (0.9%) saline; concentration 20mg/mL (2%)
 - number of doses: NR
 - route: administered intravenously
 - source: human
- Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage
- For studies including a control group: comparator (type): placebo ((0.9%) saline in approximately the same volume as each cohort in the experimental drug arm)
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome:
 - Incidence and severity of other adverse events and severe adverse events (SAE)(up to day 29)
 - Number of Participants Having Transfusion-Related Adverse Events (up to day 29)

NCT04469179 (Continued)

- Primary review outcomes
 - All-cause mortality: NR
 - Admission to hospital: NR
- Secondary review outcomes
 - Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR
 - Time to symptom onset: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Length of hospital stay, for hospitalised patients: NR
 - Admission to the intensive care unit (ICU): NR
 - Viral clearance, assessed with RT-PCR test: yes (day 29)
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: yes
- Additional study outcomes
 - Incidence and severity of other adverse events and severe adverse events (SAE)(up to day 90)
 - Assessment of the PD of SAB-185 administered intravenously (up to day 90)
 - Immune response elicited by SAB-185 (up to day 90)
 - Concentration of subject anti-SAB-185 antibodies elicited by SAB-185 (up to day 90)
 - Level of SARS-CoV-2 in swab specimens as measured by quantitative RT-PCR through Study (day 29)

Starting date	20 August 2020
Contact information	<ul style="list-style-type: none"> • Principal Investigator:David Hoover, MD
Notes	<ul style="list-style-type: none"> • Recruitment status: Active, not recruiting • Prospective completion date: March 2021 • Sponsor/funding: SAB Biotherapeutics, Inc., Biomedical Advanced Research and Development Authority, Joint Program Executive Office (JPEO) Chemical, Biological, Radiological, and Nuclear Defense (CBRND) Enabling Biotechnologies (EB)

NCT04472572

Study name	Expanded access to convalescent plasma for the treatment of patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: expanded access • Sample size: nil • Setting: severe or life-threatening disease • Country: USA • Language: English • Number of centres: 1 • Trial registration number: NCT04472572 • Date of registration: 15 July 2020

NCT04472572 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ provide access to investigational CP for patients at Hackensack University Medical Center infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease ◦ informed consent • Exclusion criteria: NR • Donor eligibility criteria: NR • Donor exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: 200-500 mL of ABO compatible CP ◦ Number of doses: NR ◦ Antibody test and antibody-titre: yes, no details regarding type of test or titre ◦ Pathogen inactivated or not: NR ◦ RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> ◦ Gender: NR ◦ HLA and HNA antibody: NR ◦ Severity of disease: NR ◦ Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): severe-life-threatening disease • Comparator: No CP • Concomitant therapy: NR • Duration of follow-up: NR • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Safety (SAE) • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: reported ◦ Time to death: reported • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported ◦ Number of participants with SAEs: reported ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported (days intubated) ◦ WHO ordinal scale: NR ◦ 30-day and 90-day mortality: reported ◦ Admission on the ICU: reported ◦ Length of stay on the ICU: reported ◦ Time to discharge from hospital: reported ◦ QoL: NR ◦ Virological response: NR • Additional outcomes: NR
Starting date	15 July 2020
Contact information	Principal Investigator: Michele Donato, Hackensack Meridian Health

NCT04472572 (Continued)

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|-------|---|
| Notes | <ul style="list-style-type: none"> • Recruitment status: temporarily not available • Prospective completion date: NR • Sponsor/funding: Hackensack Meridian Health |
|-------|---|

NCT04483960

- | | |
|---------------|---|
| Study name | An international multi-centre randomised clinical trial to assess the clinical, virological and immunological outcomes in patients diagnosed with SARS-CoV-2 infection (COVID-19) |
| Methods | <ul style="list-style-type: none"> • Trial design: RCT (randomised factorial design, participants enrolled into the study have the option of deciding whether to be randomised in one or both (if available) treatment domains concurrently, if they meet the eligibility criteria) • Sample size: 2400 • Setting: hospitalised patients • Country: Australia • Language: English • Number of centres: 77 • Trial registration number: NCT04483960 • Date of registration: 23 July 2020 |
| Participants | <ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Age ≥ 18 years ◦ Confirmed SARS-CoV-2 by nucleic acid testing in the past 12 days ◦ Able to be randomised within 12 days of symptom onset ◦ Expected to remain an inpatient for at least 48 h from the time of randomisation • Exclusion criteria <ul style="list-style-type: none"> ◦ Overall exclusions: <ul style="list-style-type: none"> ■ Currently receiving acute intensive respiratory support (invasive or noninvasive ventilation) or vasopressor/inotropic support. Note, participants already on non-invasive ventilation (either CPAP or BiPAP) in the community can still be recruited if they are continuing on their usual degree of non-invasive ventilation. Humidified high-flow nasal oxygen will not be considered an exclusion criterion ■ Previous participation in the trial ■ Known pregnancy ■ Treating team deems enrolment in the study is not in the best interests of the patient ■ Death is deemed to be imminent and inevitable within the next 24 h ■ Enrolment to other study protocols that do not allow co-enrolment in ASCOT ◦ Domain 2 (CP) specific exclusions: <ul style="list-style-type: none"> ■ CP not available at trial site ■ Participant has already received treatment with non-trial prescribed SARS-CoV-2-specific immunoglobulin therapy (CP, hyperimmune globulin or monoclonal antibody) ■ Known previous history of TRALI ■ Known previous history of serious allergic reaction to blood product transfusion ■ Known religious objection to receiving blood products ■ Treating team deems enrolment in antibody interventions is not in the best interests of the patient • Donor eligibility criteria: NR • Donor exclusion criteria: NR |
| Interventions | <ul style="list-style-type: none"> • Intervention(s): CP therapy |

NCT04483960 (Continued)

- Details of CP:
 - Type of plasma: C)
 - Volume: NR
 - Number of doses: 2 (days 1, 2)
 - Antibody test and antibody-titre: NR
 - Pathogen inactivated or not: NR
 - RT-PCR tested: NR
- Details of donors:
 - Gender: NR
 - HLA and HNA antibody: NR
 - Severity of disease: NR
 - Timing from recovery from disease: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): hospitalised patients currently not receiving invasive/noninvasive ventilation
- Comparator: no CP, also antiviral domain (antiviral - standard of care, lopinavir/ritonavir, lopinavir and ritonavir + hydroxychloroquine)
- Concomitant therapy: standard of care, antiviral domain
- Duration of follow-up: 90 days
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - Proportion of participants alive and not having required new intensive respiratory support (invasive or non-invasive ventilation) or vasopressors/inotropic support in the 28 days after randomisation (time frame: 28 days)
- Primary review outcomes reported
 - All-cause mortality at hospital discharge: yes
 - Time to death: yes
- Secondary review outcomes reported
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported
 - Number of participants with SAEs: reported
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported
 - WHO ordinal scale: reported
 - 30-day and 90-day mortality: reported
 - Admission on the ICU: reported
 - Length of stay on the ICU: reported
 - Time to discharge from hospital: reported
 - QoL: NR
 - Virological response: viral clearance (at 3 and 7 days)
- Additional outcomes:
 - Presence of chest infiltrates on chest X-ray or CT (time frame: 3 and 7 days)
 - Time to defervescence from randomisation (time frame: 28 days)
 - Biomarker levels (time frame: 28 days)
 - Antibiotic use (time frame: 10 days)
 - AEs (time frame: 10 days)
 - Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital (time frame: 28 days)
 - Acute kidney injury (time frame: 28 days)
 - Thrombotic events (-time frame: 28 days)

Starting date

21 July 2020

NCT04483960 (Continued)

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| Contact information | <ul style="list-style-type: none"> Contact: Naomi Perry+61 3 83442647 naomi.perry@unimelb.edu.au Contact: Jocelyn Mora+61 3 8344 0770 jocelyn.mora@unimelb.edu.au |
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| Notes | <ul style="list-style-type: none"> Recruitment status: recruiting Prospective completion date: December 31, 2021 Sponsor/funding: University of Melbourne |
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NCT04497324

Study name	PERUCONPLASMA: randomized clinical trial to evaluate safety and efficacy of the use of convalescent plasma in hospitalized patients with COVID-19
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| Methods | <ul style="list-style-type: none"> Trial design: multicentre, randomised, open, parallel, controlled trial Sample size: 100 Setting: Inpatient Country: Peru Language: English Number of centres: 1 Trial registration number: NCT04497324; PER-016-20 20997 (Registry Identifier: Peruvian Clinical Trial Registry (REPEC))- Prospective Date of registration: 4 August 2020 |
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| Participants | <ul style="list-style-type: none"> Inclusion criteria <ul style="list-style-type: none"> Hospitalised ≥ 18 years patient with COVID-19 disease, confirmed by a molecular test or a serologic test, along with a typical COVID-19 clinical presentation Severe or critical disease caused by COVID-19. Severe disease is defined as ≥ 2 of the following criteria: <ul style="list-style-type: none"> Respiratory frequency > 22 O_2 saturation $\leq 93\%$ PaO_2 50 mmHg $PaO_2/FiO_2 < 300$ Or critical disease with ≥ 1 of the following criteria: <ul style="list-style-type: none"> Respiratory insufficiency with requirement of mechanical ventilation within the last 72h Shock Informed consent signed by patient or direct family member Exclusion criteria <ul style="list-style-type: none"> Contraindication for transfusion (history of TRALI or TACO, history of anaphylaxis to blood components) Multi-organ failure, defined by a SOFA score of > 5 haemodynamically unstable, with mean arterial pressure < 60 mmHg, refractory to vasopressors use Uncontrolled concomitant infection DIC Myocardial infarction Acute coronary disease Patient on dialysis Intracranial bleeding active within the last 7 days Pregnancy |
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| Interventions | <ul style="list-style-type: none"> Intervention(s): CP therapy vs standard care Details of CP: |
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NCT04497324 (Continued)

- Type of plasma: details or NR
 - Volume: 200 mL-250 mL per dose
 - Number of doses: 1 to 2
 - Antibody-titre: NR
 - Pathogen inactivated: NR
- Treatment details, including time of plasma therapy: within 48 h (possible from admission: unclear) with severe or life-threatening disease
- Comparator: standard of care
- Concomitant therapy: standard care
- Treatment cross-overs: NA

Outcomes

- Primary study outcome(s):
 - Transfusion-related SAEs (time frame: 14 days after randomisation)
 - Incidence of transfusion-related SAEs, according to the Haemovigilance Module Surveillance Protocol v 2.5.2
- 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 adverse events, including potential relationship between intervention and adverse reaction: yes
 - Transfusion-related SAEs (time frame: 14 days after randomisation). Incidence of transfusion-related SAEs, according to the Haemovigilance Module Surveillance Protocol v 2.5.2
 - Number of participants with SAEs: yes. Transfusion-related SAEs
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8 -15 days; 16 to 30 days: NR
 - 30-day and 90-day mortality: all-cause in-hospital mortality (time frame: 30 days after randomisation). Death during hospitalisation within the first 30 days after enrolment
 - Admission on ICU: yes
 - Length of stay on the ICU: Yes. Length of ICU stay (time frame: 30 days after randomisation or until hospital discharge, whatever comes first)
 - Time to discharge from hospital: Yes. Length of hospital stay (time frame: 30 days after randomisation or until hospital discharge, whatever comes first)
 - QoL: NR
 - Virological response: NR
- Additional outcomes: NR

Starting date

21 September 2020

Contact information

- **Full Name:** Patricia García Funegra
- **Zip Code:** NR
- **City:** Lima
- **Address:** Universidad Peruana Cayetano Heredia, Av. Honorio Delgado 430, San Martin de Porres
- **Telephone:** 991886872
- **Email:** patricia.garcia@upch.pe

Notes

- Recruitment status: Recruiting
- Prospective completion date: April 30, 2021
- Sponsor: Universidad Peruana Cayetano Heredia

NCT04497779

Study name	Evaluation of coronavirus disease 19 (COVID-19) convalescent plasma
Methods	<ul style="list-style-type: none"> • Trial design: observational • Sample size: 800 • Setting: not specified • Country: USA • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria: <ul style="list-style-type: none"> ◦ Be willing to provide blood samples ◦ Permit medical record review ◦ Have documented informed consent ◦ ≥ 18 years • Exclusion criteria: NR
Interventions	<ul style="list-style-type: none"> • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: NR ◦ Number of doses: NR ◦ Antibody test and antibody-titre: SARS-CoV-2 immunoassay, coronavirus (CoV) PepSeq assay, and SARS-CoV-2 lenti-based neutralising antibody titre ◦ Pathogen inactivated or not: NR ◦ RT-PCR tested: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: nil • Concomitant therapy: NR • Duration of follow-up: 12 months • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome <ul style="list-style-type: none"> ◦ CP units infused in COVID-19 patients (time frame: up to 12 months after enrolment) ◦ All-cause mortality (time frame: at day 28 post-CP infusion) • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: reported ◦ Time to death: reported • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported ◦ Number of participants with SAEs: reported ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported ◦ WHO ordinal scale: reported ◦ 30-day and 90-day mortality: NR ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: reported ◦ QoL: NR ◦ Virological response: NR • Additional outcomes: nil
Starting date	21 August 2020

NCT04497779 (Continued)

 Contact information Contact: John Zaia 626-218-1817 jzaia@coh.org

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| Notes | <ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: August 21, 2021 • Sponsor: City of Hope Medical Center |
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NCT04514302

Study name	Safety and efficacy of anti-SARS-CoV-2 equine antibody fragments (INOSARS) for hospitalized patients with COVID-19
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| Methods | <ul style="list-style-type: none"> • Trial design: RCT: parallel assignment • Sample size: 51 • Setting: inpatient (level 4-6) • Country: Mexico • Language: English • Number of centres: 2 |
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| Participants | <ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Subjects of both sexes aged ≥ 18 years ◦ Patients with a confirmed infection with SARS-CoV-2 by PCR ◦ Patients admitted for hospitalisation for COVID-19 disease that fulfils any of the following: <ol style="list-style-type: none"> a. Clinical or imaging evidence of pneumonia defined as: $SpO_2 < 94\%$ or PaO_2/FiO_2 (SpO_2/FiO_2) < 300 or chest imaging consistent with pneumonia or clinical evidence of pneumonia (fever, cough, dyspnoea and respiratory frequency > 24 respirations/min) OR b. Score of 4 (hospitalised no oxygen requirement, requires medical care), 5 (hospitalised, low-flow oxygen requirement) or 6 (hospitalised, high-flow oxygen or non-invasive mechanical ventilation requirement) in the NIAID 8-point ordinal scale of clinical status for COVID-19 c. High risk markers of disease progression (at least on serum inflammatory marker elevated: C-reactive protein, D-dimer, lactate dehydrogenase, ferritin) ◦ Agrees to participate in the study and signs written informed consent (signed by relative if applicable) • Exclusion criteria <ul style="list-style-type: none"> ◦ Patients with known equine allergies ◦ Patients with past medical history of serum sickness ◦ Patients with more than 4 days of hospitalisation before being randomised in study ◦ Patients who have received convalescent plasma or intravenous immunoglobulin (IVIG) for COVID-19 ◦ Pregnant or breastfeeding women ◦ Patients with chronic kidney disease under dialysis ◦ Patients under invasive mechanical ventilation and/or extracorporeal membrane oxygenation at the beginning of study ◦ Patients participating in another intervention clinical trial ◦ Patients who are immunocompromised or with another chronic condition, that is judged by medical staff, to be at higher risk of infection or complications from participating in study ◦ Patients who are judged by medical staff who are unlikely to survive at 48 hours |
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| Interventions | <ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: equine immunoglobulin |
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NCT04514302 (Continued)

- Details of hyperimmune immunoglobulin therapy:
 - drug name: fragments INOSARS
 - dose:
 - number of doses
 - 1 dose of 2 vials of INOSARS in 150 mL of saline solution
 - 1 dose of 6 vials of INOSARS in 150 mL of saline solution
 - route: intravenously
 - source (eg human/equine/other): equine
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- For studies including a control group: comparator (type): Placebo (saline)
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome: Proportion of patients with improvement in clinical status [Time Frame: 28 days]
 - Clinical improvement is defined as (whichever is first): a) hospital discharge or b) reduction of 1 point in the NIAID 8-point ordinal scale.
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: NR
- Secondary review outcomes
 - 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): yes, immediate adverse events and late adverse events
 - Number of participants with serious adverse events: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale ([WHO 2020e](#)), WHO Ordinal Scale for Clinical Improvement ([WHO 2020f](#))) at up to 7 days, 8 to 15 days, 16 to 30 days: yes but with NIAID 8-point ordinal scale
 - Mortality (time to event): NR
 - 90-day mortality:NR
 - Time to discharge from hospital: yes, Duration of hospitalisation
 - Admission to the intensive care unit (ICU):NR
 - Length of stay on the ICU:NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes, at day 3
 - QoL: NR
- Additional study outcomes
 - Time to clinical improvement [Time Frame: 28 days]

Starting date

20 October 2020 (estimated start date)

Contact information

- Contact: Servando Cardona-Huerta, MD, Ph. D.+5218112121946, servandocardona@tec.mx
- Contact: Alejandro Torres-Quintanilla, MD, MSc+528180205853, atorresq@tec.mx

Notes

- Recruitment status: : Not yet recruiting
- Planned completion date: February 20, 2021
- Sponsors: Hospital San Jose Tec de Monterrey

NCT04516811

Study name	A prospective, randomized, placebo-controlled, double-blinded, phase III clinical trial of the therapeutic use of convalescent plasma in the treatment of patients with moderate to severe COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: randomised, double-blinded, placebo-controlled, phase III clinical trial • Sample size: 600 • Setting: inpatient • Country: South Africa • Language: English • Number of centres: 1 • Trial registration: NCT04516811 • Date of registration: 18 August 2020
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Laboratory-confirmed SARS-CoV-2 by positive RT-PCR on any respiratory sample • Age \geq 18 years • Require hospital admission for COVID-19 pneumonia as defined by the presence of pulmonary infiltrates on chest X-ray • Moderate to severe COVID-19 disease, defined as: $SpO_2 \leq 93\%$ on room air; plus requiring non-invasive oxygen therapy (WHO R&D BOSCI 4 or 5) • Signed informed consent • Pregnant women will be allowed to participate <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Current participation in another therapeutic clinical trial for COVID-19 • Invasive mechanical ventilation • Expected survival $<$ 24 h based on clinical assessment (however, the study does not exclude critically ill patients who are not, due to resource limitations, candidates for critical care admission and/or mechanical ventilation) • Known hypersensitivity to immunoglobulin or any components of the formulation
Interventions	<ul style="list-style-type: none"> • Intervention(s): standard care and CP therapy • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: 200-250 mL ◦ Number of doses: 1 ◦ Antibody test and antibody-titre: NR ◦ Pathogen inactivated or not: NR ◦ RT-PCR tested: NR • Details of donors: <ul style="list-style-type: none"> ◦ Gender: NR ◦ HLA and HNA antibody: NR ◦ Severity of disease: NR ◦ Timing from recovery from disease: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): moderate or severe COVID-19 • Comparator: standard care and saline (200 mL) • Concomitant therapy: NR • Duration of follow-up: NR • Treatment cross-overs: nil

NCT04516811 (Continued)

Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Clinical Improvement (time frame: Day 28). Proportion of participants with successful treatment outcome, defined as clinical improvement (≥ 2 points on WHO R&D BOSCI 1) by Day 28 post-randomisation • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: reported ◦ Time to death: reported • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: reported ◦ Number of participants with SAEs: reported ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: reported ◦ WHO ordinal scale: NR ◦ 30-day and 90-day mortality: NR ◦ Admission on the ICU: reported ◦ Length of stay on the ICU: reported ◦ Time to discharge from hospital: reported ◦ QoL: NR ◦ Virological response: reported • Additional outcomes: <ul style="list-style-type: none"> ◦ Inflammatory markers (time frame: Day 28) ◦ Radiography (time frame: Day 28) ◦ Fever and hypoxia (time frame: Day 28) ◦ Participants with HIV infection and other comorbidities (time frame: Day 28) ◦ Timing of IP and efficacy outcome (time frame: Day 28) ◦ Neutralising Ab (time frame: Day 28) ◦ SARS-CoV antibody titre (time frame: Day 28)
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Starting date	3 September 2022
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Contact information	<ul style="list-style-type: none"> • Contact: Cynthia Nyoni, +27117619279 ext 9279, Cynthia.Nyoni@sanbs.org.za • Contact: Mpumi Maxebengula, BCom, +27214066497 ext 6497, mpumi.maxebengula@uct.ac.za
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Notes	<ul style="list-style-type: none"> • Recruitment status: Recruiting • Prospective completion date: Dezember 2021 • Sponsor/funding: Karin vandenBerg, Dr, South African National Blood Service
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NCT04521036

Study name	Convalescent plasma for COVID-19 patients (CPCP) (CPCP)
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Methods	<ul style="list-style-type: none"> • Trial design: RCT, parallel assignment • Sample size: 44 • Setting: inpatient • Country: Vietnam • Language: English • Number of centres: NR
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NCT04521036 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Age 18-75 years ◦ SARS-CoV-19 PCR positive ◦ Moderate stage and above ◦ Time from onset to screening ≤ 21 days, the SARS-CoV-2 test is still positive • Exclusion criteria <ul style="list-style-type: none"> ◦ Patients with a history of autoimmune disease or IgA deficiency ◦ Patients with a history of allergy ◦ Multi-organ/system failure ◦ Pregnant or breastfeeding at the time of study ◦ Cancer, history of heart failure, stroke, bronchial asthma ◦ Multi-organ/system failure with indications for dialysis, severe hypoxia, failure with conventional treatment methods, indications for ECMO. ◦ The patient is infected with multidrug-resistant bacteria. ◦ The patient is participating in another study. ◦ Time from onset to screening > 21 days
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: convalescent plasma ◦ volume: 500 ml ◦ number of doses: 1 ◦ antibody-titre: neutralizing antibody titers of at least 1:80 ◦ 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 • Concomitant therapy: (Supportive care, oxygen, antibiotics, no convalescent plasma) • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: Change in mortality [Time Frame: until hospital discharge or a maximum of 60 days whichever comes first] • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: yes (time frame: until hospital discharge or a maximum of 60 days, whichever comes first) • Secondary review outcomes <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions): Incidence of Treatment-Emergent Adverse Events ◦ Number of participants with serious adverse events: NR ◦ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: NR ◦ Mortality (time to event): NR ◦ 90-day mortality: NR ◦ Time to discharge from hospital: NR ◦ Admission to the intensive care unit (ICU): NR ◦ Length of stay on the ICU: NR ◦ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR ◦ QoL: NR

NCT04521036 (Continued)

	<ul style="list-style-type: none"> • Additional study outcomes <ul style="list-style-type: none"> ◦ Change in requirement for mechanical ventilation [Time Frame: until hospital discharge or a maximum of 60 days whichever comes first] ◦ Change in the time a participant will remain on the ventilator
Starting date	December 1, 2020
Contact information	<ul style="list-style-type: none"> • Contact: Phuong Hoang Nguyen, MPH, (+84) 39756885 ext 2321, v.phuongnh9@vinmec.com • Contact: Liem Thanh Nguyen, PhD, (+84) 39756885 ext 2308, v.liemnt@vinmec.com
Notes	<ul style="list-style-type: none"> • Recruitment status: Not yet recruiting • Planned completion date: 30 June 2021 • Sponsors: <ul style="list-style-type: none"> ◦ Vinmec Research Institute of Stem Cell and Gene ◦ Technology National Institute of Hygiene and Epidemiology, Vietnam ◦ National Hospital for Tropical Diseases, Hanoi, Vietnam ◦ National Institute of Hematology and Blood Transfusion, Vietnam

NCT04524507

Study name	COVID-19 antibody plasma research study in hospitalized patients (UNC CCP RCT)
Methods	<ul style="list-style-type: none"> • Trial design: randomised, double-blinded, phase 2 trial • Sample size: 56 • Setting: inpatient • Country: United States • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Age at least 18 years ◦ Ability and willingness of participant or Legally Authorised Representative (LAR) to give written informed consent. ◦ Laboratory confirmed diagnosis of infection with SARS-CoV-2 by PCR ◦ Hospitalised for COVID-19 with one or more respiratory or gastrointestinal (GI) symptoms: <ul style="list-style-type: none"> ■ COVID-19 associated respiratory symptoms include but are not limited to: cough, shortness of breath, difficulty breathing, or sore throat ■ COVID-19 associated GI symptoms include but are not limited to: loss of taste, loss of sense of smell, diarrhoea, nausea, or vomiting • Exclusion criteria <ul style="list-style-type: none"> ◦ Receipt of pooled immunoglobulin in past 30 days ◦ Current or prior enrolment in a SARS-CoV-2 antibody or T-cell therapeutic study. ◦ Contraindication to transfusion or history of prior reactions to transfusion blood products. This may include religious or cultural objections to receiving blood products and transfusions. ◦ ABO-compatible titered plasma is not available ◦ > 10 days from noted COVID-related subjective or objective fever at randomization. Patients without subjective or objective fever, > 10 days from symptom onset as determined by study PI.
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP

NCT04524507 (Continued)

- Details of CP:
 - type of plasma: NR
 - volume: NR
 - number of doses: 2-3 doses
 - antibody-titre: high-titre
 - 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): 2-3 doses of low titre plasma
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome:
 - Cumulative Incidence of serious adverse events (SAEs) at 14 days
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: NR
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days): NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: yes (day 28)
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: yes
- Additional study outcomes
 - none

Starting date 27 August 2020

Contact information Corresponding Author

Name: JoAnn Kuruc, RN, MSN

Affiliation: NR

Full Address: NR

Email: joann_kuruc@med.unc.edu

Notes

- Recruitment status: recruiting
- Prospective completion date: May 2021
- Sponsor/funding: University of North Carolina, Chapel Hill

NCT04528368

Study name	Convalescent plasma for treating patients with COVID-19 pneumonia without indication of ventilatory support
Methods	<ul style="list-style-type: none"> • Trial design: RCT, parallel assignment • Sample size: 60 • Setting: • Country: Brazil • Language: English • Number of centres: NR
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Confirmed diagnosis of COVID-19 by RT-PCR; ◦ Time between symptom onset and inclusion ≤ 7 days; ◦ Chest tomography with $< 50\%$ involvement of the lung parenchyma; ◦ No indication of ventilatory support at the time of randomisation; ◦ Sign the consent form. • Exclusion criteria <ul style="list-style-type: none"> ◦ Contraindication to transfusion or history of previous reactions to blood products for transfusion; ◦ Pregnant women; ◦ Limiting comorbidity for administering the therapies provided for in this protocol in the opinion of the investigator.
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: convalescent plasma ◦ volume: 400 mL ◦ number of doses: 1 ◦ antibody-titre: SARS-CoV-2 antispikes antibody titre with a dilution $\geq 1: 320$ ◦ 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 treatment • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: Area under the curve of SARS-COV-2 viral load obtained from nasopharyngeal and /or oropharyngeal swabs. [Time Frame: 0, 3, 6, 9, 12, 15, 18 and 21 days] • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: yes at 28 days • Secondary review outcomes <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction (e.g. transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions): yes, rate of transfusion reactions to convalescent plasma infusion ◦ Number of participants with serious adverse events: NR ◦ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days: yes, assessment of clinical improvement using an Ordinal Severity Scale [Time Frame: 0, 7, 10, 14, 21 and 28 days] ◦ Mortality (time to event): NR ◦ 90-day mortality: NR ◦ Time to discharge from hospital: yes

NCT04528368 (Continued)

- Admission to the intensive care unit (ICU): NR
- Length of stay on the ICU: yes
- Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
- QoL: NR
- Additional study outcomes
 - Evaluate oxygen saturation [Time Frame: 0, 3, 6, 9, 12, 15, 18 and 21 days]
 - Evaluate oxygen supplementation [Time Frame: 0, 3, 6, 9, 12, 15, 18 and 21 days]
 - Assess respiratory rate
 - Evaluate the PaO₂/FiO₂ ratio (for patients on mechanical mechanisms)
 - Assess the rate of orotracheal intubation
 - Change in the profile of cytokines/chemokines in both groups
 - Presence of antibodies against SARS-CoV-2 in serum after convalescent plasma administration

Starting date	August 18, 2020
Contact information	Contact: Eduardo M Rego, MD, PhD: edumrego@hotmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: Recruiting • Planned completion date: April 30, 2021 • Sponsors: D'Or Institute for Research and Education Hospital do Coracao

NCT04539275

Study name	VA coronavirus research and efficacy studies-1 (VA CURES-1)
Methods	<ul style="list-style-type: none"> • Trial design: double-blind, placebo-controlled RCT • Sample size: 702 • Setting: inpatient • Country: USA • Language: English • Number of centres: 20
Participants	<ul style="list-style-type: none"> • Inclusion criteria: • Veterans must meet ALL of the following criteria to be eligible to participate: <ul style="list-style-type: none"> ○ Admitted to a participating VA clinical site with symptoms suggestive of SARS-CoV-2 infection. ○ Participant (or legally authorised representative) provides informed consent prior to initiation of any study procedures. ○ Participant (or legally authorised representative) understands and agrees to comply with planned study procedures. ○ Veteran 18 years of age at time of screening. ○ Has laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or antigen test, as documented by either of the following: <ul style="list-style-type: none"> ■ (1) RT-PCR or antigen positive (nasopharyngeal, oropharyngeal, saliva, lower respiratory) in sample collected 72 hours prior to screening; ■ (2) RT-PCR or antigen positive in sample collected > 72 hours but 168 hours (i.e. 7 days) prior to screening, documented inability to obtain a repeat sample (e.g. due to lack of testing supplies, limited testing capacity, results taking > 24 hours, etc.), AND progressive disease suggestive of ongoing SARS-CoV-2 infection. ○ Requiring oxygen by nasal cannula or by face-mask as a new treatment (or if previously on home oxygen, at a litre flow at least 2 Lpm greater than home prescription), but not on humidified heated high-flow nasal cannula (HHHFNC) at 15 Lpm. ○ Can be randomised within 72 hours of hospital admission. 8. Agrees not to participate in another therapeutic clinical trial for the treatment of COVID-19 or SARS-CoV-2 through Day 29 with-

NCT04539275 (Continued)

out approval from the investigator(s). Taking part in other research studies, including those unrelated to SARS-CoV-2, without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other study.

- Exclusion criteria
- An individual who meets any of the following criteria will be excluded from participation in this study:
 - Respiratory failure requiring mechanical ventilation, non-invasive ventilation including CPAP (for an indication other than previously diagnosed sleep apnea and maintained on outpatient settings), or extra-corporeal membrane oxygenation or anticipated to require any of those treatments or to die within 24 hours.
 - Anticipated discharge from the hospital or transfer to another hospital that is not a study site within 72 hours.
 - History of previous transfusion reaction.
 - Previously documented serum IgA deficiency (< 7 mg/dL)
 - Documented to have received convalescent plasma in the last 60 days.

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - type of plasma: Convalescent plasma from persons recovered from SARS-CoV-2
 - volume: 200-500 mL
 - number of doses: 2 doses
 - 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): Masked saline placebo
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome:
 - Proportion of participants developing acute hypoxemic respiratory failure or all-cause death [Time Frame: Day 1 through Day 28]
- Primary review outcomes
 - All-cause mortality at hospital discharge: probably reported
 - 30-day mortality: probably reported
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: reported
 - Mortality (time to event): reported
 - 90-day mortality: NR
 - Time to discharge from hospital: Length of hospital stay
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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): probably reported
 - Number of participants with serious adverse events: probably reported

NCT04539275 (Continued)

- Additional study outcomes
 - Time (in days) to recovery [Time Frame: Day 1 through Day 28]
 - Time (in days) to death or respiratory failure [Time Frame: Day 1 through Day 28]
 - Proportion of patients who died from any cause, had respiratory failure, or required humidified heated high-flow nasal cannula (HHHFNC) at 15 Lpm [Time Frame: Day 1 through Day 28]
 - Time (in days) to death or respiratory failure or HHHFNC at 15 Lpm [Time Frame: Day 1 through Day 28]
 - Subject 28-day all-cause mortality [Time Frame: Day 1 through Day 28]
 - Time to an improvement of one category using an ordinal scale: Modified WHO 8-point Ordinal Scale for Clinical Improvement [Time Frame: Up through 28 days.]
 - Time to an improvement of two categories using an ordinal scale: Modified WHO 8-point Ordinal Scale for Clinical Improvement [Time Frame: Up through 28 days.]
 - Participant's clinical status by ordinal scale [Time Frame: Up through 28 days.]
 - Mean change in the ordinal scale [Time Frame: Days 2, 4, 7, 11, 14, 21, and 28.]
 - Time to discharge or to a National Early Warning Score (NEWS)-2 of = 2 and maintained for 24 hours, whichever occurs first [Time Frame: Up through 28 days.]
 - Change in NEWS-2 Score from Day 1 (baseline) to Days 2, 4, 7, 11, 15, and 29 [Time Frame: From Day 1 (baseline) to Days 2, 4, 7, 11, 15, and 29]
 - Duration of hospitalisation [Time Frame: Day 1 through Day 28]
 - Number of hospitalizations related to COVID-19 [Time Frame: Day 1 through Day 28]
 - Cumulative incidence of Serious Adverse Events (SAEs) [Time Frame: Day 1 through Day 29]
 - Cumulative incidence of Grade 3 and 4 clinical and/or laboratory adverse events (AEs) [Time Frame: Day 1 through Day 29]
 - Incidence of discontinuation or temporary suspension of study product administrations (for any reason) [Time Frame: Day 1 through Day 29]
 - Change from baseline in hemoglobin [Time Frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).]
 - Change from baseline in platelets [Time Frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).]
 - Change from baseline in creatinine [Time Frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).]
 - Change from baseline in glucose [Time Frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).]
 - Change from baseline in total bilirubin [Time Frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).]
 - Change from baseline in alanine transaminase (ALT) [Time Frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).]
 - Change from baseline in aspartate transaminase (AST) [Time Frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).]
 - Change from baseline in prothrombin time (PT) [Time Frame: Day 1 to Days 2, 4, and 7 (while hospitalised); and Days 15 and 29 (if attends in-person visit or still hospitalised).]

Starting date	16/11/2020
Contact information	Edward N Janoff, MD: (730) 723-6255; Edward.Janoff@va.gov
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: July 18, 2022 • Sponsor/funding: VA Office of Research and Development

NCT04542967

Study name	Convalescent plasma as a treatment for patients with severe COVID-19 disease
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NCT04542967 (Continued)

Methods	<ul style="list-style-type: none"> • Trial design: Randomised, double-blind controlled trial • Sample size: 150 • Setting: inpatient • Country: Mexico • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ O₂ saturation <93% ◦ Radiographic evidence of moderate pneumonia according to Rale's classification. ◦ Acute respiratory distress syndrome (PaO₂/FiO₂ < 300 or SpO₂/FiO₂ ≤ 315) ◦ Authorisation to participate in the study and have informed consent letter, signed by the patient or the person responsible for the patient in case of critical patients (intubated) • Exclusion criteria <ul style="list-style-type: none"> ◦ Pregnant patients ◦ History of transfusion reactions ◦ Patients with congestive heart failure ◦ Patients with a history of chronic kidney failure on dialysis ◦ Patients with multiple organ failure ◦ Patients who does not accept or agree with the treatment.
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: NR ◦ volume: 200 mL ◦ number of doses: 2 doses ◦ antibody-titre: NR ◦ pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): If a third dose of convalescent plasma is necessary, it may be used, as long as an evaluation of the research team is carried out • For studies including a control group: comparator (type): standard of care • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Disease progression [Time Frame: Up to 30 days later from study entry] = Change in ordinal Scale for Clinical Improvement (WHO). The progression of disease, its change in the severity score; a bigger number to the obtained after randomization ◦ Side effects [Time Frame: Up to 30 days later from study entry] = Side effects associated with the administration of convalescent plasma ◦ Mortality [Time Frame: Up to 30 days later from study entry] = any cause of death • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: reported

NCT04542967 (Continued)

- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: partially (see primary study outcomes)
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: NR
- Additional study outcomes
 - Respiratory improvement [Time Frame: 10 days]
 - Clinical improvement [Time Frame: 10 days]
 - Acute adverse events (AAE) [Time Frame: After receiving intervention, an average time one hour, until 24 hours after administration.] = Transfusion reactions during transfusion.
 - Inflammatory biomarkers (D dimer) [Time Frame: 10 days]
 - Inflammatory biomarkers (Ferritin) [Time Frame: 10 days]
 - Inflammatory biomarkers (CPR) [Time Frame: 10 days]
 - Inflammatory biomarkers (LDH) [Time Frame: 10 days]

Starting date	23 June 2020
Contact information	Contact: Carmen G Torres, MD: dragabytorresalarcon@icloud.com
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: September 30, 2020 • Sponsor/funding: Hospital Central Militar

NCT04545047

Study name	CSP #2030 - Observational study of convalescent plasma for treatment of veterans with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: Observational study • Sample size: 10000 • Setting: inpatient • Country: USA • Language: English • Number of centres: 2

NCT04545047 (Continued)

Participants

- Inclusion criteria
 - US Veterans aged 21-80 years old
 - Hospitalised at VA Medical Center with a SARS-CoV-2 positive test within 7 days before or after hospital admission
 - Minimum oxygen saturation (measured within the past day) \geq 90%
 - Currently hospitalised at a VA medical center where CP has been administered to at least 2 patients
 - Admitted during the time when the VA medical center was administering CP therapy
 - Vitals (pulse, respiration, temperature, systolic blood pressure) measured within past 2 days
 - Acute labs (Hemoglobin, platelet, white blood cells) measured within the past 2 days
 - Albumin, ALT, creatinine labs measured within the past 30 days
 - Weight measurement recorded in the past 2 years
- Exclusion criteria
 - Prior intubation, ventilation, high flow oxygen, ECMO, dialysis, or vasopressors during current hospitalisation
 - Record of prior treatment with CP
 - Received long-term care in a domiciliary or nursing home in the past 90 days
 - First CP recipient at a site
 - Less than 30 days of follow-up

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - type of plasma: Convalescent plasma collected from individuals who have recovered from COVID-19
 - 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): no plasma, no further specification
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome:
 - All-cause mortality [Time Frame: 30 days]Death from trial start date to 30 days recorded in the electronic health record.
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: reported
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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 in-

NCT04545047 (Continued)

jury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions): NR

- Number of participants with serious adverse events: NR
- Additional study outcomes
 - All-cause mortality [Time Frame: 1 year] Long-term outcomes will include death at one year following the index date.

Starting date	5 May 2020
Contact information	<p>Sponsors and Collaborators</p> <ul style="list-style-type: none"> • VA Office of Research and Development • Mayo Clinic <p>Investigators</p> <ul style="list-style-type: none"> • Study Chair: Nicholas L. Smith, PhD: VA Puget Sound Health Care System Seattle Division, Seattle, WA • Study Chair: Michael J Gaziano, MD MPH: VA Boston Healthcare System Jamaica Plain Campus, Jamaica Plain, MA
Notes	<ul style="list-style-type: none"> • Recruitment status: not recruiting • Prospective completion date: December 31, 2021 • Sponsor/funding: Veterans Affairs Office of Research and Development

NCT04546581

Study name	Inpatient treatment with anti-coronavirus immunoglobulin (ITAC)
Methods	<ul style="list-style-type: none"> • Trial design: International multicentre, adaptive, randomised, double-blind, placebo-controlled trial • Sample size: 593 • Setting: inpatient • Countries: Denmark, Greece, Japan, Nigeria, Spain, United Kingdom, United States • Language: English • Number of centres: 39
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ○ SARS-CoV-2 infection documented by PCR or other nucleic acid test (NAT) within 3 days prior to randomization OR documented by NAT more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection ○ Symptomatic COVID-19 disease ○ Duration of symptoms attributable to COVID-19 \leq 12 days ○ Requiring inpatient hospital medical care for clinical manifestations of COVID-19 (admission for public health or quarantine only is not included) ○ Willingness to abstain from participation in other COVID-19 treatment trials until after study Day 7 ○ Provision of informed consent by participant or legally authorised representative

NCT04546581 (Continued)

- Exclusion criteria
 - Prior receipt of SARS-CoV-2 hIVIG or convalescent plasma from a person who recovered from COVID-19 at any time
 - Prior receipt of standard IVIG (not hyperimmune to SARS-CoV-2) within 45 days
 - Current or predicted imminent (within 24 hours) requirement for any of the following:
 - a. Invasive ventilation
 - b. Non-invasive ventilation
 - c. Extracorporeal membrane oxygenation
 - d. Mechanical circulatory support
 - e. Continuous vasopressor therapy
 - History of allergy to IVIG or plasma products
 - History of selective IgA deficiency with documented presence of anti-IgA antibodies
 - Any medical conditions for which receipt of the required volume of intravenous fluid may be dangerous to the patient (includes New York Association Class III or IV stage heart failure)
 - Any of the following thrombotic or procoagulant disorders:
 - a. Acute coronary syndromes, cerebrovascular syndromes and pulmonary or deep venous thrombosis within 28 days of randomisation
 - b. History of prothrombin gene mutation 20210, homozygous Factor V Leiden mutations, antithrombin III deficiency, protein C deficiency, protein S deficiency or antiphospholipid syndrome
 - Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject or that could prevent, limit, or confound the protocol-specified assessments

Interventions

- Details of hyperimmune immunoglobulin therapy:
 - drug name: Hyperimmune immunoglobulin to SARS-CoV-2 (hIVIG)
 - dose: 100mg/ml
 - number of doses: 1
 - route: intravenous use
 - source: human
- Treatment details, including time of plasma therapy (e.g. early stage of disease):
- For studies including a control group: comparator (type): placebo (saline infusion)
- Concomitant therapy: Remdesivir
- Treatment cross-overs: none

Outcomes

- Primary study outcome:
 - clinical status on ordinal scale (day 7)
 - 7. Death
 - 6. End-organ failure
 - 5. Life-threatening end-organ dysfunction
 - 4. Serious end-organ dysfunction
 - 3. Moderate end-organ dysfunction
 - 2. Limiting symptoms due to COVID-19
 - 1. No limiting symptoms due to COVID-19
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: yes (day 28)

NCT04546581 (Continued)

- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: partially (see primary study outcomes)
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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): yes
 - Number of participants with serious adverse events: yes
- Additional study outcomes
 - Clinical status on ordinal scale (see: primary study outcome) (days 3, 5, 14, 28)
 - Change in National Early Warning Score (NEWS) (day 0 to day 7)
 - Time to worsening of at least 3 favourable categories on the primary ordinal scale (see: primary study outcome) (days 7, 14, 28)
 - Percentage of discharged patients (days 7, 14, 28)
 - Days alive outside the hospital (up to 28 days)
 - Pulmonary-only components of the primary ordinal outcome (days 3, 5, 7, 14, 28)
 - Thrombotic components of the primary ordinal outcome (days 3, 5, 7, 14, 28)
 - Time to recovery, defined as the 2 most favourable categories on the primary ordinal scale (days 7, 14, 28)
 - Clinical organ dysfunction, defined as new onset of any one or more of the following (up to day 28)
 - A) Respiratory dysfunction
 - B) Cardiac and vascular dysfunction
 - C) Renal dysfunction
 - D) Hepatic dysfunction
 - E) Neurological dysfunction
 - F) Haematological dysfunction
 - G) Serious infection
 - Infusion reactions, interruptions, or cessation (days 1, 3, 7, 28)
 - Change in neutralizing antibody level (days 1, 3, 7, 28)

Starting date	8 October 2020
Contact information	Corresponding author Name: Jacqueline Nordwall Affiliation: NR Full Address: NR Email: jacquie@ccbr.umn.edu
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: July 2021

NCT04546581 (Continued)

- Sponsor/funding: University of Minnesota, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), The International Network for Strategic Initiatives in Global HIV Trials

NCT04555148

Study name	A prospective, open-label, randomized, multi-center, Phase 2a study to evaluate the dose response, efficacy and safety of hyper-Ig (hyper-immunoglobulin) GC5131 in patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 60 • Setting: Inpatient • Country: Republic of Korea • Language: English • Number of centres: 1 • Trial registration number: NCT04555148 • Date of registration: 18 September 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Adults > 19 years with diagnosis of COVID-19 ◦ Hospitalised, with COVID-19 symptoms within 7 days ◦ Positive PCR test ≤ 3 days prior to randomisation • Exclusion criteria <ul style="list-style-type: none"> ◦ Asymptomatic ◦ Requiring ventilation or ECMO ◦ Requiring oxygen therapy before onset of COVID-19 illness ◦ Receipt of antiviral drugs for another illness within previous 4 weeks ◦ History of allergy to IVIG or plasma ◦ Prior receipt of IVIG or CP therapy ◦ IgA deficiency ◦ Creatinine > 2 X ULN ◦ History of thrombosis or high risk of thromboembolism ◦ Reduced heart function [NYHA (New York Heart Association) Functional Class III or IV]; or cerebral cardiovascular disorder, or history of ischaemic disease, cardiovascular disease, cerebrovascular disorder, blood vessel disorder, etc. • Donor eligibility criteria NR • Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): Hyperimmune immunoglobulin • Details of therapy: <ul style="list-style-type: none"> ◦ Type of therapy: GC5131 Hyperimmune immunoglobulin ◦ Volume: NR - 3 dose regimens, low medium and high ◦ Number of doses: NR ◦ Antibody-titre: 3 dose regimens, low medium and high ◦ Pathogen inactivated: n/a • Treatment details, including time of plasma therapy (e.g. early stage of disease): within 7 days of symptom onset • Comparator: Placebo (saline) • Concomitant therapy: Standard care • Treatment cross-overs: NR

NCT04555148 (Continued)

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| Outcomes | <ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Reduction of 2 points or more on ordinal scale (days 7, 14, 21 & 28) • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: Yes ◦ Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: NR ◦ Number of participants with SAEs: NR ◦ Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: Yes ◦ 30-day and 90-day mortality: Up to 28 days ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: NR ◦ QoL: NR ◦ Virological response: Yes • Additional outcomes: Change in NEWS from baseline (Days 7, 14, 21 and 28 days) |
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Starting date	20 September 2020
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Contact information	<ul style="list-style-type: none"> • Full Name: Dr. Kyoung Ran Peck • Zip Code: NR • City: Seoul • Address: Samsung Medical Center • Telephone: 82-2-3410-3631 • Email: krpeck@skku.edu
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Notes	<ul style="list-style-type: none"> • Recruitment status: Recruiting • Prospective completion date: 30 December 2020 • Sponsor/funding: Green Cross Corporation
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NCT04558476

Study name	A multicenter randomized trial to assess the efficacy of convalescent plasma therapy in patients with invasive COVID-19 and acute respiratory failure treated with mechanical ventilation: the CONFIDENT trial
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Methods	<ul style="list-style-type: none"> • Trial design: Phase II Multi-centre open-label randomised controlled trial • Sample size: 500 (250 with plasma, 250 without plasma) • Setting: inpatient • Country: Belgium • Language: English • Number of centres: 16
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NCT04558476 (Continued)

- Participants
- Inclusion criteria
 - age at least 18 years
 - hospitalisation in an intensive care unit participating to the study
 - medical diagnosis with SARS-CoV-2 pneumonia as defined by both:
 - extended interstitial pneumonia on CT scan or a chest X-ray, consistent with viral pneumonia, within 10 days prior to inclusion
 - Positive result of SARS-CoV-2 PCR test, or any emerging and validated diagnostic laboratory test for COVID-19, within 15 days prior to inclusion
 - under mechanical ventilation administered through an endotracheal tube, for less than 5 days
 - prior Clinical Frailty Scale < 6.
 - written consent of the patient, or - if impossible - of a relative acting as the legal representative, or - if impossible - of a physician from a non-participating department of the same hospital acting as an impartial witness
 - Exclusion criteria
 - Pregnancy
 - Prior episode of transfusion-related side effect
 - Medical decision to limit therapy
 - Current participation in another trial testing a COVID-19 therapy

- Interventions
- CP therapy or hyperimmune immunoglobulin therapy: CP
 - Details of CP:
 - type of plasma: Plasma from 2 different donors
 - volume: 400-500ml
 - number of doses: 2 units
 - antibody-titre: NR
 - pathogen inactivated or not: NR
 - Treatment details, including time of plasma therapy (e.g. early stage of disease): Under medical ventilation
 - For studies including a control group: comparator (type): Standard of care according to the latest gold standard
 - Concomitant therapy: NR
 - Treatment cross-overs: none

- Outcomes
- Primary study outcome:
 - Vital status (dead or alive) at day 28
 - Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: probably reported
 - Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: reported
 - Time to discharge from hospital: Length of hospital stay
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: probably reported
 - QoL: reported
 - 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 in-

NCT04558476 (Continued)

- jury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions): NR
- Number of participants with serious adverse events: NR
 - Additional study outcomes
 - day 90 mortality [Time Frame: at day 90]
 - number of ventilator-free days at day 28 [Time Frame: at day 28]
 - number of renal replacement therapy free days at day 28 [Time Frame: at day 28]
 - number of vasopressors free-days at day 28 [Time Frame: at day 28]
 - use of ECMO before day 28 [Time Frame: till day 28]
 - value of the SOFA score at days 7, 14 and 28 [Time Frame: Day 1, 7, 14, 28]
 - changes in SOFA scores (delta SOFA) over 7, 14 and 28 days [Time Frame: Day 7, 14 and 28 days]
 - assessment of the SARS-CoV-2 viral load [Time Frame: Days 7, 14 and 28]
 - blood C reactive protein (CRP) concentration [Time Frame: Days 7, 14 and 28]
 - ferritin concentration [Time Frame: Days 7, 14 and 28]
 - lymphocyte count [Time Frame: Days 7, 14 and 28]
 - length of stay in the acute care hospital [Time Frame: through study completion, 1 year]
 - location of the patient [Time Frame: Day 90]
 - Katz Index of independence in Activity Day Living functional score [Time Frame: Day 90 and 365]
 - Hospital Anxiety and Depression Scale (HADS) [Time Frame: Day 90 and 365]
 - Quality of life scale EQ-5D-5L [Time Frame: Day 90 and 365]
 - Transfusion related adverse events [Time Frame: till 28 days]

Starting date	1 September 2020
Contact information	Benoit Misset, MD,PhD: benoit.misset@chuliege.be
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 1 September 2022 • Sponsor/funding: University of Liege

NCT04567173

Study name	A randomized, open-label, single center clinical trial to assess the efficacy and safety of convalescent plasma to hospitalized adult COVID-19 patients as adjunctive therapy to reduce the need for ICU admission: Co-CLARITY trial
Methods	<ul style="list-style-type: none"> • Trial design: phase 3, randomised, non-placebo controlled, open-label, non-blinded, single-centre clinical trial • Sample size: 136 • Setting: inpatient • Country: Philippines • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ○ Patient must be 19 years of age or older ○ Hospitalised with COVID-19 and confirmed via SARS-CoV-2 RT-PCR testing ○ Patient is willing and able to provide written consent and comply with all protocol requirements ○ Patient agrees to storage of specimens for future testing

NCT04567173 (Continued)

- Exclusion criteria
 - Female subjects with positive pregnancy test, are breastfeeding or planning to become pregnant/breastfeed during the study period
 - Symptomatic illness exceeding 14 days from onset of illness at time of enrolment
 - ICU admission on initial presentation at the hospital (includes patients with clinical indications for ICU admission as follows:
 - a. Respiratory distress with requirement of O₂ > 6 lpm to maintain O₂ sat > 92%
 - b. Rapid escalation of O₂ requirement/significant work of breathing
 - c. Hemodynamic instability: SBP < 90, MAP < 65
 - Receipt of any blood products including pooled immunoglobulin or intravenous immunoglobulin (IVIg) in the past 30 days prior to enrolment
 - Known IgA deficiency
 - Presence of any contraindication to transfusion (or history of prior severe reactions to transfusion of blood products)

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - type of plasma: type-specific anti-SARS-CoV-2 convalescent plasma
 - volume: 500 mL
 - number of doses: 2 doses
 - antibody-titre: NR
 - pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): 3rd to 14th day of illness after the onset of symptoms in preventing ICU admission
- For studies including a control group: comparator (type): standard of care
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome:
 - Incidence of serious adverse events (time frame: 28 days from enrolment)
 - Cumulative incidence of serious adverse events (transfusion-related acute lung injury, transfusion associated circulatory overload, transfusion related infection and anaphylaxis/severe allergic reactions) during the study period
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: probably reported
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: partially (see primary study outcomes)
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: Length of hospital stay
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: reported
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: reported

NCT04567173 (Continued)

- Additional study outcomes
 - Quick SOFA (qSOFA) score (time frame: 28 days from enrolment)
 - Cardiopulmonary arrest (time frame: 28 days from enrolment)
 - ICU mortality (time frame: 28 days from enrolment)
 - ICU length of stay (time frame: 28 days from enrolment)
 - Hospital mortality (time frame: 28 days from enrolment)
 - Hospital length of stay (time frame: 28 days from enrolment)
 - Dialysis-free days (time frame: 28 days from enrolment)
 - Vasopressor-free days (time frame: 28 days from enrolment)
 - ICU-free days (time frame: 28 days from enrolment)
 - 28-day mortality (time frame: 28 days from enrolment)
 - Anti-SARS-CoV-2 antibody titers (time frame: days 0, 1, 7 and 14 from enrolment)
 - SARS-CoV-2 RNA by RT-PCR (time frame: days 0, 1, 7 and 14 from enrolment)

Starting date	28 September 2020
Contact information	Deonne Thaddeus V Gauran, MD: +639088150248.; dvgauran@up.edu.ph
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 30 June 2021 • Sponsor/funding: University of the Philippines

NCT04573855

Study name	Treatment with anti-SARS-CoV-2 immunoglobulin in patients with COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 41 • Setting: Inpatient • Country: Brazil • Language: NR • Number of centres: NR • Trial registration number: NCT04573855 • Date of registration: 5 October 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Adults > 18 and < 75 years with diagnosis of COVID-19 by PCR ◦ Time between symptom onset and inclusion ≤ 10 days ◦ No indication of invasive ventilatory support at the time of randomization • Exclusion criteria <ul style="list-style-type: none"> ◦ Pregnancy or lactation ◦ Severe comorbidity: Severe heart disease, severe COPD or O₂-dependent COPD, terminal cancer ◦ Any confirmed or suspected immunosuppressive or immunodeficiency state, including HIV (regardless of treatment, CD4 count or viral load status); asplenia; severe recurrent infections and chronic use (more than 14 days) of immunosuppressive medication in the last 6 months, except for topical steroids or short-term oral steroids (cycle lasting ≤ 14 days) ◦ History of anaphylaxis or severe allergic reaction ◦ Previous use of any heterologous serum ◦ Participation in trials of prophylactic drugs or vaccines for COVID-19 ◦ Administration of immunoglobulins and / or any blood products in the previous three months. • Donor eligibility criteria NR

NCT04573855 (Continued)

	<ul style="list-style-type: none"> • Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): Hyperimmune immunoglobulin • Details of therapy: <ul style="list-style-type: none"> ◦ Type of plasma: Anti-SARS-CoV-2 immunoglobulin ◦ Volume: NR ◦ Number of doses: NR ◦ Antibody-titre: n/a ◦ Pathogen inactivated: n/a • Treatment details, including time of plasma therapy (e.g. early stage of disease): Within 10 days of symptom onset • Comparator: Standard care • Concomitant therapy: Standard care • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Rate of infusion-related adverse events (28 days) ◦ Clearance of viral RNA (72 hours) • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: Yes ◦ Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: 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: Yes ◦ QoL: NR ◦ Virological response: Yes • Additional outcomes: <ul style="list-style-type: none"> ◦ Infusion reaction rate (28 days) ◦ Modulation of serum and cellular inflammatory marker (Day 0, 3, and 7)
Starting date	1 December 2020
Contact information	<ul style="list-style-type: none"> • Full Name: NR • Zip Code: NR • City: NR • Address: NR • Telephone: NR • Email: NR
Notes	<ul style="list-style-type: none"> • Recruitment status: Not yet recruiting • Prospective completion date: 28 February 2021 • Sponsor/funding: D'Or Institute for Research and Education

NCT04589949

Study name	Early convalescent plasma therapy for high-risk patients with COVID-19 in primary care (the CoV-Early Study)
Methods	<ul style="list-style-type: none"> • Trial design: multi-centre, double-blind, randomised controlled trial • Sample size: 690 • Setting: outpatient • Country: The Netherlands • Language: English • Number of centres: 11
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ RT-PCR-confirmed COVID-19. ◦ Symptomatic (e.g but not limited to fatigue, fever, cough, dyspnoea, loss of taste or smell, diarrhoea, falls or confusion) ◦ 70 years or older OR 50-69 years and 1 or more of the risk factors described in the protocol • Exclusion criteria <ul style="list-style-type: none"> ◦ Life expectancy < 28 days in the opinion of the treating physician ◦ Patient or legal representative is unable to provide written informed consent ◦ Symptomatic for 8 days or more ◦ Being admitted to the hospital at the informed consent procedure ◦ Known previous history of transfusion-related acute lung injury ◦ Known Immunoglobulin A (IgA) deficiency
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: NR ◦ volume: 300 mL ◦ number of doses: 1 dose ◦ antibody-titre: NR ◦ pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage (see inclusion criteria) • For studies including a control group: comparator (type): 300 mL Fresh Frozen plasma (FFP) • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Highest disease status on the 5-point ordinal disease severity scale (up to 28 days) • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality: yes (day 28) ◦ Admission to hospital: yes (day 28)

NCT04589949 (Continued)

- Secondary review outcomes
 - Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR
 - Time to symptom onset: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Length of hospital stay, for hospitalised patients: NR
 - Admission to the intensive care unit (ICU): yes (28 days)
 - Viral clearance, assessed with RT-PCR test: yes (Change in proportion of detectable SARS-CoV-2 RT-PCR results) (days 3, 7, 14, 28)
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: NR
- Additional study outcomes
 - Disease duration in days of symptoms (28 days)
 - Age and clinical frailty score (28 days)

Starting date	12 October 2020
Contact information	<p>Corresponding Author</p> <p>Name: Bart Rijnders, MD, PhD</p> <p>Affiliation: Erasmus Medical Center</p> <p>Full Address: Erasmus Medical Center, Rotterdam, Zuid-Holland, Netherlands, 3000 CA</p> <p>Email: b.rijnders@erasmusmc.nl</p>
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 1 November 2023 • Sponsors/funding: Erasmus Medical Center, Sanquin Plasma Products BV, ZonMw: The Netherlands Organisation for Health Research and Development, Leiden University Medical Center

NCT04600440

Study name	Convalescent plasma in the treatment of COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: Randomised, open-label trial • Sample size: 100 • Setting: inpatient • Country: Sweden • Language: English • Number of centres: NR

NCT04600440 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Verified diagnosis of COVID-19 ◦ Adults (> 18 years) ◦ < 94% oxygen saturation ◦ willingness to participate ◦ ability to sign informed consent • Exclusion criteria <ul style="list-style-type: none"> ◦ inability to understand information and sign informed consent ◦ immunosuppressed patient
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: NR ◦ volume: 200 mL ◦ number of doses: 3 ◦ antibody-titre: High-titre donor plasma ◦ 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): ordinary treatment • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Number of days in need of oxygen (time frame: 28 days) • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: Probably reported ◦ 30-day mortality: Probably reported • Secondary review outcomes <ul style="list-style-type: none"> ◦ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days): NR ◦ Mortality (time to event): NR ◦ 90-day mortality: Reported ◦ Time to discharge from hospital: Length of hospital stay ◦ Admission to the intensive care unit (ICU): NR ◦ Length of stay on the ICU: NR ◦ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR ◦ QoL: NR ◦ 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): NR ◦ Number of participants with serious adverse events: NR • Additional study outcomes <ul style="list-style-type: none"> ◦ Number of days before discharge from hospital (time frame: 3 months) ◦ Mortality within 3 months (time frame: 3 months) ◦ Number of days before need of assisted ventilation (time frame: 28 days)
Starting date	23 October 2020
Contact information	Magnus Rasmussen, MD, Prof: +4646171000; magnus.rasmussen@med.lu.se
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 31 December 2021

NCT04600440 (Continued)

- Sponsor/funding: Skane University Hospital

NCT04621123

Study name	Plasma for early treatment in non-hospitalised mild or moderate COVID-19 patients
Methods	<ul style="list-style-type: none"> • Trial design: randomised (1:1), double-blind, placebo-controlled • Sample size: 474 • Setting: outpatient • Country: Spain • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Adult male or female individuals of ≥ 50 years old ◦ In women of childbearing potential, negative pregnancy test at inclusion/baseline ◦ Has confirmed SARS-CoV-2 infection as determined by PCR or validated antigen rapid diagnostic test² from nasopharyngeal swabs ≤ 5 days prior to inclusion/baseline visit. ◦ Symptomatic with mild or moderate COVID-19 with symptoms onset date ≤ 7 days prior to inclusion/baseline visit. <ul style="list-style-type: none"> ■ Mild COVID-19: Individuals who have any of the common signs and/or symptoms of COVID-19 (i.e., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. ■ Moderate COVID-19: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) $\geq 94\%$ on room air at sea level. ◦ Willing to comply with the requirements of the protocol and available for follow-up for the planned duration of the study. ◦ Has understood the information provided and capable of giving informed consent • Exclusion criteria <ul style="list-style-type: none"> ◦ If female, pregnant, breastfeeding, or planning a pregnancy during the study. ◦ Severe or critical COVID-19: <ul style="list-style-type: none"> ■ Severe COVID-19: respiratory frequency > 30 breaths per minute, $SpO_2 < 94\%$ on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) < 300 mmHg, or lung infiltrates $> 50\%$. ■ Critical COVID-19: respiratory failure, septic shock, and/or multiple organ dysfunction. ◦ Current hospital admission for any cause. ◦ History of previous confirmed SARS-CoV-2 infection. ◦ History of significantly abnormal liver function (Child Pugh C). ◦ History of chronic kidney disease (CKD) \geq stage 4, or need of dialysis treatment. ◦ Any pre-existing condition that increases risk of thrombosis. ◦ History of allergic reactions to blood or plasma products or methylene blue. ◦ Known IgA deficiency with anti-IgA antibodies. ◦ Medical conditions for which 250 ml of intravenous fluid is considered dangerous (i.e., decompensated heart failure or renal failure with fluid overload). ◦ Inability to consent and/or comply with study requirements, in the opinion of the investigator. ◦ Currently participating or planning to participate in any interventional study for the treatment of COVID-19 or SARS-CoV-2 infection until day 60.
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP

NCT04621123 (Continued)

- Details of CP:
 - type of plasma: Convalescent anti-SARS-CoV-2 MBT plasma
 - volume: 200 to 250 mL
 - number of doses: 1 dose
 - 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): Placebo (infusion of 200 to 250 ml of sterile saline solution 0.9%)
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome:
 - Hospitalisation rate (28 days)
 - SARS-CoV-2 viral load (day 7)
- Primary review outcomes
 - All-cause mortality: yes (up to day 60)
 - Admission to hospital: NR
- Secondary review outcomes
 - Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): yes
 - Time to symptom onset: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8 to 15 days, 16 to 30 days: yes
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Length of hospital stay, for hospitalised patients: NR
 - Admission to the intensive care unit (ICU): NR
 - Viral clearance, assessed with RT-PCR test: NR (viral load)
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: NR
- Additional study outcomes
 - COVID-19 symptoms severity score (FLU- patient-reported outcome measure (FLU-PRO) PLUS instrument, 27 Items) (day 14)
 - Resolution of symptoms (day 28)
 - Proportion of patients with adverse events (AE) and proportion of grade ≥ 4 AE, based on the FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers scale (day 28)
 - Change in inflammatory prognostic markers (Ferritin, Prealbumin, Interleukin 6, D-dimer, CRP, Leukocyte count, Lymphocyte count) (day 7)
 - SARS-CoV-2 viral load of self-collected middle turbinate (MT) swab and saliva samples compared to nasopharyngeal swabs collected by a healthcare worker
 - Reduction of SARS-CoV-2 viral load

Starting date 30 October 2020

Contact information Corresponding Author
 Name: Oriol Mitjà Villar, PhD, MD
 Affiliation: Germans Trias i Pujol Hospital
 Full Address: NR

NCT04621123 (Continued)

 Email: omitja@flsida.org

Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: October 2021 • Sponsor/funding: Fundación FLS de Lucha Contra el Sida, las Enfermedades Infecciosas y la Promoción de la Salud y la Ciencia
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NCT04634422

Study name	Plasma exchange (PLEX) and convalescent plasma (CCP) in COVID-19 patients with multiorgan failure - the COVID PLEX+CCP Trial
Methods	<ul style="list-style-type: none"> • Trial design: Multi-centre, parallel-grouped, stratified, centrally randomised controlled trial • Sample size: 220 • Setting: inpatient • Country: Denmark • Language: English • Number of centres: NR
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Confirmed SARS-CoV-2 (COVID-19) requiring intensive care AND use of advanced respiratory support as invasive mechanical ventilation OR non-invasive ventilation or continuous use of continuous positive airway pressure (CPAP) for hypoxia OR oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system AND RRT (continuous or intermittent) OR ECMO • Exclusion criteria <ul style="list-style-type: none"> ◦ who have received convalescent plasma for COVID-19 ◦ who have known hypersensitivity to plasma ◦ who are pregnant ◦ who the clinical team has decided not to escalate therapy (except that for cardiac arrest; patients who are not for cardio-pulmonary-resuscitation may be enrolled) ◦ Who have received RRT for more than 72 hours ◦ Who have received mechanical ventilation for more than 14 days ◦ We will not exclude patients enrolled in other interventional trials unless the protocols of the two trials collide (e.g. use of CCP by protocol). Co-enrolment agreements will be established with the sponsor/investigator to maintain an updated list of trials approved for co-enrolment
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: NR ◦ volume: 300 mL ◦ number of doses: 2 doses ◦ antibody-titre: NR ◦ pathogen inactivated or not: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): Also full plasma exchange therapy tested • For studies including a control group: comparator (type): standard of care • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Alive at day 90

NCT04634422 (Continued)

- Primary review outcomes
 - All-cause mortality: Probably reported
 - Admission to hospital: NR
- Secondary review outcomes
 - Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR
 - Time to symptom onset: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: Probably reported
 - Length of hospital stay, for hospitalised patients: NR
 - Admission to the intensive care unit (ICU): NR
 - Viral clearance, assessed with RT-PCR test: NR
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: reported (day 8)
- Additional study outcomes
 - Day 8 serious adverse events
 - Day 28 all cause mortality
 - Days alive without life support at day 90

Starting date	18/11/2020
Contact information	Wladimir M Szpirt, MD: 4535451767; mail@covid-plex.com
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 30 June 2021 • Sponsor/funding: Wladimir Szpirt

NCT04642014

Study name	A multi-centre, 18-months, single-group study of application of convalescent plasma in the treatment of SARS CoV-2 disease (COVID-19) with metabolomic and laboratory evaluation of plasma therapy effectiveness
Methods	<p>Methods</p> <ul style="list-style-type: none"> • Trial design: Multi-centre, 18-months, single-group study • Sample size: 500 • Setting: inpatient • Country: Poland • Language: English • Number of centres: NR

NCT04642014 (Continued)

Participants

- Inclusion criteria (donors)
 - Age > 18 and < 65 years
 - Confirmed previous SARS-CoV-2 infection
 - Signed informed consent to participate in this clinical trial, to donate plasma and to store the specimen for future testing.
 - At least 28 days from the end of isolation or resolution of symptoms of infection
 - 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
- Inclusion criteria (recipients)
 - Signed informed consent to participate in this clinical trial.
 - Confirmed previous SARS-CoV-2 infection
 - Respiratory distress with tachypnoea \geq 30 breaths per minute,
 - Oxygen level less than 94% in resting-state,
 - Partial pressure of oxygen (PO₂) \leq 80 mmHg
- Exclusion criteria (donors)
 - Age: < 18 or > 65 years
 - Female subjects who are pregnant
 - HIV-1, HIV-2; hepatitis B, hepatitis C; syphilis infection
 - Donors ineligible for regular voluntary blood donation
- Exclusion criteria (recipients)
 - No informed consent to participate in the study
 - Patients with a history of plasma hypersensitivity, including anaphylactic shock in previous transfusions, allergic reactions to citrate or primary IgA deficiency
 - Patients with symptoms of severe multi-organ failure
 - Patients with known allergic reactions to chemical compounds used or generated in the procedure of inactivation of pathogens
 - Patients with active thrombosis

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - type of plasma: ABO compatible inactivated convalescent plasma with a confirmed neutralization activity
 - volume: 200 mL
 - number of doses: 1 doses
 - 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): NA
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome:
 - Death, for any reason [Time Frame: 7 days after transfusion]
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR (only for 7 days)
 - 30-day mortality: NR

NCT04642014 (Continued)

- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days): NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: Length of hospital stay
 - Admission to the intensive care unit (ICU): probably reported
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: Reported
 - QoL: NR
 - 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): NR
 - Number of participants with serious adverse events: NR
- Additional study outcomes
 - For patients with respiratory support, the time to take one's own breath (extubation) [Time Frame: 7 days after transfusion]
 - Stay in the intensive care unit (ICU) [Time Frame: 7 days after transfusion]
 - Time to disconnect CPAP respiratory support [Time Frame: 7 days after transfusion]
 - Time to elimination of SARS-Cov-2 (RT-PCR) [Time Frame: 7 days after transfusion]
 - Time to serological response (anti-SARS-COV-2 antibodies) [Time Frame: 7 days after transfusion]

Starting date	24 November 2020
Contact information	Siddarth Agrawal, PhD: 0048717364000; siddarth.agrawal@umed.wroc.pl
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: 1 May 2022 • Sponsor/funding: This multi-centric study was funded by Wroclaw Medical University

NCT04649879

Study name	Convalescent plasma for treatment of COVID-19: an open randomised controlled trial
Methods	<ul style="list-style-type: none"> • Trial design: open-label randomised controlled trial (2:1) • Sample size: 920 • Setting: inpatient • Country: Sweden • Language: English • Number of centres: 3

NCT04649879 (Continued)

- Participants
- Inclusion criteria
 - Age greater than or equal to 18
 - Admitted to a study hospital
 - Active COVID-19 defined as symptoms + SARS-CoV-2 identified from upper or lower airway samples and blood
 - 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 the ABO system is required)
 - Unavailability of plasma
 - Estimated glomerular filtration rate < 30 (kidney failure stage III or more)
 - Pregnancy (urinary-hcg)
 - Breast feeding
 - Inability to give informed consent

- Interventions
- CP therapy or hyperimmune immunoglobulin therapy: CP
 - Details of CP:
 - type of plasma: convalescent plasma
 - volume: 200 ml over 2 hours
 - number of doses: daily infusion until SARS-CoV-2 is no longer detectable in the blood up to a maximum of 10 CP infusions
 - 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 for COVID-19 patients
 - Concomitant therapy: If steroid therapy has not already been initiated, betamethasone 3 mg daily will be given concomitantly with steroid therapy or longer if clinically indicated but for a maximum of 10 days.
 - Treatment cross-overs: none

- Outcomes
- Primary study outcome:
 - COVID-19 related mortality within 28 days
 - Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: reported
 - Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: probably reported
 - QoL: NR
 - 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 in-

NCT04649879 (Continued)

- jury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions): NR
- Number of participants with serious adverse events: NR
 - Number of participants with serious adverse events: reported
 - Additional study outcomes
 - COVID-19 related mortality within 60 days
 - Requirement of invasive ventilation or $\text{Pao}_2/\text{FiO}_2 \leq 70$ for ≥ 12 hours in the case of patients not eligible for intensive care
 - Adverse events
 - Dose of plasma needed to clear viraemia
 - Time to clearance of viraemia

Starting date	12 February 2020
Contact information	Contact: Joakim Dillner, MD, PhD+46 (0) 72-468 24 60; joakim.dillner@ki.se
Notes	<ul style="list-style-type: none"> • Recruitment status: Not yet recruiting • Prospective completion date: 1 February 2022 • Sponsor/funding: Joakim Dillner

NCT04669990

Study name	Remdesivir and convalescent plasma therapy for treatment of COVID-19 infection in Nepal: a registry study
Methods	<ul style="list-style-type: none"> • Trial design: Observational study • Sample size: 2000 • Setting: inpatient • Country: Nepal • Language: English • Number of centres: 4
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Tested positive for COVID 19 • All patients who receive treatment with CPT or remdesivir will be eligible for the study • Treatment decision will be based on decision of the treating physicians. However, following guidelines for treatment are provided based on current standard of care: For remdesivir: Patients with severe COVID-19 infection who require to be on oxygen supplementation. • For convalescent plasma therapy: Patients who meet one of the following criteria are likely to benefit from convalescent plasma therapy: <ol style="list-style-type: none"> 1. Patients on life-threatening COVID-19 infection when combined with remdesivir. 2. Patients who progress to life-threatening infection despite being on remdesivir for 48 hours or longer. The following definitions are used to define severe and life threatening COVID-19 infection <p>Written and informed consent</p> <p>Severe COVID-19 infection is defined by one or more of the following criteria:</p> <ul style="list-style-type: none"> • Shortness of breath (dyspnoea) • Respiratory frequency ≥ 30/min • Blood oxygen saturation $\leq 93\%$ • Partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 30 • Lung infiltrates increased more than 50% within 24 to 48 hours • Life-threatening COVID-19 infection is defined as one or more of the following:

NCT04669990 (Continued)

- Respiratory failure
- Septic shock
- Multiple organ dysfunction or failure

Exclusion criteria

- If the diagnosis is not confirmed with PCR or similar alternative tests for COVID-19 infection
- Any patient with contraindications for receiving plasma transfusion should not receive plasma
- Any patient with contraindications for receiving remdesivir should not receive remdesivir

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): NR
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome:
 - Demographics of recipients (time frame: 9 months): type of patients receiving plasma therapy; age in years; sex (M/F)
 - Comorbidity of recipient (time frame: 9 months): smoking, diabetes, heart disease, chronic lung disease, chronic liver disease, cancer, organ transplant, HIV infection, TB, HIV, HBV, HCV, syphilis
 - Adverse events of convalescent COVID-19 plasma and remdesivir Therapy (time frame: 9 months): any expected and unexpected adverse events during or after treatment (up to 7 days); any other complications related or unrelated to plasma transfusion and remdesivir during hospital stay
 - Hospital and ICU length of stay (time frame: 9 months): number of days of hospital stay and ICU stay
 - Disposition of patients including survival (time frame: 9 months): condition at discharge: complete recovery, partial recovery with complications, death
- Primary review outcomes
 - All-cause mortality at hospital discharge: Probably reported
 - 30-day mortality: NR
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: Length of hospital stay
 - Admission to the intensive care unit (ICU): Number of days of ICU stay
 - Length of stay on the ICU: reported
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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 in-

NCT04669990 (Continued)

jury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions): NR

- Number of participants with serious adverse events: NR
- Any adverse events: reported

Starting date	17 December 2020
Contact information	Janak Koirala, MD,MPH: 9818762117 ext +977; clinicaltrialsnepal@gmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 19 November 2021 • Sponsor/funding: This multi-centric study was funded by Nepal Health Research Council.

NCT04681430

Study name	Reconvalescent plasma/camostat mesylate early in SARS-CoV-2 Q-PCR (COVID-19) positive high-risk individuals (RES-Q-HR)
Methods	<ul style="list-style-type: none"> • Trial design: 4-arm, multi-centre, randomised, partly double-blind, controlled trial • Sample size: 1094 • Setting: outpatient • Country: Germany • Language: English • Number of centres: 4
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ○ Individuals (female, male, diverse) ≥ 18 years with SARS-CoV-2 infection, confirmed by PCR before study enrolment ○ SARS-CoV-2 positive PCR ≤ 3 days old (date of NP swab) ○ Presence of ≥ 1 SARS-CoV-2 typical symptom (fever, cough, shortness of breath, sore throat, headache, fatigue, smell/and or taste disorder, diarrhoea, abdominal symptoms, exanthema) and symptom duration ≤ 3 days. ○ Ability to provide written informed consent ○ Presence of at least one of the following criteria: <ul style="list-style-type: none"> ■ Patients > 75 years ■ Patients > 65 years with at least one other risk factor (BMI > 35 kg/m², coronary artery disease, chronic kidney disease (CKD) with glomerular filtration rate (GFR) < 60 ml/min but ≥ 30 ml/min, diabetes mellitus, active tumour disease) ■ Patients with a BMI > 35 kg/m² with at least one other risk factor (CAD, CKD with GFR < 60 ml/min but ≥ 30 ml/min, diabetes mellitus, active tumour disease) ■ Patients with a BMI > 40 kg/m² ■ Patients with chronic obstructive pulmonary disease (COPD) and/or pulmonary fibrosis

NCT04681430 (Continued)

- Exclusion criteria
 - Age < 18 years
 - Unable to give informed consent
 - Pregnant women or breast-feeding mothers
 - Previous transfusion reaction or other contraindication to a plasma transfusion
 - Known hypersensitivity to camostat mesylate and/or severe pancreatitis
 - Volume stress due to CP administration would be intolerable
 - Known IgA deficiency
 - Life expectancy < 6 months
 - Duration SARS-CoV-2 typical symptoms > 3 days
 - SARS-CoV-2 PCR detection older than 3 days
 - SARS-CoV-2 associated clinical condition \geq WHO stage 3 (patients hospitalised for other reasons than COVID-19 may be included if they fulfil all inclusion and none of the exclusion criteria).
 - Previously or currently hospitalised due to SARS-CoV-2
 - Previous antiviral therapy for SARS-CoV-2
 - alanine aminotransferase (ALT) or aspartate transferase (AST) > 5 times upper limit of normal (ULN) at screening
 - Liver cirrhosis > Child A (patients with Child B/C cirrhosis are excluded from the trial)
 - Chronic kidney disease with GFR < 30 ml/min
 - Concurrent or planned anticancer treatment during trial period
 - Accommodation in an institution due to legal orders (§40(4) AMG).
 - Any psycho-social condition hampering compliance with the study protocol.
 - Evidence of current drug or alcohol abuse.
 - Use of other investigational treatment within 5 half-lives of enrolment is prohibited
 - Previous use of convalescent plasma for COVID-19
 - Concomitant proven influenza A infection
 - Patients with organ or bone marrow transplant in the three months prior to screening visit

Interventions

- Details of CP:
 - type of plasma: convalescent plasma (CP) with neutralizing antibodies against anti-SARS-CoV-2
 - volume: NR
 - number of doses: 2 doses
 - antibody-titre: at least 1:160
 - pathogen inactivated or not: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): early stage of disease (before hospitalisation)
- For studies including a control group: comparator (type): standard of care, camostat mesylate, placebo camostat
- Concomitant therapy: NR
- Treatment cross-overs: NR

Outcomes

- Primary study outcome:
 - WHO ordinal COVID-19 scale up to day 28
- Primary review outcomes
 - All-cause mortality: yes
 - Admission to hospital: Cumulative number of participants not hospitalised at day 90

NCT04681430 (Continued)

- Secondary review outcomes
 - Development of severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 6 (WHO 2020e): NR
 - Time to symptom onset: NR
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement) at up to 7 days, 8 to 15 days, 16 to 30 days:
 - Cumulative number WHO categories 4b-8 [Time Frame: day 8, day 14, day 56 and day 90]
 - Cumulative number WHO categories 3-4a [Time Frame: day 8, day 14, day 28, day 56 and day 90]
 - Mortality (time to event): NR
 - 90-day mortality: yes
 - Length of hospital stay, for hospitalised patients: yes
 - Admission to the intensive care unit (ICU): NR, but duration in intensive care/intermediate care (IMC) (in days)
 - Viral clearance, assessed with RT-PCR test: yes
 - QoL: NR
 - 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): yes (up to 90 days)
 - Number of participants with serious adverse events: yes (up to 90 days)
- Additional study outcomes
 - Number of patient with SARS-CoV-2 reinfection up to day 90
 - Number of patient with secondary sclerosis cholangitis at day 90
 - Number of patient with COVID-19 associated chronic pulmonary disease
 - The proportion of patients with remdesivir therapy
 - COVID-19 WHO status of patients at start of remdesivir treatment
 - The proportion of patients on dexamethasone therapy
 - COVID-19 WHO status of patients at start of dexamethasone treatment
 - Time to resolution of COVID-19 related symptoms
 - Duration of oxygen therapy (in days)
 - Frequency of occurrence of COVID-19 pneumonia
 - Percentage of participants requiring mechanical ventilation
 - Number of ventilation days per participant up to day 90
 - All-cause mortality at day 28
 - SARS-CoV-2 antibody concentrations (IgA in g/l) in serum on day 8, day 14, day 90
 - SARS-CoV-2 antibody concentrations (IgG in g/l) in serum on day 8, day 14, day 90
 - SARS-CoV-2 neutralizing antibody titers in serum on day 8, day 14, day 90
 - Number of screening failures due to the lack of a suitable plasma preparation

Starting date	8 January 2021
Contact information	Corresponding Author Name: Verena Keitel-Anselmino, Prof.Dr.med. Affiliation: Universitätsklinikum Düsseldorf Klinik für Hepatologie und Infektiologie Full Address: Universitätsklinikum Düsseldorf Klinik für Hepatologie und Infektiologie, Duesseldorf, Germany, 40225 Email: keitelan@uni-duesseldorf.de
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: November, 2021

NCT04681430 (Continued)

- Sponsor/funding:
 - Heinrich-Heine University, Duesseldorf
 - The Federal Ministry of Health, Germany (Bundesministerium für Gesundheit, BMG)

NCT04712344

Study name	Assessment of efficacy and safety of therapy with COVID-19 convalescent plasma in subjects with severe COVID-19 (IPCO)
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 58 • Setting: inpatient • Country: Germany • Language: English • Number of centres: 1
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Male or female subject aged ≥ 18 years. ◦ Estimated BMI ≥ 19 kg/m² to ≤ 40kg/m². ◦ Florid1 SARS-CoV-2 infection confirmed by RT-PCR in tracheo-bronchial secretion sample or pharyngeal swab sample. ◦ ARDS with Horovitz index < 300mmHg. ◦ Necessity of invasive mechanical ventilation. ◦ Written informed consent obtained from the subject's legal representative or under such arrangement as is legally acceptable in Germany ◦ Subject's assent if obtainable • Exclusion criteria <ul style="list-style-type: none"> ◦ Previous exposure to COVID-19 convalescent plasma. ◦ Adverse reaction to plasma proteins in medical history. ◦ Interval > 72h since endotracheal intubation. ◦ Current or imminent necessity of ECMO treatment. ◦ Pre-existing COPD GOLD stage 4. ◦ Chronic congestive heart failure NYHA ≥ 3. ◦ Pre-existing left ventricular ejection fraction $< 30\%$.
Interventions	<ul style="list-style-type: none"> • CP therapy or hyperimmune immunoglobulin therapy: CP • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: convalescent plasma ◦ volume: NR ◦ number of doses: 2-3 ◦ 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 care • Concomitant therapy: NR • Treatment cross-overs: none
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Change in SOFA score from Baseline Visit [Time Frame: [Day 1, Visit 2] to Day 8 [Visit 9]] • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: yes, day 29

NCT04712344 (Continued)

- Secondary review outcomes
 - 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):NR
 - Number of participants with serious adverse events:
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale ([WHO 2020e](#)), WHO Ordinal Scale for Clinical Improvement ([WHO 2020f](#))) at up to 7 days, 8 to 15 days, 16 to 30 days: NR
 - Mortality (time to event): NR
 - 90-day mortality: NR
 - Time to discharge from hospital: NR
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: NR
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
- Additional study outcomes
 - Mean number of days without invasive mechanical ventilation during the period from Baseline Visit [Day 1, Visit 2] until and including Day 8 [Visit 9], Day 15 [Visit 13], and Day 29 [Visit 15], per treatment group and per subject.
 - Number of subjects without supplemental oxygen on Day 8 [Visit 9], on Day 15 [Visit 13], and on Day 29 [Visit 15].
 - Proportion of subjects without supplemental oxygen on Day 8 [Visit 9], on Day 15 [Visit 13], and on Day 29 [Visit 15].
 - Mean number of days without supplemental oxygen during the period from Baseline Visit [Day 1, Visit 2] until and including Day 8 [Visit 9], Day 15 [Visit 13], and Day 29 [Visit 15], per treatment group and per subject.
 - Mean relative change of PEEP from Baseline Visit [Day 1, Visit 2] to all subsequent visits until and including Day 29 [Visit 15] or until stop of invasive mechanical ventilation, whichever comes first.
 - Mean relative change of FiO₂ from Baseline Visit [Day 1, Visit 2] to all subsequent visits until and including Day 29 [Visit 15] or until stop of invasive mechanical ventilation, whichever comes first.
 - Mean relative change of driving pressure from Baseline Visit [Day 1, Visit 2] to all subsequent visits until and including Day 29 [Visit 15] or until stop of invasive mechanical ventilation, whichever comes first.
 - Time from Baseline Visit [Day 1, Visit 2] to stop of invasive mechanical ventilation.

Starting date	18 January 2021
Contact information	Contact: Mario Schiffer, MD: +49913185 ext 39002; mario.schiffer@uk-erlangen.de
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: September 2021 • Sponsor/funding: University of Erlangen-Nürnberg Medical School

NCT04716556

Study name	Tranfusion of convalescent plasma for the early treatment of pneumonia in COVID-19 patients
Methods	<ul style="list-style-type: none"> • Trial design: Multicentre, open-label, randomised study • Sample size: 474 • Setting: inpatient • Country: Italy

NCT04716556 (Continued)

	<ul style="list-style-type: none"> • Language: English • Number of centres: 12
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Age ≥ 18 years old ◦ adult patients with positive RT-PCR test for SARS-CoV-2 (nasal swabs or lower respiratory tract sample), diagnosed with pneumonia (≤ 10 days) according to the following definitions: <ul style="list-style-type: none"> ■ Suggestive radiological imaging (CT, RX, ultrasound); ■ Respiratory failure not fully explained by heart failure or fluid overload; ■ PaO₂/FiO₂ 200-350 mmHg; ■ Signed informed consent • Exclusion criteria <ul style="list-style-type: none"> ◦ need of non invasive or invasive mechanical ventilation at the time of randomization; ◦ PaO₂/FiO₂ < 200; ◦ patients with hypersensitivity or allergic reaction to blood products or immunoglobulins; ◦ patients who expressly refuse to adhere the clinical study; ◦ use of IL-6 receptor inhibitors, IL-1 inhibitors, JAK inhibitors, TNF inhibitors; ◦ patients participating to other clinical trial.
Interventions	<ul style="list-style-type: none"> • Details of CP: <ul style="list-style-type: none"> ◦ type of plasma: NR ◦ volume: 200-300 mL ◦ number of doses: 1-3 ◦ 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 • Concomitant therapy: NR • Treatment cross-overs: NR
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Number of patients who meet invasive mechanical ventilation (PaO₂/FiO₂ <150) or death at 30 days • Primary review outcomes <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ 30-day mortality: yes • Secondary review outcomes <ul style="list-style-type: none"> ◦ Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days): NR ◦ Mortality (time to event): NR ◦ 90-day mortality: NR ◦ Time to discharge from hospital: yes ◦ Admission to the intensive care unit (ICU): NR ◦ Length of stay on the ICU: NR ◦ Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: yes ◦ QoL: NR ◦ 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): yes ◦ Number of participants with serious adverse events: yes

NCT04716556 (Continued)

- Additional study outcomes
 - Time to invasive mechanical ventilation or death
 - Evaluation of CD4/CD8 ratio (14 days)

Starting date	16 July 2020
Contact information	Corresponding Author Name: Elena Toschi Affiliation: Istituto Superiore di Sanità Full Address: INR Email: elena.toschi@iss.it
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: May 2021 • Sponsor/funding: Istituto Superiore di Sanità, Gruppo Italiano Malattie EMatologiche dell'Adulto, Agenzia Italiana del Farmaco

NCT04730401

Study name	Convalescent plasma in the treatment of COVID-19 (CP_COVID-19)
Methods	<ul style="list-style-type: none"> • Trial design: Double blind, randomised, placebo-controlled trial • Sample size: 390 • Setting: inpatient • Country: Finland • Language: English • Number of centres: NR
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Acute COVID-19 disease at the time of recruitment, laboratory-confirmed by upper respiratory tract PCR • Patient recently (0-4 days earlier) admitted to hospital due to COVID-19 infection • the day should be recorded from the duration of the COVID-19 symptoms/positive test result • The dose of Low-molecular-weight heparin (LMWH) thromboprophylaxis should be recorded • Written informed consent • Availability for all visits scheduled in this study <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Chronic (longer than 14 days) administration of immunosuppressants or other immune-modifying drugs within 6 months before the first dose of IMP; oral corticosteroids in dosages of ≥ 0.5 mg/kg/d prednisolone or equivalent are excluded (inhaled or topical steroids allowed) • Regular (daily), systemic administration of corticosteroids at the time on inclusion (inhaled or topical corticosteroids are allowed) • Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection • Pregnancy or lactation • Alcohol or drug abuse • Suspected non-compliance • Presence of VTE, including pulmonary embolism or other manifestations of thrombosis

NCT04730401 (Continued)

- Use of any investigational drug (other than hydroxychloroquine) or vaccine within 30 days prior to first dose of study vaccine or planned use during study period
- Any clinically significant history of known or suspected anaphylaxis or hypersensitivity reaction as judged by investigator
- Known immunoglobulin A (IgA) deficiency
- Existing treatment limitations: do-not-resuscitate (DNR) order or withholding treatment in ICU
- Any other criteria which, as judged by investigator, might compromise a patient's well-being or ability to participate in the study or its outcome

Interventions

- CP therapy or hyperimmune immunoglobulin therapy: CP
- Details of CP:
 - type of plasma: convalescent plasma
 - volume: 200 mL
 - number of doses: 2-3
 - antibody-titre: low titre and high titre
 - 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): 200 mL saline
- Concomitant therapy: NR
- Treatment cross-overs: none

Outcomes

- Primary study outcome
 - Safety (SAE) (time frame: SAEs will be reviewed, recorded and reported up to 6 hours after administration of CP or placebo)
 - Safety (SAE) (time frame: SAEs will be recorded and reported up to 7 days after administration of CP or placebo)
 - Rate of intubation (time frame: through study completion, up to 6 months)
 - Number of participants initiating systemic corticosteroids (time frame: through study completion, up to 6 months)
- Primary review outcomes
 - All-cause mortality at hospital discharge: NR
 - 30-day mortality: yes, up to 1 year
- Secondary review outcomes
 - Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale, WHO Ordinal Scale for Clinical Improvement at up to 7 days, 8 to 15 days, 16 to 30 days): NR
 - Mortality (time-to-event): NR
 - 90-day mortality: yes, up to 1 years
 - Time to discharge from hospital: yes
 - Admission to the intensive care unit (ICU): NR
 - Length of stay on the ICU: yes
 - Viral clearance, assessed with RT-PCR test at baseline, up to 3, 7, and 15 days: NR
 - QoL: NR
 - 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): yes
 - Number of participants with serious adverse events: yes

NCT04730401 (Continued)

- Additional study outcomes
 - Ventilator days
 - Number of participants developing ARDS
 - Viral load, up to 1 years
 - Antibody measurements
 - Development of a thrombotic complication, including VTE or arterial thrombosis
 - The rate of participants presenting with coagulopathy disorders
 - Number of participants with oxygenation change
 - Change in inflammatory (CRP, ferritin) and coagulopathy markers during the COVID-19 infection hospital period
 - Convalescent plasma (high- or low-titre) efficacy versus placebo: rate of intubation or initiating systemic corticosteroids during the COVID-19 infection hospital period

Starting date	27 January 2021
Contact information	<ul style="list-style-type: none"> • Contact: Sari Pakkanen: 0405166165; anu.kantele@hus.fi
Notes	<ul style="list-style-type: none"> • Recruitment status: recruiting • Prospective completion date: 31 December 2021 • Sponsor/funding: Helsinki University Central Hospital; Finnish Red Cross

NL8633

Study name	A randomized, double blinded clinical trial of convalescent plasma compared to standard plasma for treatment of hospitalized non-ICU patients with COVID-19 infections (COV-PLAS)
Methods	<ul style="list-style-type: none"> • Trial design: randomised, prospective, multi-centre, double-blinded phase 2/3 trial • Sample size: 215 each arm (430) • Setting: inpatient • Country: The Netherlands • Language: English • Number of centres: multi-centre • Trial registration number: prospective - NL8633 • Date of registration: 13 May 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Maximal 3 days hospitalised at plasma infusion ◦ Age ≥ 18 years and ≤ 85 years ◦ SARS-CoV-2 infection: confirmed by PCR (BAL, sputum, nasal and/or pharyngeal swap) < 7 days before ◦ Symptoms not expected to lead to IC transfer within 6 h of study plasma administration ◦ Written informed consent including storing of specimen for future testing

NL8633 (Continued)

- Exclusion criteria
 - A potential participant who meets any of the following criteria will be excluded from participation in this study:
 - Accompanying diseases other than COVID-19 with an expected survival time of < 6 months
 - Chronic severe pulmonary dysfunction like COPD, GOLD stage 4; severe emphysema; or lung fibrosis with usual interstitial pneumonia pattern
 - Chronic heart failure NYHA ≥ 3 and/or pre-existing reduction of left ventricular ejection fraction to $\leq 30\%$ for which among others e.g. strict fluid restriction is needed
 - Clinical diagnosis of circulatory overload for which active therapy (like increased doses of diuretics) is initiated
 - Clinical judgement of deterioration in oxygenation (e.g. > 2 L increase in additional O₂ by nose tube), respiratory rates (e.g. > 5 / min increase) in the 2 h before the planned randomisation/plasma infusion
 - Signs of severe coagulopathy: thrombocytopenia by consumption (< 100 x 10⁹/L) or prolongation of the PT (+3 sec) , PTT (+ 5 sec)
 - Any history of severe adverse reactions to plasma proteins
 - Known deficiency of IgA
 - Pregnancy
 - Breastfeeding women
 - Psychiatric or cognitive illness or recreational drug/alcohol use that in the opinion of the principal investigator, would affect subject safety and/or compliance

Interventions

- Intervention(s): CP therapy vs standard plasma
- Details of CP:
 - Type of plasma: convalescent thawed FFP
 - Volume: 1 unit (250-325 mL)
 - Number of doses: 1 unit
 - Antibody-titre: NR
 - Pathogen inactivated: NR
- Treatment details, including time of plasma therapy:
 - Early. Maximally 3 days hospitalised COVID-19 patients that are not at or bound to be referred to the ICU or expected to go to the ICU within 6 h of first plasma administration. Patients with COVID-19 that are sick enough to warrant hospitalisation but have not (yet) experienced overwhelming disease including a systemic inflammatory response, sepsis, and/or ARDS warranting ventilation and (eminent) ICU referral
- Comparator: standard thawed FFP 1 unit (250-325 mL)
- Concomitant therapy: NR
- Treatment cross-overs: no - parallel

Outcomes

- Primary study outcome(s):
 - Ordinal outcome at day 14 of all cause mortality, mechanical ventilation, ICU admission and long duration of hospital stay (6 days or more), with < 6 hospitalised days as reference category
- Primary review outcomes reported
 - All-cause mortality at hospital discharge: ordinal outcome of all-cause mortality at day 6, 14, 21, 18 and 56
 - Length of ICU mortality
 - Time to death: ordinal outcome of all-cause mortality at day 14, 21, 18 and 56
 - ICU mortality

NL8633 (Continued)

- Secondary review outcomes reported
 - Number of participants with grade 3 and grade 4 adverse events, including potential relationship between intervention and adverse reaction: yes. Deterioration of respiratory, circulatory or otherwise the clinical status during transfusion; transfusion transmitted infections
 - Number of participants with SAEs: numbers not mentioned: "The following safety parameters will be assessed during this trial: deterioration of respiratory, circulatory or otherwise the clinical status during transfusion; transfusion transmitted infections."
 - Improvement of clinical symptoms, assessed through need for respiratory support at up to 7 days; 8-15 days; 16-30 days: maybe. Ordinal outcome includes mechanical ventilation, ICU admission and long duration of hospital stay day 6, 14, 21, 28
 - 30-day and 90-day mortality: yes. Ordinal outcome of all-cause mortality, mechanical ventilation, ICU admission and long duration of hospital stay day 21, 28 and 56
 - Admission on ICU: yes within ordinal outcome of all-cause mortality, mechanical ventilation, ICU admission and long duration of hospital stay day 6, 14, 21, 28 and 56
 - Length of stay on the ICU: Yes. "Length of stay in ICU."
 - Time to discharge from hospital: yes. "duration of hospitalisation in days"
- Additional outcomes
 - e.g. proportion of viral nucleic acid negatives (3 days after transfusion): yes. "The time until negative SARS-CoV-2 PCR (nasal/ pharyngeal swab)"
 - e.g. results of lab tests and vital signs: NR

Starting date	13 May 2020
Contact information	Name: Jaap Jan Zwaginga Email: j.j.zwaginga@lumc.nl Phone: 0715264006
Notes	<ul style="list-style-type: none"> • Recruitment status: open for patient inclusion • Prospective completion date: 1 May 2021 • Sponsor: Leiden University Medical Center • www.trialregister.nl/trial/8633

PACTR202006760881890

Study name	Lagos COVID-19 convalescent plasma trial (LACCPT)
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 100 • Setting: Inpatient • Country: Nigeria • Language: English • Number of centres: 6 • Trial registration number: PACTR202006760881890 • Date of registration: 24 June 2020

PACTR202006760881890 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Adults > 18 years ◦ Moderate to severe COVID-19 disease confirmed by PCR ◦ Agrees to the collection of N-P, OP swabs, sputum and venous blood per protocol. ◦ Illness of any duration, and at least one of the following: <ul style="list-style-type: none"> ■ > 50% radiographic infiltrates by imaging (chest x-ray, CT scan, etc.) ■ Clinical assessment (evidence of rales/crackles on exam) AND SpO₂ ≤ 94% on room ■ Requiring mechanical ventilation and/or supplemental oxygen. ◦ If female of childbearing age, should agree to use at least one primary form of contraception for the duration of the study (acceptable methods will be determined by the site) • Exclusion criteria <ul style="list-style-type: none"> ◦ ALT/AST > 5 times the upper limit of normal. ◦ Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30) ◦ Pregnancy or lactation ◦ Anticipated transfer to another hospital which is not a study site within 72 hours. ◦ Allergy to any study medication • Donor eligibility criteria NR • Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: 200 ml ◦ Number of doses: 2 ◦ Antibody-titre: NR ◦ Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): NR • Comparator: Saline with multivitamin • Concomitant therapy: Standard care • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ SARS-CoV-2 detectable in NP, OP or sputum samples at days 1, 3, 5, 7, 9, & 11. ◦ Clinical status at day 11 (7 point ordinal scale) • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: yes ◦ Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): 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 ◦ Virological response: Yes • Additional outcomes: <ul style="list-style-type: none"> ◦ Changes in laboratory safety indices assessed on Days 1, 5, & 11 (except for D-dimer which will be assessed on days 1, 3, 5, 7, & 11)

PACTR202006760881890 (Continued)

Starting date	24 September 2020
Contact information	<ul style="list-style-type: none"> • Full Name: Akin Abayomi • Zip Code: NR • City: Ikeja • Address: Block 4, State Secretariat, Alausa • Telephone: +2349031101982 • Email: profakinabayomi@gmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: Recruiting • Prospective completion date: 30 November 2020 • Sponsor/funding: Lagos State Government

PACTR202007653923168

Study name	A clinical trial comparing use of convalescent plasma therapy plus standard treatment to standard treatment alone in patients with severe COVID-19 infection
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 206 • Setting: Inpatient • Country: Kenya • Language: English • Number of centres: 1 • Trial registration number: PACTR202007653923168 • Date of registration: 16th July 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Adults > 18 years with confirmed diagnosis of COVID-19 ◦ Severe disease defined as oxygen saturation ≤ 93 in resting state and $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg • Exclusion criteria <ul style="list-style-type: none"> ◦ History of allergic reaction to blood or blood products ◦ Participation in other clinical trials. ◦ Known IgA deficiency ◦ Medical conditions in which receipt of 350 mL volume may be detrimental to the patient (e.g., decompensated congestive heart failure, renal failure) ◦ Pregnancy or lactation • Donor eligibility criteria: <ul style="list-style-type: none"> ◦ Confirmation of previous infection with SARS-CoV-2 by a record of RT-PCR test result. ◦ At least 2 negative RT-PCR tests after recovery ◦ An interval of at least 14 days after initial illness which is assumed to be the day when the patient had a positive RT-PCR test for SARS-COV-2. ◦ Age (> 18yrs), ◦ Weight (> 50kg) ◦ At least 3 months since last donation ◦ Vital signs within normal ranges ◦ Non-reactivity of blood samples for transfusion transmitted infections including HIV, HBV, HCV, syphilis (for whole blood) and malaria ◦ To avoid the risk of transfusion-related acute lung injury (TRALI), preference will be given to use of plasma from male donors or from female donors who have never been pregnant including abortions.

PACTR202007653923168 (Continued)

- Donor exclusion criteria:
 - Patients aged less than 18 years of age
 - Symptomatic patients with COVID-19
 - Fever of unknown origin
 - Anaemic patients, underweight (less than 50 kg), chronic diseases such as HIV, hepatitis B and C, cancers, uncontrolled hypertension
 - Females who have given birth or had an abortion

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - Type of plasma: CP
 - Volume: 350 ml
 - Number of doses: 1
 - Antibody-titre: NR
 - Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): Transfused over 4 hours
- Comparator: Standard care
- Concomitant therapy: Standard care
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - Safety of CP therapy
 - Time to clinical improvement: time to decline 2 categories on WHO score (28 days)
- Primary review outcomes reported
 - All-cause mortality at hospital discharge: Yes, mortality up to 28 days
 - Time to death: NR
- Secondary review outcomes reported
 - Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: 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 (28 days)
 - Admission on the ICU: Yes
 - Length of stay on the ICU: Yes
 - Time to discharge from hospital: Yes
 - QoL: NR
 - Virological response: Yes, time to negative SARS-COV-2 RT-PCR
- Additional outcomes: Duration of severe illness based on SOFA score

Starting date

1 August 2020

Contact information

- **Full Name:** Isaac Adembesa
- **Zip Code:** 00100
- **City:** Nairobi
- **Address:** Kenyatta University Teaching Referral and Research Hospital, 7674, Nairobi,
- **Telephone:** +254720949430
- **Email:** kadembesa@yahoo.com

Notes

- Recruitment status: Not yet recruiting
- Prospective completion date: 31 December 2020

PACTR202007653923168 (Continued)

- Sponsor/funding: Kenyatta University Teaching Referral and Research Hospital

PER-013-20

Study name	Convalescent plasma as treatment for COVID-19
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 192 • Setting: Inpatient • Country: Peru • Language: English • Number of centres: 1 • Trial registration number: PER-013-20 • Date of registration: 25 June 2020
Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Adults > 18 years with confirmed diagnosis of COVID-19 ◦ Patients at risk of progression with 2 or more of the following: <ul style="list-style-type: none"> ■ Ferritin > 500 ng/mL ■ D-dimer > 1 mg/L ■ Reactive C-protein > 15 mg/L ■ Total lymphocytes < 1000/mm³ ■ Neutrophil/lymphocyte ratio > 3.13 ◦ Admission to a Intense care unit for management of COVID-19 OR 2 or more of the following: <ul style="list-style-type: none"> ■ Dyspnoea ■ Respiratory rate ≥ 30 per minute ■ Oxygen saturation < 93% ■ PO₂/FioO₂ < 300 ■ Lung infiltrates > 50% in chest X-ray or ■ Chest CT scan with increasing compromise in a 24-48 hours period • Exclusion criteria <ul style="list-style-type: none"> ◦ Previous transfusion of any haemoderivate in the 120 days prior to convalescent plasma administration ◦ Pregnancy • Donor eligibility criteria NR • Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: NR ◦ Number of doses: NR ◦ Antibody-titre: NR ◦ Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): Day 1 after randomisation • Comparator: Standard care • Concomitant therapy: Standard care • Treatment cross-overs: nil

PER-013-20 (Continued)

Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Oxygen requirement (14 days, 28 days) ◦ Ventilation requirement (14 days, 28 days) ◦ Mortality (14 days, 28 days, 56 days) ◦ Adverse events (28 days) • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: Yes ◦ Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions: 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: Yes ◦ 30-day and 90-day mortality: 30 days yes; 90 days NR ◦ Admission on the ICU: NR ◦ Length of stay on the ICU: NR ◦ Time to discharge from hospital: NR ◦ QoL: NR ◦ Virological response: NR • Additional outcomes: Time to ventilation
Starting date	19th September 2020
Contact information	<ul style="list-style-type: none"> • Full Name: Martin Oyanguren Miranda • Zip Code: • City: Lima • Address: Hospital Nacional Edgardo Rebagliati Martins, Caminos del Inca, Jesus María • Telephone: 952393544 • Email: Bettochunga17@hotmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: Recruiting • Prospective completion date: NR • Sponsor/funding: Seguro Social De Salud- Essalud

PER-060-20

Study name	Randomized phase 2 clinical trial to evaluate safety and efficacy of the use of plasma from convalescent patients with the new coronavirus disease (COVID-19) for the experimental treatment of patients hospitalized in the Centro Médico Naval 'Cirujano Mayor Santiago Távara'
Methods	<ul style="list-style-type: none"> • Trial design: RCT • Sample size: 100 • Setting: Hospitalised patients • Country: Peru • Language: English • Number of centres: 1 • Trial registration number: PER-060-20 • Date of registration: 21 Sept 2020

PER-060-20 (Continued)

Participants	<ul style="list-style-type: none"> • Inclusion criteria <ul style="list-style-type: none"> ◦ Adults > 18 years with diagnosis of COVID-19 ◦ Diagnosis of moderate to severe ARDS according to the definition of the Berlin criteria <10 days. ◦ Mechanical ventilation or continuous oxygenation at positive pressure. • Exclusion criteria <ul style="list-style-type: none"> ◦ Diagnosis of Mild ARDS according to the definition of the Berlin criteria. ◦ Diagnosis of moderate to severe ARDS, > 10 days. ◦ Demonstrated hypersensitivity or history of allergy to blood products or immunoglobulins. ◦ Pregnancy or lactation • Donor eligibility criteria NR • Donor exclusion criteria NR
Interventions	<ul style="list-style-type: none"> • Intervention(s): CP therapy • Details of CP: <ul style="list-style-type: none"> ◦ Type of plasma: CP ◦ Volume: 200 ml ◦ Number of doses: up to 2 ◦ Antibody-titre: NR ◦ Pathogen inactivated: NR • Treatment details, including time of plasma therapy (e.g. early stage of disease): repeat dose given after 24 hours, if required • Comparator: standard of care • Concomitant therapy: standard of care • Treatment cross-overs: nil
Outcomes	<ul style="list-style-type: none"> • Primary study outcome: <ul style="list-style-type: none"> ◦ Mortality (60 days) • Primary review outcomes reported <ul style="list-style-type: none"> ◦ All-cause mortality at hospital discharge: NR ◦ Time to death: NR • Secondary review outcomes reported <ul style="list-style-type: none"> ◦ Number of participants with grade 3 and grade 4 AEs, including potential relationship between intervention and adverse reaction (e.g. TRALI, transfusion-transmitted infection, TACO, TAD, acute transfusion reactions): 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: Yes ◦ QoL: NR ◦ Virological response: NR • Additional outcomes: NR
Starting date	19 October 2020
Contact information	<ul style="list-style-type: none"> • Full Name: Mario Ortiz Mondragón • Zip Code: 20153408191 • City: Lima • Address: Marina de Guerra del Perú, Av. La Marina Cdra 36 Nro. S/N Cuartel La Perla (Av. La Marina Cdra. 36 Esq. Insurgentes) • Telephone: 2078900 Anx 1400 / 1401

PER-060-20 (Continued)

- **Email:** ortiz60marina51@hotmail.com

Notes

- Recruitment status: Recruiting
- Prospective completion date: NR
- Sponsor/funding: Marina De Guerra Del Perú

RBR-7jqpnw

Study name Therapeutic effectiveness of COVID-19 convalescent plasma produced by HEMOPE: a multicenter, randomized and controlled clinical trial

Methods

- Trial design: RCT
- Sample size: 220
- Setting: hospitalised patients
- Country: Brazil
- Language: Portuguese/English
- Number of centres: 77
- Trial registration number: U1111-1254-0612
- Date of registration: 22 June 2020

Participants

- Inclusion criteria
 - Adults > 18 years with diagnosis of COVID-19, who are hospitalised; and considered as having a condition that increases the risk of a worse prognosis: obesity; diabetes mellitus; systemic arterial hypertension; chronic lung disease, obesity, diseases that alter immunity (AIDS, neoplasms or autoimmune diseases in immunosuppressive therapy), chronic liver disease
- Exclusion criteria
 - History of anaphylactic reaction related to blood transfusion
- Donor eligibility criteria NR
- Donor exclusion criteria NR

Interventions

- Intervention(s): CP therapy
- Details of CP:
 - Type of plasma: CP
 - Volume: NR
 - Number of doses: NR
 - Antibody-titre: NR
 - Pathogen inactivated: NR
- Treatment details, including time of plasma therapy (e.g. early stage of disease): NR
- Comparator: standard of care
- Concomitant therapy: standard of care
- Treatment cross-overs: nil

Outcomes

- Primary study outcome:
 - Mortality
- Primary review outcomes reported
 - All-cause mortality at hospital discharge: yes
 - Time to death: NR

RBR-7jqpnw (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: yes
 - Admission on the ICU: yes
 - Length of stay on the ICU: yes
 - Time to discharge from hospital: yes
 - QoL: NR
 - Virological response: NR
- Additional outcomes: NR

Starting date	1 July 2020
Contact information	<ul style="list-style-type: none"> • Full Name: Democritus of Barros Miranda Filho • Zip Code: 55100-130 • City: Recife / Brazil • Address: Rua Arnóbio Marques, 310, Santo Amaro • Telephone: +55 081 999764712 • Email: demofilho@gmail.com
Notes	<ul style="list-style-type: none"> • Recruitment status: not yet recruiting • Prospective completion date: NR • Sponsor/funding: University of Pernambuco

AE: adverse event; **ALT:** alanine transaminase; **ANC:** absolute neutrophil count; **ARDS:** acute respiratory distress syndrome; **AST:** aspartate transaminase; **BAL:** bronchoalveolar lavage; **BAT:** best available therapy; **B(i)PAP:** bi-level positive airway pressure; **BMI:** body mass index; **CDC:** Centers for Disease Control and Prevention; **COI:** conflict of interest; **COPD:** chronic obstructive pulmonary disease; **CAP:** community-acquired pneumonia; **CP:** convalescent plasma; **CPAP:** continuous positive airway pressure; **CPK:** creatine phosphokinase; **CRP:** C-reactive protein; **CT:** computed tomography; **DBP:** diastolic blood pressure; **DFPP:** double-filtration plasmapheresis; **DIC:** disseminated intravascular coagulation; **DMARD:** disease-modifying anti-rheumatic drug; **DVT:** deep vein thrombosis; **ECG:** electrocardiogram; **ECMO:** extracorporeal membrane oxygenation; **ED:** emergency department; **FDA:** US Food and Drug Administration; **FFP:** fresh frozen plasma; **FiO₂:** fractional inspired oxygen; **GFR:** glomerular filtration rate; **HBV/HCV:** hepatitis B/C; **HCPOA:** healthcare power of attorney; **HLA:** human leukocyte antigen; **ICU:** intensive care unit; **IgA (B/G/M):** immunoglobulin A (B/G/M); **IL-6:** interleukin-6; **IV:** intravenous; **IVIG:** intravenous immunoglobulin; **LAR:** legal authorised representative; **LDH:** lactate dehydrogenase; **NR:** not reported; **NYHA:** New York Heart Association; **PaO₂:** arterial blood oxygen partial pressure; **PCR:** polymerase chain reaction; **PE:** pulmonary embolism; **QoL:** quality of life; **RCT:** randomised controlled trial; **RF:** respiratory failure; **RNA:** ribonucleic acid; **RRT:** renal replacement therapy; **RT-PCR:** reverse transcription polymerase chain reaction; **SAE:** serious adverse event; **SARS:** severe acute respiratory syndrome; **SBP:** systolic blood pressure; **SC:** subcutaneous; **SOFA:** Sequential Organ Failure Assessment; **SpO₂:** peripheral capillary oxygen saturation; **SRD:** severe respiratory disease; **TACO:** transfusion-associated circulatory overload; **TAD:** transfusion-associated dyspnoea; **TB:** tuberculosis; **TRALI:** transfusion-related acute lung injury; **TTP:** thrombotic thrombocytopenic purpura; **UIP:** usual interstitial pneumonia; **ULN:** upper limit of normal; **WBC:** white blood count; **WHO:** World Health Organization

RISK OF BIAS

Legend:  Low risk of bias  High risk of bias  Some concerns

Risk of bias for analysis 1.1 All-cause mortality at up to day 28

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Subgroup 1.1.1 Individuals with moderate disease						
Agarwal 2020	✓	~	✓	✓	✓	~
AlQahtani 2020	✓	✓	✓	✓	~	~
Avendano-Sola 2020	✓	✓	✓	✓	✓	✓
Simonovich 2020	✓	✓	✓	✓	✓	✓
Subgroup 1.1.2 Individuals with severe disease						
Li 2020	✓	✓	✓	✓	✓	✓
Subgroup 1.1.3 Individuals with moderate or severe disease						
Horby 2021	✓	✓	✓	✓	✓	✓
Ray 2020	~	✓	✓	✓	✓	~

Risk of bias for analysis 1.2 Mortality (time to event)

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Subgroup 1.2.1 Individuals with moderate disease						
Simonovich 2020	✓	✓	✓	✓	✓	✓
Subgroup 1.2.2 Individuals with severe disease						
Gharbharan 2020	✓	~	✓	✓	✓	~
Li 2020	✓	✓	✓	✓	✓	✓
Subgroup 1.2.3 Individuals with moderate or severe disease						

Bias						
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Horby 2021						
Ray 2020						

Risk of bias for analysis 1.3 All-cause mortality at hospital discharge

Bias						
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Subgroup 1.3.1 Individuals with moderate disease						
Agarwal 2020						
AlQahtani 2020						
Subgroup 1.3.2 Individuals with severe disease						
Gharbharan 2020						

Risk of bias for analysis 1.4 Clinical improvement: liberation from supplemental oxygen in surviving patients, for subgroup of participants requiring any supplemental oxygen or ventilator support at baseline

Bias						
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Gharbharan 2020						

Risk of bias for analysis 1.5 Clinical improvement: weaning or liberation from invasive mechanical ventilation in surviving patients, for subgroups of participants requiring invasive mechanical ventilation at baseline

Bias						
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Gharbharan 2020						
Horby 2021						

Risk of bias for analysis 1.6 Clinical worsening: need for invasive mechanical ventilation, for subgroup of participants not requiring invasive mechanical ventilation at baseline

Bias						
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Agarwal 2020						
AlQahtani 2020						
Horby 2021						
Simonovich 2020						

Risk of bias for analysis 1.7 Time to discharge from hospital

Bias						
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Avendano-Sola 2020						
Gharbharan 2020						
Li 2020						
Ray 2020						

Bias						
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Simonovich 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.9 Viral clearance at up to day 3

Bias						
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Agarwal 2020	✓	~	~	✗	✓	✗
Avendano-Sola 2020	✓	✓	✓	✓	✓	✓
Hamdy Salman 2020	✓	✓	✓	✓	~	~
Li 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.10 Viral clearance at up to day 7

Bias						
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Agarwal 2020	✓	~	~	✗	✓	✗
Avendano-Sola 2020	✓	✓	✓	✓	✓	✓
Li 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.11 Viral clearance at up to day 15

Bias						
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Avendano-Sola 2020	✓	✓	✓	✓	✓	✓
Li 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.13 Any grade adverse events

Bias						
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Subgroup 1.13.1 Individuals with moderate disease						
Simonovich 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.14 Grade 3 and 4 adverse events

Bias						
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Subgroup 1.14.1 Individuals with moderate disease						
Agarwal 2020	✓	⚠	✓	⚠	✓	⚠
AlQahtani 2020	✓	✓	✓	⚠	✓	⚠
Avendano-Sola 2020	✓	✓	✓	✓	✓	✓
Simonovich 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.15 Serious adverse events

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Subgroup 1.15.1 Individuals with moderate disease						
Avendano-Sola 2020	✓	✓	✓	✓	✓	✓
Simonovich 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.1 All-cause mortality at up to day 28

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Bajpai 2020	✓	✓	✓	✓	✓	✓
O'Donnell 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.2 Clinical worsening: need for invasive mechanical ventilation

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Bajpai 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.3 Duration of hospitalisation

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Bajpai 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.4 Any grade adverse events

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
O'Donnell 2021						

Risk of bias for analysis 2.5 Serious adverse events

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
O'Donnell 2021						

Risk of bias for analysis 3.1 All-cause mortality

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Libster 2020						

Risk of bias for analysis 3.2 Development of severe symptoms: need for invasive mechanical ventilation

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Libster 2020						

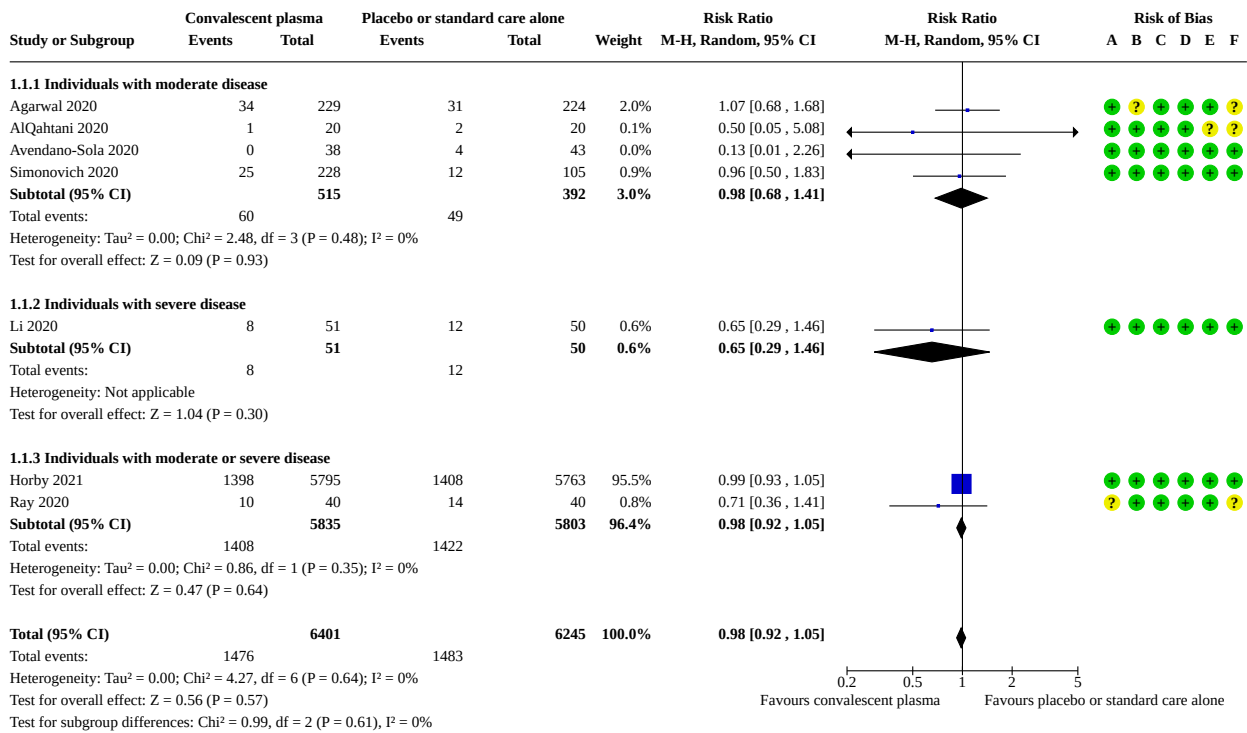
DATA AND ANALYSES

Comparison 1. Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality at up to day 28	7	12646	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.05]
1.1.1 Individuals with moderate disease	4	907	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.68, 1.41]
1.1.2 Individuals with severe disease	1	101	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.29, 1.46]
1.1.3 Individuals with moderate or severe disease	2	11638	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.92, 1.05]
1.2 Mortality (time to event)	5	12160	Hazard Ratio (IV, Random, 95% CI)	0.99 [0.92, 1.07]
1.2.1 Individuals with moderate disease	1	333	Hazard Ratio (IV, Random, 95% CI)	0.93 [0.47, 1.85]
1.2.2 Individuals with severe disease	2	189	Hazard Ratio (IV, Random, 95% CI)	0.64 [0.33, 1.25]
1.2.3 Individuals with moderate or severe disease	2	11638	Hazard Ratio (IV, Random, 95% CI)	1.00 [0.93, 1.07]
1.3 All-cause mortality at hospital discharge	3	577	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.53, 1.53]
1.3.1 Individuals with moderate disease	2	491	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.71, 1.76]
1.3.2 Individuals with severe disease	1	86	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.22, 1.34]
1.4 Clinical improvement: liberation from supplemental oxygen in surviving patients, for subgroup of participants requiring any supplemental oxygen or ventilator support at baseline	1	77	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.81, 1.48]
1.5 Clinical improvement: weaning or liberation from invasive mechanical ventilation in surviving patients, for subgroups of participants requiring invasive mechanical ventilation at baseline	2	630	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.57, 1.93]
1.6 Clinical worsening: need for invasive mechanical ventilation, for subgroup of participants not requiring invasive mechanical ventilation at baseline	4	11765	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.08]
1.7 Time to discharge from hospital	5	683	Hazard Ratio (IV, Random, 95% CI)	1.15 [0.95, 1.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8 Admission to the intensive care unit (ICU)	1	333	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.74, 1.09]
1.9 Viral clearance at up to day 3	4	552	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.98, 3.04]
1.10 Viral clearance at up to day 7	3	485	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.99, 2.43]
1.11 Viral clearance at up to day 15	2	149	Risk Ratio (M-H, Random, 95% CI)	1.59 [0.74, 3.43]
1.12 Need for dialysis	1	11442	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.87, 1.22]
1.13 Any grade adverse events	1	332	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.89, 1.26]
1.13.1 Individuals with moderate disease	1	332	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.89, 1.26]
1.14 Grade 3 and 4 adverse events	4	905	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.58, 1.41]
1.14.1 Individuals with moderate disease	4	905	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.58, 1.41]
1.15 Serious adverse events	2	414	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.81, 1.90]
1.15.1 Individuals with moderate disease	2	414	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.81, 1.90]

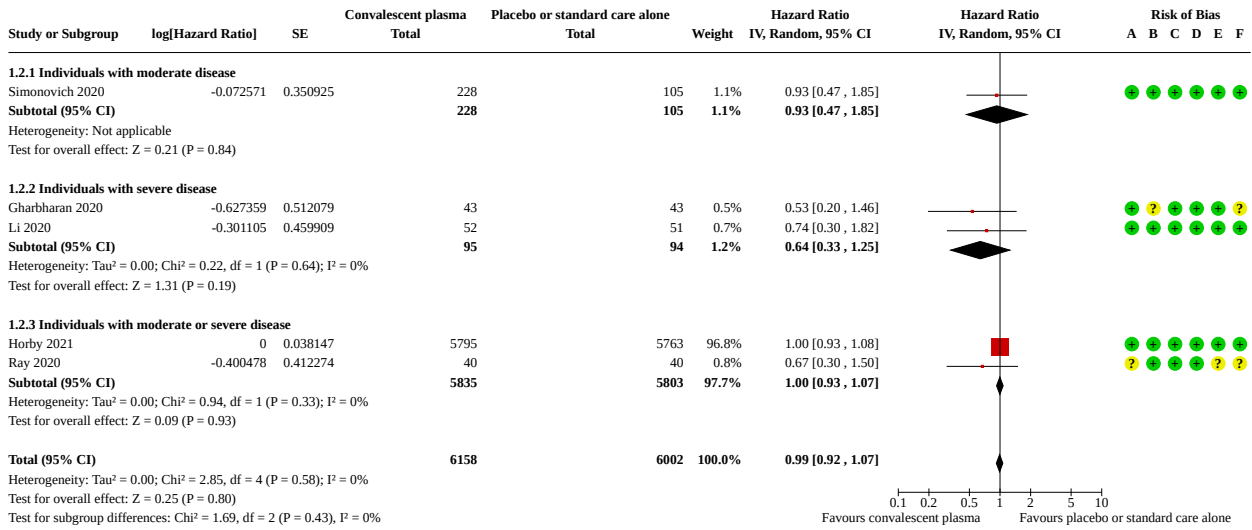
Analysis 1.1. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: All-cause mortality at up to day 28
- (C) Bias due to missing outcome data: All-cause mortality at up to day 28
- (D) Bias in measurement of the outcome: All-cause mortality at up to day 28
- (E) Bias in selection of the reported result: All-cause mortality at up to day 28
- (F) Overall bias: All-cause mortality at up to day 28

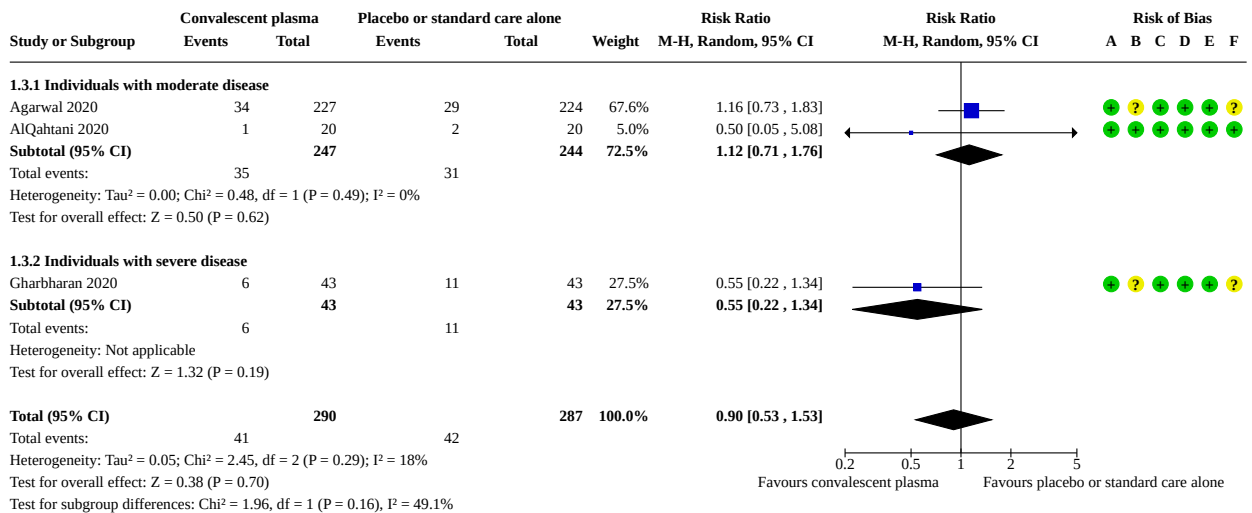
Analysis 1.2. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 2: Mortality (time to event)



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: Mortality (time to event)
- (C) Bias due to missing outcome data: Mortality (time to event)
- (D) Bias in measurement of the outcome: Mortality (time to event)
- (E) Bias in selection of the reported result: Mortality (time to event)
- (F) Overall bias: Mortality (time to event)

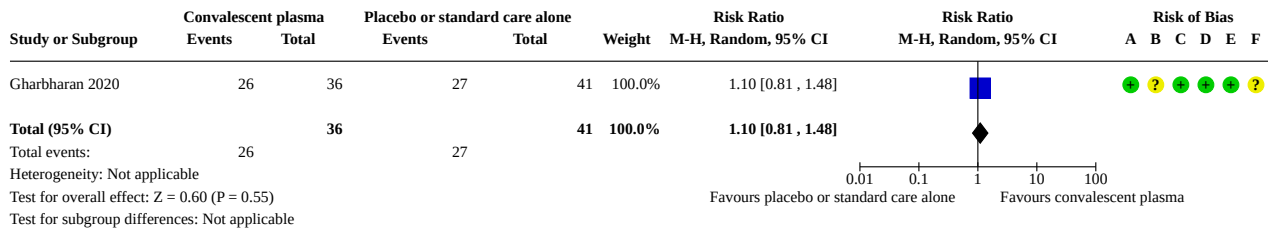
Analysis 1.3. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 3: All-cause mortality at hospital discharge



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: All-cause mortality at hospital discharge
- (C) Bias due to missing outcome data: All-cause mortality at hospital discharge
- (D) Bias in measurement of the outcome: All-cause mortality at hospital discharge
- (E) Bias in selection of the reported result: All-cause mortality at hospital discharge
- (F) Overall bias: All-cause mortality at hospital discharge

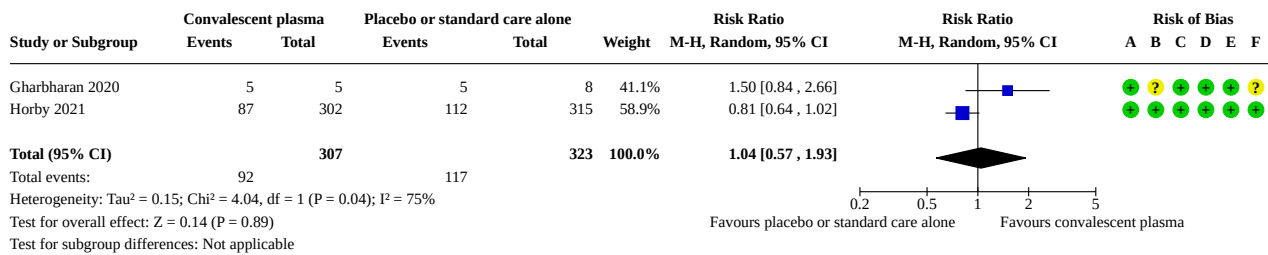
Analysis 1.4. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 4: Clinical improvement: liberation from supplemental oxygen in surviving patients, for subgroup of participants requiring any supplemental oxygen or ventilator support at baseline



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: Clinical improvement: liberation from supplemental oxygen in surviving patients, for subgroup of participants requiring any supplemental oxygen
- (C) Bias due to missing outcome data: Clinical improvement: liberation from supplemental oxygen in surviving patients, for subgroup of participants requiring any supplemental oxygen or ventilator support
- (D) Bias in measurement of the outcome: Clinical improvement: liberation from supplemental oxygen in surviving patients, for subgroup of participants requiring any supplemental oxygen or ventilator support
- (E) Bias in selection of the reported result: Clinical improvement: liberation from supplemental oxygen in surviving patients, for subgroup of participants requiring any supplemental oxygen or ventilator support
- (F) Overall bias: Clinical improvement: liberation from supplemental oxygen in surviving patients, for subgroup of participants requiring any supplemental oxygen or ventilator support at baseline

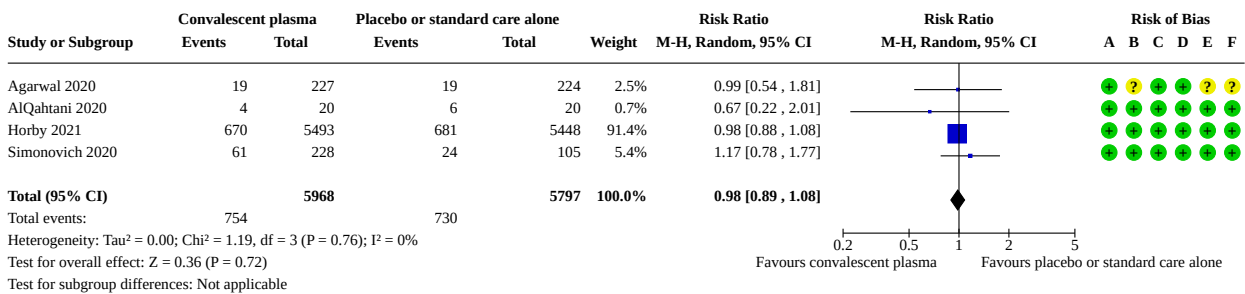
Analysis 1.5. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 5: Clinical improvement: weaning or liberation from invasive mechanical ventilation in surviving patients, for subgroups of participants requiring invasive mechanical ventilation at baseline



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: Clinical improvement: weaning or liberation from invasive mechanical ventilation in surviving patients, for subgroups of participants requiring invasive mechanical ventilation
- (C) Bias due to missing outcome data: Clinical improvement: weaning or liberation from invasive mechanical ventilation in surviving patients, for subgroups of participants requiring invasive mechanical ventilation
- (D) Bias in measurement of the outcome: Clinical improvement: weaning or liberation from invasive mechanical ventilation in surviving patients, for subgroups of participants requiring invasive mechanical ventilation
- (E) Bias in selection of the reported result: Clinical improvement: weaning or liberation from invasive mechanical ventilation in surviving patients, for subgroups of participants requiring invasive mechanical ventilation
- (F) Overall bias: Clinical improvement: weaning or liberation from invasive mechanical ventilation in surviving patients, for subgroups of participants requiring invasive mechanical ventilation at baseline

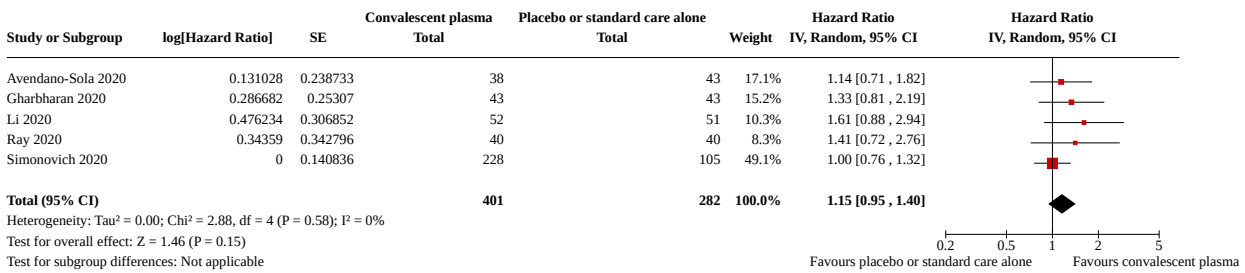
Analysis 1.6. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 6: Clinical worsening: need for invasive mechanical ventilation, for subgroup of participants not requiring invasive mechanical ventilation at baseline



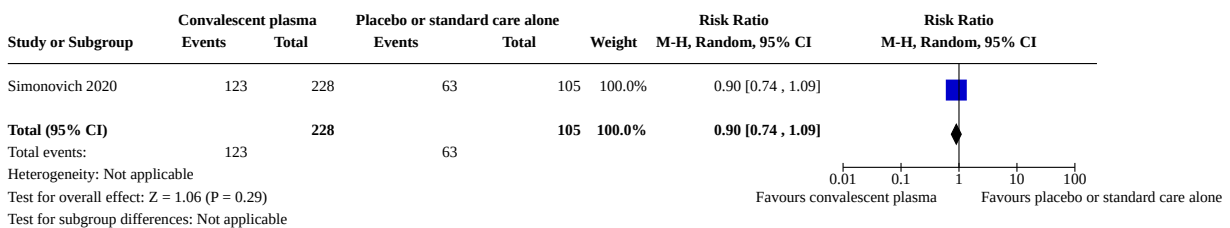
Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: Clinical worsening: need for invasive mechanical ventilation, for subgroup of participants not requiring invasive mechanical ventilation at baseline
- (C) Bias due to missing outcome data: Clinical worsening: need for invasive mechanical ventilation, for subgroup of participants not requiring invasive mechanical ventilation at baseline
- (D) Bias in measurement of the outcome: Clinical worsening: need for invasive mechanical ventilation, for subgroup of participants not requiring invasive mechanical ventilation at baseline
- (E) Bias in selection of the reported result: Clinical worsening: need for invasive mechanical ventilation, for subgroup of participants not requiring invasive mechanical ventilation at baseline
- (F) Overall bias: Clinical worsening: need for invasive mechanical ventilation, for subgroup of participants not requiring invasive mechanical ventilation at baseline

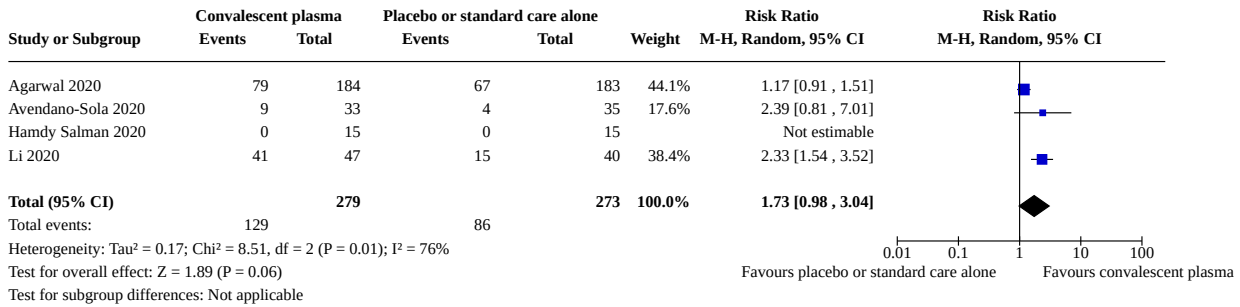
Analysis 1.7. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 7: Time to discharge from hospital



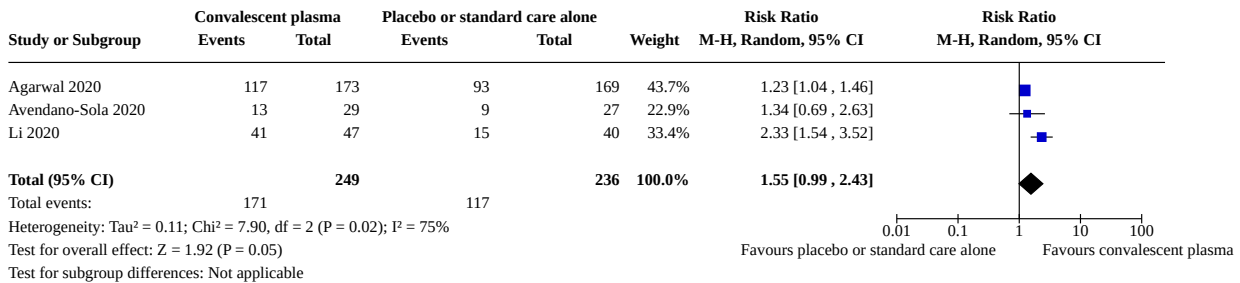
Analysis 1.8. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 8: Admission to the intensive care unit (ICU)



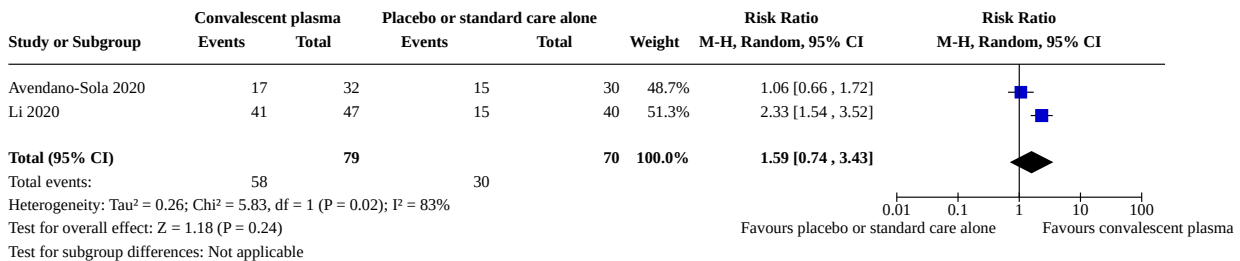
Analysis 1.9. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 9: Viral clearance at up to day 3



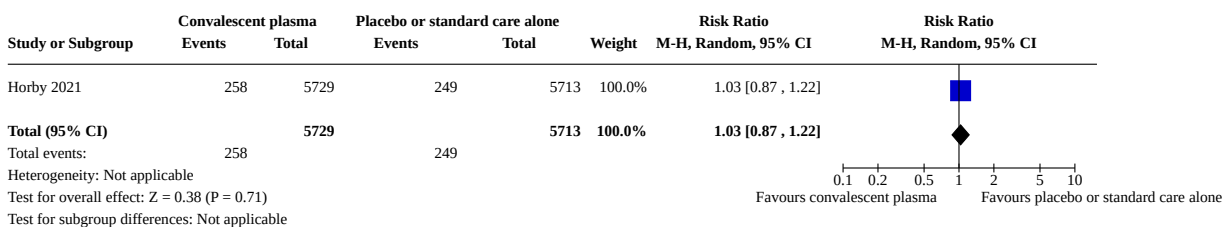
Analysis 1.10. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 10: Viral clearance at up to day 7



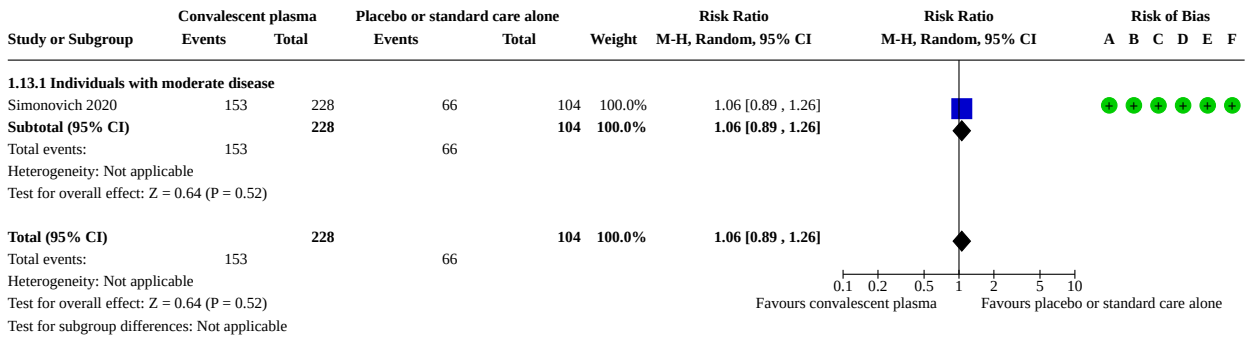
Analysis 1.11. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 11: Viral clearance at up to day 15



Analysis 1.12. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 12: Need for dialysis



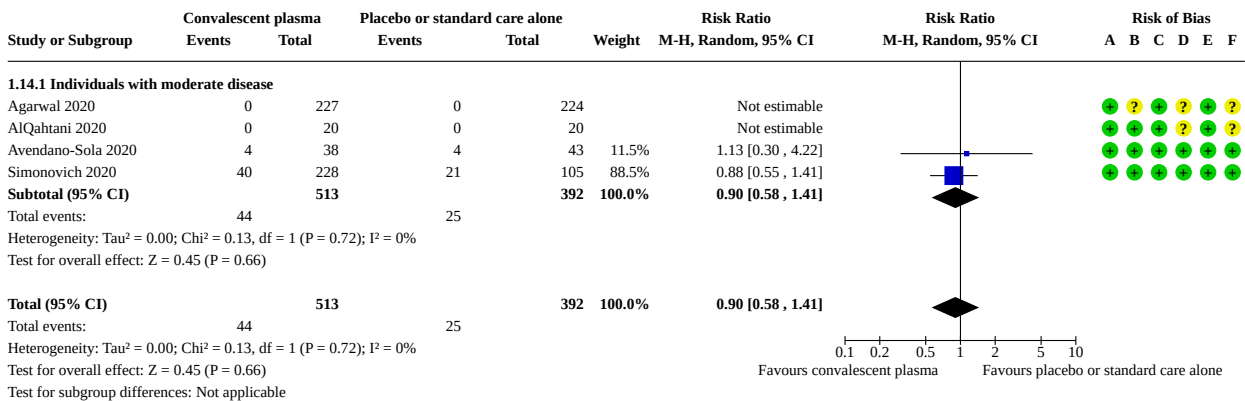
Analysis 1.13. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 13: Any grade adverse events



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: Any grade adverse events
- (C) Bias due to missing outcome data: Any grade adverse events
- (D) Bias in measurement of the outcome: Any grade adverse events
- (E) Bias in selection of the reported result: Any grade adverse events
- (F) Overall bias: Any grade adverse events

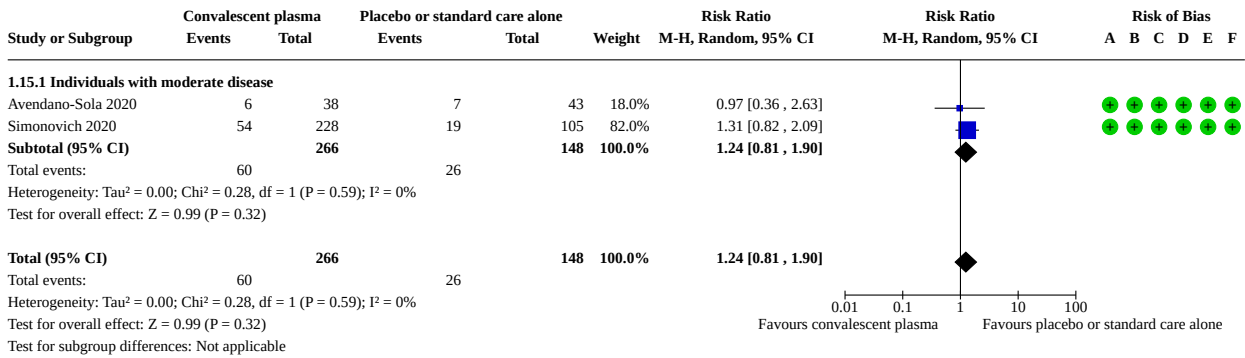
Analysis 1.14. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 14: Grade 3 and 4 adverse events



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: Grade 3 and 4 adverse events
- (C) Bias due to missing outcome data: Grade 3 and 4 adverse events
- (D) Bias in measurement of the outcome: Grade 3 and 4 adverse events
- (E) Bias in selection of the reported result: Grade 3 and 4 adverse events
- (F) Overall bias: Grade 3 and 4 adverse events

Analysis 1.15. Comparison 1: Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 15: Serious adverse events



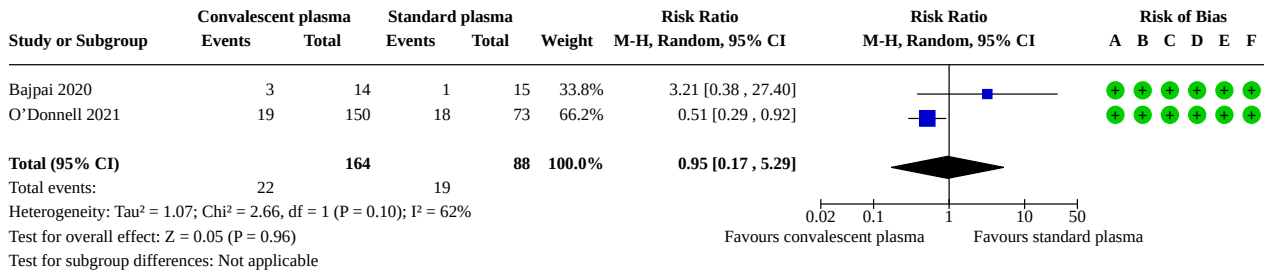
Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: Serious adverse events
- (C) Bias due to missing outcome data: Serious adverse events
- (D) Bias in measurement of the outcome: Serious adverse events
- (E) Bias in selection of the reported result: Serious adverse events
- (F) Overall bias: Serious adverse events

Comparison 2. Convalescent plasma versus standard plasma for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality at up to day 28	2	252	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.17, 5.29]
2.2 Clinical worsening: need for invasive mechanical ventilation	1	29	Risk Ratio (M-H, Random, 95% CI)	3.21 [0.38, 27.40]
2.3 Duration of hospitalisation	1	29	Mean Difference (IV, Random, 95% CI)	-4.00 [-7.56, -0.44]
2.4 Any grade adverse events	1	219	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.93, 1.49]
2.5 Serious adverse events	1	219	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.49, 1.11]

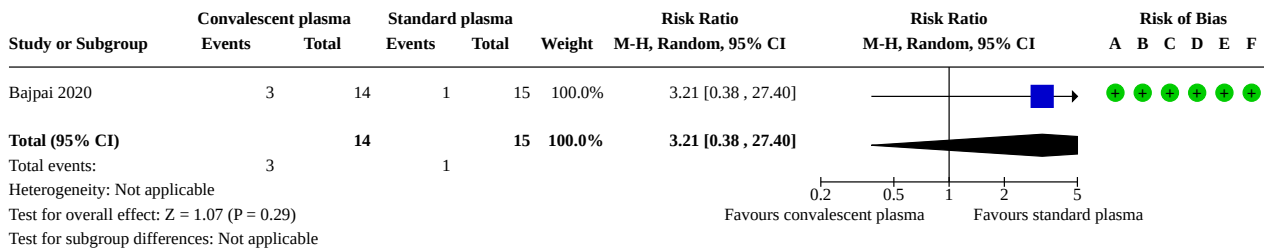
Analysis 2.1. Comparison 2: Convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: All-cause mortality at up to day 28
- (C) Bias due to missing outcome data: All-cause mortality at up to day 28
- (D) Bias in measurement of the outcome: All-cause mortality at up to day 28
- (E) Bias in selection of the reported result: All-cause mortality at up to day 28
- (F) Overall bias: All-cause mortality at up to day 28

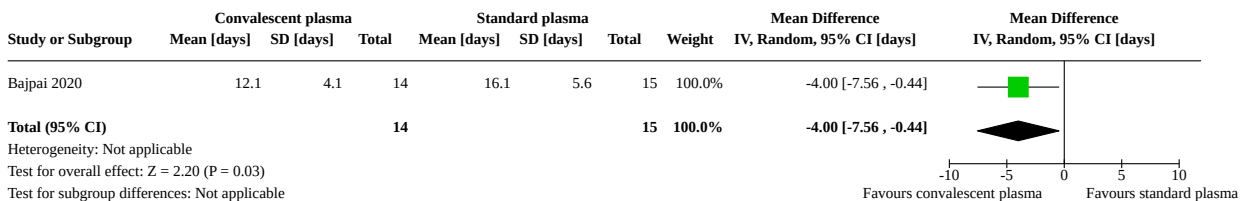
Analysis 2.2. Comparison 2: Convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 2: Clinical worsening: need for invasive mechanical ventilation



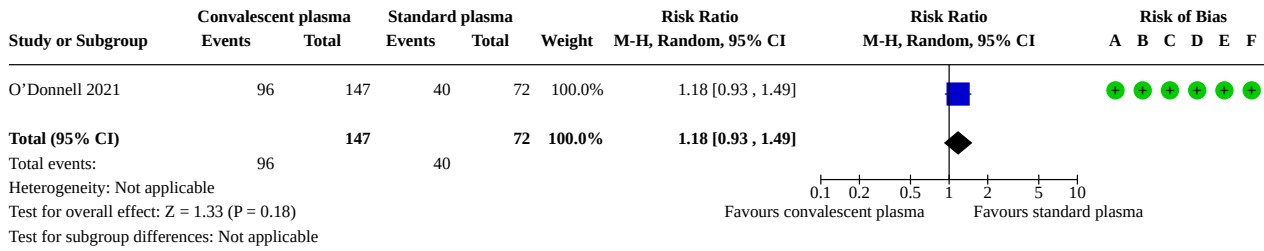
Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: Clinical worsening: need for invasive mechanical ventilation
- (C) Bias due to missing outcome data: Clinical worsening: need for invasive mechanical ventilation
- (D) Bias in measurement of the outcome: Clinical worsening: need for invasive mechanical ventilation
- (E) Bias in selection of the reported result: Clinical worsening: need for invasive mechanical ventilation
- (F) Overall bias: Clinical worsening: need for invasive mechanical ventilation

Analysis 2.3. Comparison 2: Convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 3: Duration of hospitalisation



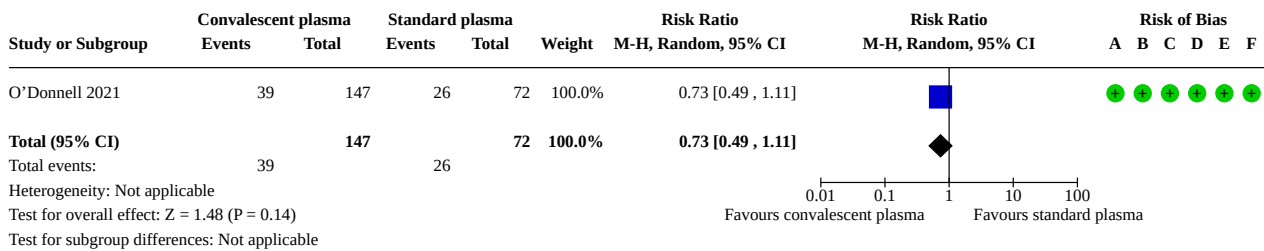
Analysis 2.4. Comparison 2: Convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 4: Any grade adverse events



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: Any grade adverse events
- (C) Bias due to missing outcome data: Any grade adverse events
- (D) Bias in measurement of the outcome: Any grade adverse events
- (E) Bias in selection of the reported result: Any grade adverse events
- (F) Overall bias: Any grade adverse events

Analysis 2.5. Comparison 2: Convalescent plasma versus standard plasma for individuals with moderate to severe disease, Outcome 5: Serious adverse events



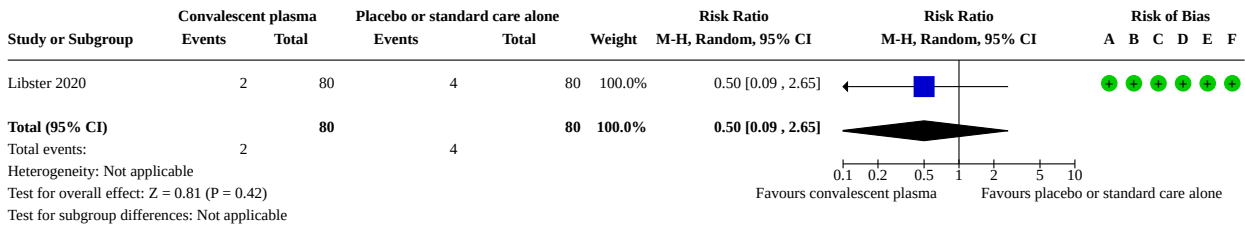
Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: Serious adverse events
- (C) Bias due to missing outcome data: Serious adverse events
- (D) Bias in measurement of the outcome: Serious adverse events
- (E) Bias in selection of the reported result: Serious adverse events
- (F) Overall bias: Serious adverse events

Comparison 3. Convalescent plasma versus placebo or standard care alone for individuals with mild disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality	1	160	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.09, 2.65]
3.2 Development of severe symptoms: need for invasive mechanical ventilation	1	160	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.09, 2.65]
3.3 Admission to the intensive care unit (ICU)	1	160	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.07, 1.60]

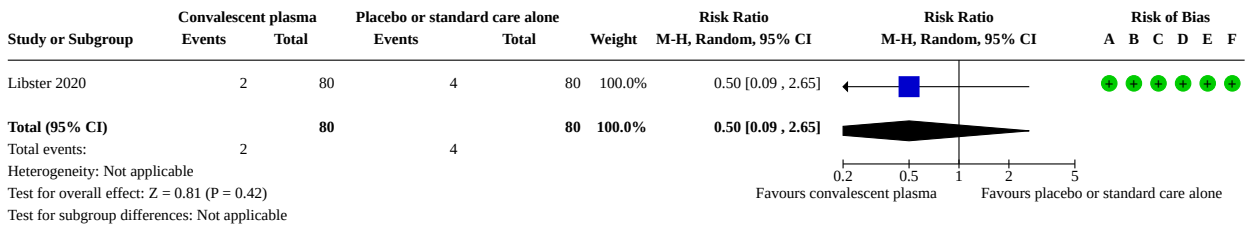
Analysis 3.1. Comparison 3: Convalescent plasma versus placebo or standard care alone for individuals with mild disease, Outcome 1: All-cause mortality



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: All-cause mortality
- (C) Bias due to missing outcome data: All-cause mortality
- (D) Bias in measurement of the outcome: All-cause mortality
- (E) Bias in selection of the reported result: All-cause mortality
- (F) Overall bias: All-cause mortality

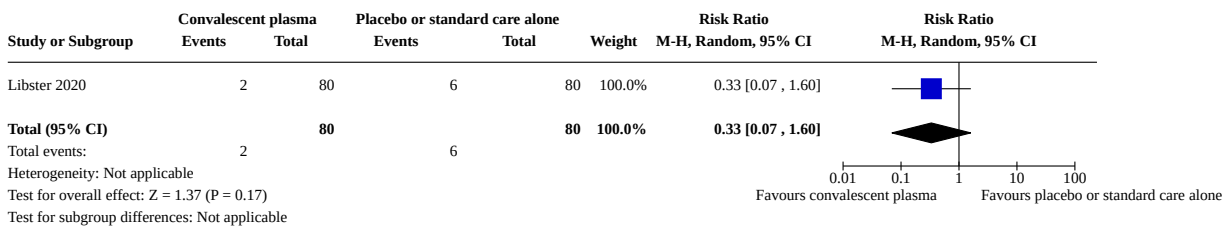
Analysis 3.2. Comparison 3: Convalescent plasma versus placebo or standard care alone for individuals with mild disease, Outcome 2: Development of severe symptoms: need for invasive mechanical ventilation



Risk of bias legend

- (A) Bias arising from the randomization process
- (B) Bias due to deviations from intended interventions: Development of severe symptoms: need for invasive mechanical ventilation
- (C) Bias due to missing outcome data: Development of severe symptoms: need for invasive mechanical ventilation
- (D) Bias in measurement of the outcome: Development of severe symptoms: need for invasive mechanical ventilation
- (E) Bias in selection of the reported result: Development of severe symptoms: need for invasive mechanical ventilation
- (F) Overall bias: Development of severe symptoms: need for invasive mechanical ventilation

Analysis 3.3. Comparison 3: Convalescent plasma versus placebo or standard care alone for individuals with mild disease, Outcome 3: Admission to the intensive care unit (ICU)

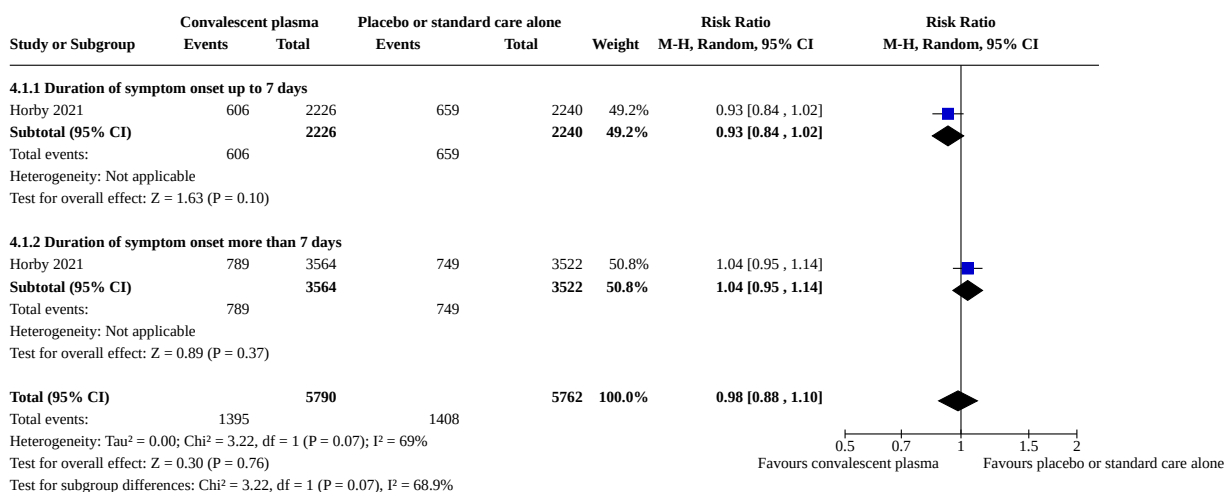


Comparison 4. Subgroup analysis: duration since symptom onset for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All-cause mortality at up to day 28	1	11552	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.1 Duration of symptom onset up to 7 days	1	4466	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.02]
4.1.2 Duration of symptom onset more than 7 days	1	7086	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.95, 1.14]

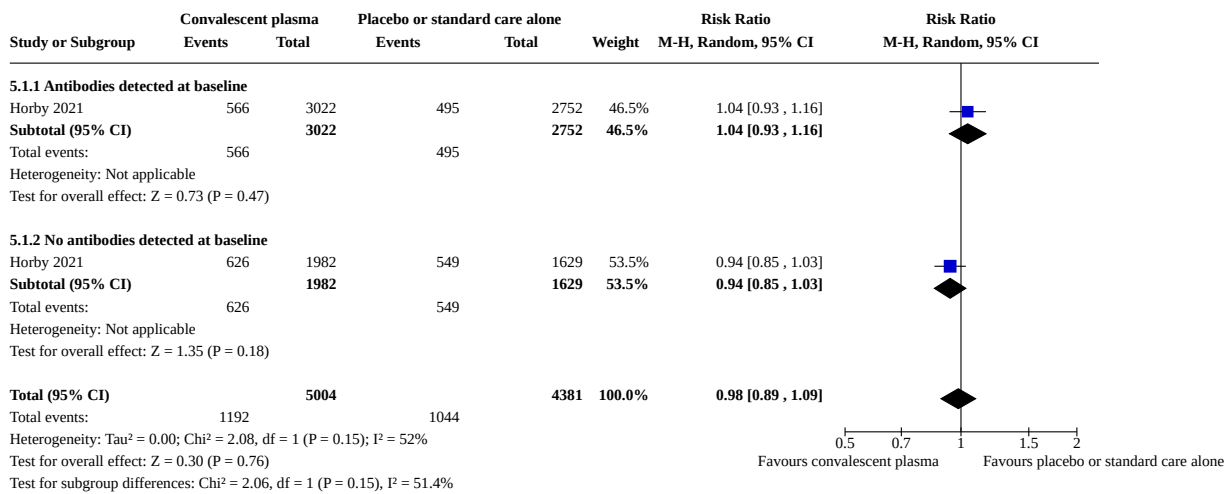
Analysis 4.1. Comparison 4: Subgroup analysis: duration since symptom onset for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28



Comparison 5. Subgroup analysis: antibodies in recipients detected at baseline for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 All-cause mortality at up to day 28	1	9385	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.09]
5.1.1 Antibodies detected at baseline	1	5774	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.93, 1.16]
5.1.2 No antibodies detected at baseline	1	3611	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.85, 1.03]

Analysis 5.1. Comparison 5: Subgroup analysis: antibodies in recipients detected at baseline for the comparison of convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease, Outcome 1: All-cause mortality at up to day 28



ADDITIONAL TABLES

Table 1. Summary of PICO development from protocol stage to current review version

	Publica-tion date	Partici-pants	Interven-tions	Compara-tors	Outcomes	Study de-signs
Protocol	17 April 2020	Inclusion	Inclusion	Inclusion	All criteria based on Core Outcome Measures in Effectiveness Trials (COMET) Initiative for COVID-19 patients (COMET 2020)	Planned inclusion priority, determined by availability of sufficient evidence: 1. Randomised controlled trials (RCTs) 2. Prospective controlled non-randomised studies of interventions (NRSIs), including quasi-randomised controlled trials, controlled before-and-
Piechotta 2020a		<ul style="list-style-type: none"> Individuals with a confirmed diagnosis of COVID-19 No age, gender or ethnicity restrictions 	<ul style="list-style-type: none"> Convalescent plasma Hyperimmune immunoglobulin 	<ul style="list-style-type: none"> Standard care Placebo Control treatment (e.g. drug treatments) 	Primary outcomes <ul style="list-style-type: none"> All-cause mortality at hospital discharge Time to death Secondary outcomes <ul style="list-style-type: none"> Improvement of clinical symptoms, assessed through need for respiratory support: <ul style="list-style-type: none"> Oxygen by mask or nasal prongs Oxygen by non-invasive ventilation (NIV) or high flow Intubation and mechanical ventilation (MV) MV Extracorporeal membrane oxygenation (ECMO) 30-day and 90-day mortality Admission to the intensive care unit Length of stay on the intensive care unit Time to discharge from hospital 	
		Exclusion				
		<ul style="list-style-type: none"> Populations with other coronavirus diseases Populations with mixed virus dis- 				

Table 1. Summary of PICO development from protocol stage to current review version *(Continued)*

		eases, unless the trial authors provide subgroup data for people with COVID-19			<ul style="list-style-type: none"> Number of participants with grade 3 and grade 4 adverse events Number of participants with serious adverse events 	after (CBA) studies, and interrupted time series (ITS) studies 3. Prospective observational studies with a control group 4. Prospective non-comparative study designs (e.g. case series)
Version 1	14 May 2020	<i>see above</i>	Inclusion	<i>see above</i>	All criteria based on COMET Initiative for COVID-19 patients (COMET 2020) Primary outcomes	Inclusion
Valk 2020			<ul style="list-style-type: none"> Convalescent plasma Hyperimmune immunoglobulin 		<ul style="list-style-type: none"> All-cause mortality at hospital discharge Time to death 	<ul style="list-style-type: none"> Prospective non-comparative study designs (e.g. case series)
			Exclusion		Secondary outcomes	No evidence available for
			<ul style="list-style-type: none"> Studies on standard immunoglobulin 		<ul style="list-style-type: none"> Improvement of clinical symptoms, assessed through need for respiratory support: <ul style="list-style-type: none"> Oxygen by mask or nasal prongs Oxygen by NIV or high flow Intubation and mechanical ventilation MV plus high-flow oxygen ECMO 30-day and 90-day mortality Admission to the intensive care unit Length of stay on the intensive care unit Time to discharge from hospital Number of participants with grade 3 and grade 4 adverse events Number of participants with serious adverse events 	<ul style="list-style-type: none"> RCTs NRSIs Prospective observational studies with a control group
Changes^b		None	Added exclusion criteria	None	Revised secondary outcome "Improvement of clinical symptoms, assessed through need for respiratory support":	none
			<ul style="list-style-type: none"> For studies on 		<ul style="list-style-type: none"> added to the fourth bullet point (MV) "plus high-flow oxygen" 	

Table 1. Summary of PICO development from protocol stage to current review version (Continued)

			stan- dard im- munoglob- ulin			
Version 2 Piechotta 2020b	10 July 2020	<i>see above</i>	<i>see above</i>	Inclusion <ul style="list-style-type: none"> • Stan- dard care • Placebo • Control treat- ment (e.g.drug treat- ments, stan- dard im- munoglob- ulin) 	All criteria based on COMET Initiative for COVID-19 patients (COMET 2020) Primary outcomes <ul style="list-style-type: none"> • All-cause mortality at hospital discharge • Time to death Secondary outcomes <ul style="list-style-type: none"> • Improvement of clinical symptoms, assessed through need for respiratory support: <ul style="list-style-type: none"> ◦ Oxygen by mask or nasal prongs ◦ Oxygen by NIV or high flow ◦ Intubation and MV ◦ MV plus high-flow oxygen ◦ ECMO • 30-day and 90-day mortality • Admission to the intensive care unit • Length of stay on the intensive care unit • Time to discharge from hospital • Quality of life • Number of participants with grade 3 and grade 4 adverse events • Number of participants with serious adverse events 	Inclusion <ul style="list-style-type: none"> • RCTs • Prospec- tive con- trolled NRSIs Further inclu- sion <ul style="list-style-type: none"> • Prospec- tive and retrospec- tive con- trolled NRSIs • Safety data of prospec- tive and retrospec- tive non- compara- tive study designs <p>According to originally planned inclu- sion priorities</p>
Changes^b		None	None	Added eligi- ble control treatment: <ul style="list-style-type: none"> • Stan- dard im- munoglob- ulin 	Added a secondary outcome: <ul style="list-style-type: none"> • Quality of life 	Added inclu- sion criteria for safety da- ta: <ul style="list-style-type: none"> • Retrospec- tive con- trolled NRSIs
Version 3 Chai 2020	12 October 2020	<i>see above</i>	<i>see above</i>	<i>see above</i>	All criteria based on COMET Initiative for COVID-19 patients (COMET 2020) Primary outcomes <ul style="list-style-type: none"> • All-cause mortality at hospital discharge • Time to death Secondary outcomes <ul style="list-style-type: none"> • Improvement of clinical symptoms, assessed by need for respiratory 	Inclusion <ul style="list-style-type: none"> • RCTs • Prospec- tive con- trolled NRSIs Further inclu- sion <ul style="list-style-type: none"> • Prospec- tive and

Table 1. Summary of PICO development from protocol stage to current review version (Continued)

				<p>support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f))</p> <ul style="list-style-type: none"> • 30-day and 90-day mortality • Admission to the intensive care unit • Length of stay on the intensive care unit • Time to discharge from hospital • Virological response • Quality of life • Number of participants with grade 3 and grade 4 adverse events • Number of participants with serious adverse events 	<p>retrospective controlled NRSIs</p> <ul style="list-style-type: none"> • Safety data of prospective and retrospective non-comparative study designs <p>According to originally planned inclusion priorities</p> <p>Exclusion</p> <ul style="list-style-type: none"> • Unregistered non-comparative studies (e.g. case series) • Efficacy data of non-comparative studies
Changes^b	None	None	None	<p>Revised and renamed secondary outcome “Improvement of clinical symptoms”</p> <ul style="list-style-type: none"> • Cut-offs are no longer self-set, but now based on standardised scales <p>Added secondary outcome:</p> <ul style="list-style-type: none"> • Virological response 	<p>Added exclusion criteria:</p> <ul style="list-style-type: none"> • Unregistered non-comparative studies (e.g. case series) • Efficacy data of non-comparative studies
Version 4	(Current version)	Inclusion	<i>see above</i>	Inclusion	Inclusion
		<ul style="list-style-type: none"> • Individuals with a confirmed diagnosis of COVID-19 • No age, gender or ethnicity restrictions 		<ul style="list-style-type: none"> • Standard care • Placebo (saline solution) • Control treatment (e.g. drug treatments, <p>All criteria based on COMET Initiative for COVID-19 patients (COMET 2020), and outcomes prioritised by consumer representatives, referees of previous versions of this review, and the German guideline panel for inpatient therapy of people with COVID-19.</p> <p>Individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease <u>Effectiveness of convalescent plasma</u></p> <p><i>Prioritised outcomes</i></p>	<ul style="list-style-type: none"> • RCTs • Prospectively registered single-arm studies with inclusion of 500 or more participants, even if upcoming RCTs report safe-

Table 1. Summary of PICO development from protocol stage to current review version (Continued)

<ul style="list-style-type: none"> • Participants with any disease severity • Separate analyses for populations with ambulatory mild disease and for hospitalised participants with moderate to severe disease^c <p>Exclusion</p> <ul style="list-style-type: none"> • Populations with other coronavirus diseases • Populations with mixed virus diseases, unless the trial authors provide subgroup data for people with COVID-19 	<ul style="list-style-type: none"> • Standard immunoglobulin) • Standard plasma 	<ul style="list-style-type: none"> • All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge • Clinical status at up to day 28, day 60, and up to longest follow-up); including <ul style="list-style-type: none"> ◦ Improvement of clinical status <ul style="list-style-type: none"> ■ Liberation from supplemental oxygen in surviving patients i.e. WHO ≤ 4 on the Clinical Progression Scale (WHO 2020e) (for the subgroup of participants requiring any supplemental oxygen or ventilator support at baseline, i.e. WHO ≥ 5); ■ Weaning or liberation from invasive MV in surviving patients i.e. WHO ≤ 6 (for the subgroup of participants requiring invasive mechanical ventilation at baseline, i.e. WHO ≥ 7); ◦ Worsening of clinical status <ul style="list-style-type: none"> ■ Need for invasive MV i.e. WHO 7-9 (for the subgroup of participants not requiring invasive MV at baseline, i.e. WHO ≤ 6) ■ Need for non-invasive MV or high flow i.e. WHO = 6 (for the subgroup of participants not requiring non-invasive or non-invasive MV, or high flow oxygen at baseline, i.e. WHO ≤ 5); ■ Need for oxygen by mask or nasal prongs i.e. WHO = 5 (for the subgroup of participants not requiring any supplemental oxygen or ventilator support at baseline, i.e. WHO ≤ 4) • 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 <p><i>Additional outcomes</i></p> <ul style="list-style-type: none"> • Duration of hospitalisation, or time to discharge from hospital • Admission to the intensive care unit (ICU) • Length of stay on the ICU, or time to discharge from ICU • Viral clearance at baseline, up to 3, 7, and 15 days • Need for dialysis <p><u>Safety of convalescent plasma</u></p> <ul style="list-style-type: none"> • Adverse events (any grade, grade 1-2, grade 3-4) 	ty for both groups
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Table 1. Summary of PICO development from protocol stage to current review version (Continued)

- Serious adverse events

Individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease
Effectiveness of convalescent plasma
Prioritised outcomes

- All-cause mortality at day 28, day 60, time-to-event, and at longest follow-up.
- Development of moderate to severe clinical COVID-19 symptoms, defined as WHO Clinical Progression Scale ≥ 4 (WHO 2020e), up to longest follow-up
 - Need for invasive MV, non-invasive MV or high flow i.e. WHO ≥ 6 , severe disease;
 - Need for invasive MV i.e. WHO 7-9;
 - Need for non-invasive mechanical ventilation or high flow i.e. WHO = 6.
 - Need for hospitalisation with or without supplemental oxygen i.e. WHO = 4-5, moderate disease;
 - Need for oxygen by mask or nasal prongs i.e. WHO = 5;
 - Need for hospitalisation without oxygen therapy i.e. WHO = 4.
- Quality of life at up to 7 days, up to 30 days, and longest follow-up available

Additional outcomes

- Admission to hospital
- Time to symptom onset
- Length of hospital stay, for subgroup of participants hospitalised during course of disease
- Admission to the ICU
- Viral clearance at baseline, up to 3, 7, and 15 days

Safety of convalescent plasma

- Adverse events (any grade, grade 1-2, grade 3-4)
- Serious adverse events

Changes ^b	Introduced separate populations ^c	None	Added eligible control treatment	Changed primary and secondary outcomes to prioritised (included in 'Summary of findings' table) and additional outcomes (not included in 'Summary of findings' table).	Added inclusion criteria:
	<ul style="list-style-type: none"> • Individuals with a 		<ul style="list-style-type: none"> • Standard plasma 	Revised and specified outcomes per population.	<ul style="list-style-type: none"> • For prospectively registered single-arm studies

Table 1. Summary of PICO development from protocol stage to current review version (Continued)

con- firmed diagno- sis of COV- ID-19and moder- ate to se- vere dis- ease <ul style="list-style-type: none"> Individuals with with con- firmed diagno- sis of SARS- CoV-2 in- fection and asymp- tomatic or mild disease	Added specifica- tions on placebo treatment <ul style="list-style-type: none"> Saline solution 	Individuals with moderate to severe dis- ease <ul style="list-style-type: none"> Outcome measures for all-cause mor- tality were summarised below one outcome Sub-outcomes for clinical improve- ment, and clinical worsening were in- troduced 'Need for dialysis' was added as addi- tional outcome 'Time to discharge from hospital' was renamed to 'duration of hospitalisa- tion, or time to discharge from hospi- tal' to clarify that we are interest- ed in both, continuous and time-to- event data. 'Virological response' was renamed to 'viral clearance' to clarify that we are interested in test-negativity and not in changes of viral load. Added outcomes for individuals with asymptomatic or mild disease	with inclu- sion of 500 or more partici- pants, even if upcom- ing RCTs re- port safe- ty data for both groups Added exclu- sion criteria <ul style="list-style-type: none"> Controlled studies not being truly randomised Studies comparing early ver- sus de- ferred plas- ma Studies on plasma donors Pharmaco- kinetics studies Studies ter- minated early be- cause the sponsor was changed
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^aIncluding changes in study designs and methodology.

^bChanges in PICO compared to the previously published version.

^cAccording to the latest WHO clinical progression score (WHO 2020e).

Abbreviations: CBA: controlled before-and-after; COMET: Core Outcome Measures in Effectiveness Trials; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; MV: mechanical ventilation; NIV: non-invasive ventilation; ITS: interrupted time series; NRSI: non-randomised studies of interventions; RCT: randomised controlled trial; WHO: World Health Organization; WHOQOL-100: WHO Quality of Life scale.

Table 2. WHO clinical progression scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild dis- ease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2

Table 2. WHO clinical progression scale (Continued)

	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy ^a	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe disease	Hospitalised; oxygen by non-invasive mechanical ventilation or high flow	6
	Intubation and mechanical ventilation; $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Invasive mechanical ventilation; $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vaso-pressors	8
	Invasive mechanical ventilation; $pO_2/FiO_2 < 150$ and vasopressors, dialysis or ECMO	9
Dead	Dead	10

World Health Organization (WHO) clinical progression scale from: [WHO 2020e](#)

^aIf hospitalised for isolation only, record status as for ambulatory patient.

Abbreviations: ECMO: extracorporeal membrane oxygenation; FiO_2 : fraction of inspired oxygen; pO_2 : partial pressure of oxygen; SpO_2 : oxygen saturation

Table 3. 'Risk of bias' assessment criteria for observational studies

Heading	Internal validity	External validity
Study group	Selection bias (representative: yes/no) <ul style="list-style-type: none"> if the described study group consisted of > 80% of individuals with COVID-19 treated with convalescent plasma therapy or hyperimmune globulin in the original cohort or <ul style="list-style-type: none"> if it was a random sample with respect to the treatment and important prognostic factors 	Reporting bias (well defined: yes/no) <ul style="list-style-type: none"> if the study population was well described (e.g. severity of disease, age, risk factors) and <ul style="list-style-type: none"> the intervention was well described (e.g. number of doses, volume)
Follow-up	Attrition bias (adequate: yes/no) <ul style="list-style-type: none"> if the outcome was assessed for > 90% of the study group of interest (++) or <ul style="list-style-type: none"> if the outcome was assessed for 60% to 90% of the study group of interest (+) 	Reporting bias (well defined: yes/no) <ul style="list-style-type: none"> if the length of follow-up was mentioned
Outcome	Detection bias (blind: yes/no) <ul style="list-style-type: none"> if the outcome assessors were blinded to the investigated determinant 	Reporting bias (well defined: yes/no) <ul style="list-style-type: none"> if the outcome definition was objective and precise, and the method of detection was provided
Risk estimation	Confounding (adjustment for other factors: yes/no)	Analyses (well defined: yes/no)

Table 3. 'Risk of bias' assessment criteria for observational studies *(Continued)*

- if important prognostic factors (i.e. age, co-treatment, comorbidities) or follow-up were taken adequately into account
- if a risk ratio, odds ratio, attributable risk, linear or logistic regression model, mean difference or Chi² statistic was calculated

Table 4. Summary of ongoing hyperimmune immunoglobulin studies: design and planned completion date

Study ID	Title	Link	Design	Planned number of participants	Planned completion date	Results available	Other study ID
IRC-T20200508047346	Evaluation of the efficacy and safety of rabbit polyclonal antibody (CoviGlobulin) in patients with coronavirus COVID-19 virus moderate to severe	en.irct.ir/trial/47953	RCT	124	NR	No	
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	No	
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	No	
NCT04453384	A randomized, double-blind, placebo-controlled phase 2a and 2b study to evaluate the safety and efficacy of XAV-19 in patients with COVID-19 induced moderate pneumonia	www.clinicaltrialsregister.eu/ctr-search/trial/2020-002574-27/FR clinicaltrials.gov/ct2/show/NCT04453384	RCT	414	31 December 2021	No	EUC-TR2020-002574-27
NCT04468958	Safety, tolerability, and pharmacokinetics of SAB-185 in healthy participants	clinicaltrials.gov/ct2/show/NCT04468958	RCT	28	23 February 2021	No	SAB-185-101
NCT04469179	Safety, tolerability, and pharmacokinetics of SAB-185 in ambulatory participants with COVID-19	clinicaltrials.gov/ct2/show/NCT04469179	RCT	21	31 December 2021	No	SAB-185-102
NCT04514302	Safety and efficacy of anti-SARS-CoV-2 equine antibody fragments (INOSARS) for hospitalized patients with COVID-19	clinicaltrials.gov/ct2/show/NCT04514302	RCT	51	20 June 2021	No	
NCT04546581	Inpatient treatment with anti-coronavirus immunoglobulin (ITAC)	clinicaltrials.gov/ct2/show/NCT04546581	RCT	500	30 July 2021	No	EUC-TR2020-002542-16

Table 4. Summary of ongoing hyperimmune immunoglobulin studies: design and planned completion date (Continued)

NCT04555148	COVIDIG (COVID-19 Hyper-ImmunoGlobulin)	clinicaltrials.gov/show/NCT04555148	RCT	60	30 August 2021	No	KCT0005649
NCT04573855	Treatment with anti-SARS-CoV-2 immunoglobulin in patients with COVID-19	clinicaltrials.gov/show/NCT04573855	RCT	41	31 March 2021	No	

NR: not reported; RCT: randomised controlled trial

Table 5. Summary of ongoing convalescent plasma studies: design and planned completion date

Study ID	Title	Link	Design	Planned number of participants	Planned completion date	Results available	Other study ID
ChiC-TR2000030010	A randomized, double-blind, parallel-controlled, trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia patients (COVID-19)	www.chic-tr.org.cn/showproj.aspx?proj=49777	RCT	100	31 May 2020	no	
ChiC-TR2000030179	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19)	www.chic-tr.org.cn/showproj.aspx?proj=50059	RCT	100	24 April 2020	no	
ChiC-TR2000030627	Study on the application of convalescent plasma therapy in severe COVID-19	www.chic-tr.org.cn/showproj.aspx?proj=50727	RCT	30	30 May 2020	no	
ChiC-TR2000030702	Convalescent plasma for the treatment of common COVID-19: a prospective randomized controlled trial	www.chic-tr.org.cn/showproj.aspx?proj=50537	RCT	30	15 August 2020	no	
ChiC-TR2000030929	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	www.chic-tr.org.cn/showproj.aspx?proj=50696	RCT	30	16 June 2020	no	

Table 5. Summary of ongoing convalescent plasma studies: design and planned completion date (Continued)

CTRI/2020/04/024944	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma to limit COVID-19 associated complications	www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43332	RCT	100	9 May 2021	no	
CTRI/2020/05/025444	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma in severe COVID-19 patients	www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=43005	RCT	90	1 June 2022	no	
CTRI/2020/06/025444	Effect of convalescent plasma in COVID-19 patients	www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=44478	RCT	400	18 June 2021	no	
CTRI/2020/06/026667	Plasma therapy in corona patients (severe COVID-19)	www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=44667	RCT	472	25 December 2020	no	
EUC-TR2020-001632-10	A randomized open label phase-II clinical trial with or without infusion of plasma from subjects after convalescence of SARS-CoV-2 infection in high-risk patients with confirmed severe SARS-CoV-2 disease	www.clinicaltrialsregister.eu/ctr-search/trial/2020-001632-10/DE	RCT	174	NR	no	NCT04433910
EUC-TR2020-001936-86	A prospective, randomized, open label phase 2 clinical trial to evaluate superiority of anti-SARS-CoV-2 convalescent plasma versus standard-of-care in hospitalized patients with mild COVID-19	www.clinicaltrialsregister.eu/ctr-search/trial/2020-001936-86/DE	RCT	340	NR	no	
EUC-TR2020-002122-82	Prospective open-label randomized controlled phase 2b clinical study in parallel groups for the assessment of efficacy and safety of immune therapy with COVID-19 convalescent plasma plus standard treatment vs. standard treatment alone of subjects with severe COVID-19	www.clinicaltrialsregister.eu/ctr-search/trial/2020-002122-82/DE	RCT	58	NR	no	
EUC-TR2020-005410-18	Multicentre, randomized, double-blind, placebo-controlled, non-commercial clinical trial to evaluate the efficacy and safety of specific anti-SARS-CoV-2 immunoglobulin in the treatment of COVID-19	www.clinicaltrialsregister.eu/ctr-search/trial/2020-005410-18/PL	RCT	480	NR	no	

Table 5. Summary of ongoing convalescent plasma studies: design and planned completion date (Continued)

IRC-T20200501047258	Investigation of the effects of COVID-19 convalescent plasma in acute respiratory distress syndrome due to COVID-19	en.irct.ir/trial/47629	RCT	120	NR	no	
NCT02735707	Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP)	clinicaltrials.gov/ct2/show/NCT02735707	RCT	7100	December 2023	no	
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	no	
NCT04338360	Expanded access to convalescent plasma for the treatment of patients with COVID-19	clinicaltrials.gov/show/NCT04338360	expanded access	NR	NR	no	
NCT04345289	Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia (CCAP)	clinicaltrials.gov/show/NCT04345289	RCT	1500	15 June 2021	no	EUC-TR2020-001367-88
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	no	
NCT04348656	Convalescent plasma for hospitalized adults with COVID-19 respiratory illness (CONCOR-1)	clinicaltrials.gov/show/NCT04348656	RCT	1200	31 December 2020	no	
NCT04352751	Experimental use of convalescent plasma for passive immunization in current COVID-19 pandemic in Pakistan in 2020	clinicaltrials.gov/show/NCT04352751	non-RCT, single	2000	April 2021	no	
NCT04358783	Convalescent plasma compared to the best available therapy for the treatment of SARS-CoV-2 pneumonia	clinicaltrials.gov/show/NCT04358783	RCT	30	30 May 2021	no	

Table 5. Summary of ongoing convalescent plasma studies: design and planned completion date (Continued)

NCT04360486	Treatment of COVID-19 with anti-SARS-CoV-2 convalescent plasma (ASCoV2CP)	clinicaltrials.gov/show/NCT04360486	expanded access	NR	NR	no
NCT04361253	Evaluation of SARS-CoV-2 (COVID-19) antibody-containing plasma therapy	clinicaltrials.gov/show/NCT04361253	RCT	220	December 2021	no
NCT04362176	Passive Immunity Trial for Our Nation to Treat COVID-19 in Hospitalized Adults (PassItOn)	clinicaltrials.gov/show/NCT04362176	RCT	1000	April 2021	
NCT04363034	Arkansas expanded access COVID-19 convalescent plasma treatment program	clinicaltrials.gov/ct2/show/NCT04363034	expanded access	NR	NR	no
NCT04364737	Convalescent plasma to limit COVID-19 complications in hospitalized patients	clinicaltrials.gov/show/NCT04364737	RCT	1000	30 April 2023	no
NCT04372979	Efficacy of convalescent plasma therapy in the early care of COVID-19 patients	clinicaltrials.gov/show/NCT04372979	RCT	80	May 2021	no
NCT04373460	Convalescent plasma to limit SARS-CoV-2 associated complications	clinicaltrials.gov/show/NCT04373460	RCT	1344	31 January 2023	no
NCT04374370	SARS-CoV-2 (COVID-19) convalescent plasma (CP) expanded access protocol (EAP)	clinicaltrials.gov/show/NCT04374370	expanded access	NR	NR	no
NCT04374487	A phase II, open label, randomized controlled trial to assess the safety and efficacy of convalescent plasma to limit COVID-19 associated complications	clinicaltrials.gov/show/NCT04374487	RCT	100	9 May 2021	no
NCT04374526	Early transfusion of convalescent plasma in elderly COVID-19 patients to prevent disease progression	clinicaltrials.gov/show/NCT04374526	RCT	182	30 June 2021	no

Table 5. Summary of ongoing convalescent plasma studies: design and planned completion date *(Continued)*

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	no
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	no
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	no
NCT04385043	Hyperimmune plasma in patients with COVID-19 severe infection	clinicaltrials.gov/show/NCT04385043	RCT	400	15 May 2021	no
NCT04385186	Inactivated convalescent plasma as a therapeutic alternative in patients CoVID-19	clinicaltrials.gov/show/NCT04385186	RCT	60	30 November 2020	no
NCT04385199	Convalescent plasma for patients with COVID-19	clinicaltrials.gov/show/NCT04385199	RCT	30	1 August 2020	no
NCT04388410	Safety and efficacy of convalescent plasma transfusion for patients with SARS-CoV-2 infection	clinicaltrials.gov/show/NCT04388410	RCT	410	31 December 2020	no
NCT04390503	Convalescent plasma for COVID-19 close contacts	clinicaltrials.gov/ct2/show/NCT04390503	RCT	150	1 April 2021	no
NCT04391101	Convalescent plasma for the treatment of severe SARS-CoV-2 (COVID-19)	clinicaltrials.gov/show/NCT04391101	RCT	231	31 December 2021	no
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	no

Table 5. Summary of ongoing convalescent plasma studies: design and planned completion date (Continued)

NCT04403477	Convalescent plasma therapy in severe COVID-19 infection	clinicaltrials.gov/show/NCT04403477	RCT	20	30 October 2020	no
NCT04408040	Use of convalescent plasma for COVID-19	clinicaltrials.gov/show/NCT04408040	non-RCT, single	700	1 June 2022	no
NCT04415086	Treatment of patients with COVID-19 with convalescent plasma	clinicaltrials.gov/show/NCT04415086	RCT	120	22 May 2022	no
NCT04418518	A trial of convalescent plasma for hospitalized adults with acute COVID-19 respiratory illness	clinicaltrials.gov/show/NCT04418518	RCT	1200	31 December 2021	no
NCT04420988	Investigational COVID-19 convalescent plasma infusion for severely or life-threateningly ill COVID-19 patients	clinicaltrials.gov/show/NCT04420988	expanded access	NR	NR	no
NCT04421404	Effects of COVID-19 convalescent plasma (CCP) on coronavirus-associated complications in hospitalized patients	clinicaltrials.gov/show/NCT04421404	RCT	50	30 April 2021	no
NCT04425837	Effectiveness and safety of convalescent plasma in patients with high-risk COVID-19	clinicaltrials.gov/show/NCT04425837	RCT	236	28 February 2021	no
NCT04425915	Efficacy of convalescent plasma therapy in patients with COVID-19	clinicaltrials.gov/show/NCT04425915	RCT	400	31 May 2021	no
NCT04428021	Standard or convalescent plasma in patients with recent onset of COVID-19 respiratory failure	clinicaltrials.gov/show/NCT04428021	RCT	180	15 December 2021	no
NCT04429854	Donated antibodies working against nCoV	clinicaltrials.gov/show/NCT04429854	RCT	483	2 November 2021	no
NCT04432272	Antibody level-based analysis of COVID-19 convalescent serum (ABACCuS)	clinicaltrials.gov/show/NCT04432272	non-RCT	500	June 2021	no

Table 5. Summary of ongoing convalescent plasma studies: design and planned completion date (Continued)

NCT04438057	Evaluating the efficacy of convalescent plasma in symptomatic outpatients infected with COVID-19	clinicaltrials.gov/ct2/show/NCT04438057	RCT	150	6 July 2021	no	
NCT04442191	Convalescent plasma as a possible treatment for COVID-19	clinicaltrials.gov/show/NCT04442191	RCT	50	31 May 2021	no	
NCT04445207	Experimental expanded access treatment with convalescent plasma for the treatment of patients with COVID-19	clinicaltrials.gov/ct2/show/NCT04445207	expanded access	NR	NR	no	
NCT04452812	Statistical and epidemiological study based on the use of convalescent plasma for the management of patients with COVID-19	clinicaltrials.gov/ct2/show/NCT04452812	RCT	15	1 April 2021	no	
NCT04456413	Convalescent plasma as treatment for subjects with early COVID-19 infection	clinicaltrials.gov/show/NCT04456413	RCT	306	31 July 2021	no	
NCT04463823	"NORPLASMA" COVID-19 convalescent plasma treatment monitoring study	clinicaltrials.gov/ct2/show/NCT04463823	non-RCT, single	500	31 May 2022	no	
NCT04468009	Treatment of critically ill patients with COVID-19 with convalescent plasma	clinicaltrials.gov/ct2/show/NCT04468009	RCT	36	30 June 2021	no	
NCT04472572	Expanded access to convalescent plasma for treatment of COVID-19	clinicaltrials.gov/show/NCT04472572	expanded access	NR	NR	no	
NCT04483960	Australasian COVID-19 trial (ASCOT)	clinicaltrials.gov/ct2/show/NCT04483960	RCT	2400	12 July 2022	no	AC-TRN12620000445976
NCT04497324	Peruconplasma: evaluating the use of convalescent plasma as management of COVID-19	clinicaltrials.gov/ct2/show/NCT04497324	RCT	100	30 April 2021	no	PER-016-20
NCT04497779	Analysis of coronavirus disease 19 (COVID-19) convalescent plasma	clinicaltrials.gov/show/NCT04497779	non-RCT, single	800	21 August 2021	no	

Table 5. Summary of ongoing convalescent plasma studies: design and planned completion date (Continued)

NCT04516811	Therapeutic use of convalescent plasma in the treatment of patients with moderate to severe COVID-19	clinicaltrials.gov/ct2/show/NCT04516811	RCT	600	31 July 2022	no
NCT04521036	Convalescent plasma for COVID-19 patients (CPCP)	clinicaltrials.gov/show/NCT04521036	RCT	44	30 October 2021	no
NCT04524507	COVID-19 antibody plasma research study in hospitalized patients	clinicaltrials.gov/ct2/show/NCT04524507	RCT	56	30 May 2021	no
NCT04528368	Convalescent plasma for treating patients with COVID-19 pneumonia without indication of ventilatory support	clinicaltrials.gov/ct2/show/NCT04528368	RCT	60	31 December 2020	no
NCT04539275	COVID-19 (VA CURES-1)	clinicaltrials.gov/show/NCT04539275	RCT	702	30 June 2022	no
NCT04542967	Study on the safety and efficacy of convalescent plasma in patients with severe COVID-19 disease	clinicaltrials.gov/ct2/show/NCT04542967	RCT	150	30 September 2020	no
NCT04545047	Observational study of convalescent plasma for treatment of veterans with COVID-19	clinicaltrials.gov/ct2/show/NCT04545047	non-RCT, controlled	4000	30 June 2022	no
NCT04558476	Efficacy of convalescent plasma in patients with COVID-19 treated with mechanical ventilation	clinicaltrials.gov/ct2/show/NCT04558476	RCT	500	30 September 2022	no
NCT04567173	Convalescent plasma as adjunctive therapy for hospitalized patients with COVID-19	clinicaltrials.gov/show/NCT04567173	RCT	136	30 June 2021	no
NCT04589949	Early convalescent plasma therapy for high-risk patients with COVID-19 in primary care (the CoV-early study)	clinicaltrials.gov/show/NCT04589949	RCT	690	1 November 2023	no
NCT04600440	Convalescent plasma in the treatment of COVID-19	clinicaltrials.gov/show/NCT04600440	RCT	100	28 February 2022	no

Table 5. Summary of ongoing convalescent plasma studies: design and planned completion date (Continued)

NCT04621123	Plasma for early treatment in non-hospitalised mild or moderate COVID-19 patients	clinicaltrials.gov/show/NCT04621123	RCT	474	1 October 2021	no	
NCT04634422	Plasma exchange (PLEX) and convalescent plasma (CCP) in COVID-19 patients with multiorgan failure (COVID-PLEX)	clinicaltrials.gov/ct2/show/NCT04634422	RCT	220	30 June 2021	no	
NCT04642014	Application of convalescent plasma in the treatment of SARS CoV-2 disease (COVID-19) with evaluation of therapy effectiveness (EPIC-19)	clinicaltrials.gov/ct2/show/NCT04642014	single-arm study	500	21 February 2022	no	
NCT04649879	Convalescent plasma for treatment of COVID-19: an open randomised controlled trial	clinicaltrials.gov/ct2/show/NCT04649879	RCT	920	1 February 2022	no	
NCT04669990	Remdesivir and convalescent plasma therapy for treatment of COVID-19 infection in Nepal: a registry study	clinicaltrials.gov/ct2/show/NCT04669990	non-RCT, single (registry)	2000	31 October 2021	no	749-2020
NCT04681430	Reconvalescent plasma/camostat mesylate early in SARS-CoV-2 Q-PCR (COVID-19) positive high-risk individuals (RES-Q-HR)	clinicaltrials.gov/ct2/show/NCT04681430	RCT	1094	1 November 2021	no	EUC-TR2020-004695-18
NCT04712344	Assessment of efficacy and safety of therapy with COVID-19 convalescent plasma in subjects with severe COVID-19 (IPCO) (IPCO)	clinicaltrials.gov/ct2/show/NCT04712344	RCT	58	30 September 21	no	
NCT04716556	Transfusion of convalescent plasma for the early treatment of pneumonia in COVID-19 patients	clinicaltrials.gov/ct2/show/NCT04716556	RCT	474	1 May 2021	no	TSUNAMI
NCT04730401	Convalescent plasma in the treatment of COVID-19 (CP_COVID-19)	clinicaltrials.gov/ct2/show/NCT04730401	RCT	390	31 December 2021	no	
NL8633	A randomized, double blinded clinical trial of convalescent plasma compared to standard plasma for treatment of hospitalized non-ICU patients with COVID-19 infections	www.trialregister.nl/trial/8633	RCT	430	1 May 2021	no	

Table 5. Summary of ongoing convalescent plasma studies: design and planned completion date (Continued)

PACTR2020067601	Lagos COVID-19 convalescent plasma trial (LACCPT)	pactr.samr-c.ac.za/TrialDisplay.aspx?TriallID=12168	RCT	100	30 November 2020	no
PACTR2020076539	A clinical trial comparing use of convalescent plasma therapy plus standard treatment to standard treatment alone in patients with severe COVID-19 infection	pactr.samr-c.ac.za/TrialDisplay.aspx?TriallID=11047	RCT	206	31 December 2021	no
PER-013-20	Convalescent plasma as treatment for COVID-19	www.ins.gob.pe/en-sayosclnicos/rpec/recuperarECPB-NuevoEN.asp?numec=013-20	RCT	192	30 June 2021	no
PER-060-20	Randomized phase 2 clinical trial to evaluate safety and efficacy of the use of plasma from convalescent plasma with the Coronavirus disease (COVID-19) for the experimental treatment of patients hospitalized in the Centro Médico Naval "Cirujano Mayor Santiago Távara"	www.ins.gob.pe/en-sayosclnicos/rpec/recuperarECPB-NuevoEN.asp?numec=060-20	RCT	100	7 March 2021	no
RBR-7jqpnw	Effect of COVID-19 convalescent plasma produced by HEMOPE: a randomized study, with a comparative group in several centers	www.ensaiosclnicos.gov.br/rg/RBR-7jqpnw/	RCT	110	30 July 2021	no

Table 6. Sensitivity analyses for the comparison of convalescent plasma versus placebo or standard care alone for the population of individuals with moderate to severe disease

Outcome	Main analysis	RoB (excluding studies ^a at high RoB)	Publication status (excluding preprints ^b)	Study termination (excluding premature termination studies ^c)
All-cause mortality at up to day 28	RR 0.98 (95% CI 0.92 to 1.05); including 12,646 participants from 7 studies	RR 0.98 (95% CI 0.92 to 1.05); including 12,646 participants from 7 studies	RR 0.95 (95% CI 0.68 to 1.34); including 887 participants from 3 studies ^b	RR 0.99 (95% CI 0.93 to 1.05); including 12,464 participants from 5 studies ^c
Clinical improvement: liberation from supplemental oxygen (for the subgroup of participants requiring any supplemental oxygen or ventilator support at baseline, i.e. WHO \geq 5)	RR 1.10 (95% CI 0.81 to 1.48); including 77 participants from 1 study	RR 1.10 (95% CI 0.81 to 1.48); including 77 participants from 1 study	/ ^b	/ ^c
Clinical improvement: liberation from invasive mechanical ventilation (for the subgroup of participants requiring invasive mechanical ventilation at baseline, i.e. WHO \geq 7)	RR 1.04 (95% CI 0.57 to 1.93); including 630 participants from 2 studies	RR 1.04 (95% CI 0.57 to 1.93); including 630 participants from 2 studies	/ ^b	RR 0.81 (95% CI 0.64 to 1.02); including 617 participants from 1 study
Clinical worsening: need for invasive mechanical ventilation (for the subgroup of participants not requiring invasive mechanical ventilation at baseline, i.e. WHO \leq 6)	RR 0.98 (95% CI 0.89 to 1.08); including 11,765 participants from 4 studies	RR 0.98 (95% CI 0.89 to 1.08); including 11,765 participants from 4 studies	RR 1.11 (95% CI 0.79 to 1.56); including 784 participants from 2 studies ^b	RR 0.98 (95% CI 0.89 to 1.08); including 11,765 participants from 4 studies
Quality of life	NR	NR	NR	NR
Grade 3 or 4 adverse events	RR 0.90 (95% CI 0.58 to 1.41); including 905 participants from 4 studies	RR 0.90 (95% CI 0.58 to 1.41); including 905 participants from 4 studies	RR 0.88 (95% CI 0.55 to 1.41); including 784 participants from 2 studies ^b	RR 0.88 (95% CI 0.55 to 1.41); including 824 participants from 3 studies ^c
Serious adverse events	RR 1.24 (95% CI 0.81 to 1.90); including 414 participants from 2 studies	RR 1.24 (95% CI 0.81 to 1.90); including 414 participants from 2 studies	RR 1.31 (95% CI 0.82 to 2.09); including 333 participants from 1 study ^b	RR 1.31 (95% CI 0.82 to 2.90); including 333 participants from 1 study ^c

^aExcluded studies with high risk of bias (RoB): no study.

^bExcluded preprints: [AlQahtani 2020](#); [Avendano-Sola 2020](#); [Gharbharan 2020](#); [Horby 2021](#); [Ray 2020](#)

^cExcluded studies with premature termination: [Gharbharan 2020](#); [Li 2020](#); [Avendano-Sola 2020](#)

Abbreviations: CI: confidence interval; NR: not reported; RoB: risk of bias; RR: risk ratio; WHO: World Health Organization.

Table 7. Overview of clinical status and progression of disease

Study ID (sample size analysed)	Disease and ventilation status at baseline	Study outcomes (time point, definition)	Reported outcome data
Convalescent plasma (CP) versus placebo or standard care alone for individuals with moderate to severe disease			
Agarwal 2020	<p>Individuals with moderate illness with partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO₂/FiO₂) ratio between 200 mmHg and 300 mmHg or a respiratory rate of more than 24/min with oxygen saturation 93% or less on room air) were included. (According to WHO clinical progression scale: level 4 and 5)</p> <p>Critically ill individuals with PaO₂/FiO₂ < 200 mmHg were excluded</p>	<ol style="list-style-type: none"> 1. Progression to severe disease (PaO₂/FiO₂ ratio < 100 mmHg) or all-cause mortality at any time within 28 days of enrolment 2. Symptom resolution on day 7 3. Oxygen requirement after plasma transfusion, measured as variation in fraction of inspired oxygen on days 1, 3, 5, 7, and 14 4. Post-enrolment duration of respiratory support until day 28 or discharge (respiratory support not further defined) 5. Proportion of participants requiring invasive ventilation post-enrolment 6. Proportion of participants requiring non-invasive ventilation post-enrolment 7. Sequential organ failure assessment score over days 0, 3, and 7 8. Clinical improvement on the WHO ordinal scale on days 0, 1, 3, 5, 7, 14, and 28 	<ol style="list-style-type: none"> 1. Progression to severe disease or death at up to day 28: 44 (19%) participants in the intervention arm and 41 (18%) in the control arm (RR 1.04, 95% CI 0.71 to 1.54) <ol style="list-style-type: none"> a. Progression to severe disease: 17/235 in CP group versus 17/229 in the control group (RR 1.04, 95% CI 0.54 to 1.98) 2. Resolution of symptoms on day 7: <ol style="list-style-type: none"> a. Shortness of breath: 140/183 versus 119/181 (RR 1.16, 95% CI 1.02 to 1.32) b. Fever: 66/67 versus 65/71 (RR 1.08, 95% CI 0.99 to 1.16) c. Cough: 102/127 versus 111/147 (RR 1.06, 95% CI 0.94 to 1.2) d. Fatigue: 114/156 versus 92/153 (RR 1.21, 95% CI 1.02 to 1.42) 3. Oxygen requirements: no difference in average fraction of inspired oxygen over 14 days of hospital stay ($\beta = -0.1$, 95% CI -25 to 2.3) 4. Median duration of respiratory support post enrolment: 9 days (IQR 6 to 13) in CP group versus 10 days (6 to 13) in control group 5. Need for invasive mechanical ventilation (included in Analysis 2.2) 6. Need for non-invasive mechanical ventilation: 31/227 versus 37/224 (RR 0.8, 95% CI 0.5 to 1.3) 7. Median scores on the sequential organ failure assessment: no difference on day 0 (2, IQR 2 to 3), day 3 (2, IQR 1 to 2) and day 7 (1, IQR to 2) 8. WHO ordinal scale scores for clinical improvement did not differ between the tri-

Table 7. Overview of clinical status and progression of disease (Continued)

			al arms at any observation point
<p>AlQahtani 2020</p>	<p>Individuals with moderate illness, with PaO₂/FiO₂ ratio of 300 or less, or an oxygen saturation of less than or equal 92% on air, or PaO₂ < 60 mmHg in arterial blood gas, requiring oxygen therapy and having radiological evidence of pneumonia were included. (According to WHO clinical progression scale: level 5-6, as</p> <p>19/20 in CP group and 17/20 in control group received oxygen via nasal cannula or face mask at baseline and 1/20 in CP group and 3/20 in control group received oxygen via nonrebreather mask or high flow nasal cannula)</p> <p>Individuals not requiring oxygen therapy and individuals requiring ventilatory support (invasive or non-invasive) were excluded.</p>	<ol style="list-style-type: none"> 1. Requirement for invasive or non-invasive ventilation until day 28 or discharge 2. Duration of ventilation until day 28 or discharge 	<ol style="list-style-type: none"> 1. Need for invasive mechanical ventilation (included in Analysis 2.2) 2. Duration of ventilation: <ol style="list-style-type: none"> a. No difference in time to ventilation (P = 0.52) b. No difference in time on ventilation: 8.25 days in CP group versus 10.5 days in control group (P = 0.81)
<p>Avendano-Sola 2020</p>	<p>Individuals with moderate illness, requiring hospitalisation for COVID-19 with either radiographic evidence of pulmonary infiltrates or clinical evidence plus SpO₂ ≤ 94% on room air were included. (According to WHO clinical progression scale: level 4-5)</p> <p>Individuals requiring mechanical ventilatory support (invasive or non-invasive) or high-flow oxygen devices were excluded.</p>	<ol style="list-style-type: none"> 1. Clinical status at day 15 and day 29, assessed on a seven-category ordinal COVID-19 scale (1, not hospitalised, no limitations on activities; 2, not hospitalised, limitation on activities; 3, hospitalised, not requiring supplemental oxygen; 4, hospitalised, requiring supplemental oxygen; 5, hospitalised, on non-invasive ventilation or high flow oxygen devices; 6, hospitalised, on invasive mechanical ventilation or ECMO and 7, death) 2. Clinical deterioration, defined as a one-category worsening in any of the daily assessments 3. Time to improvement, defined as one-category improvement in any of the daily assessments 	<ol style="list-style-type: none"> 1. Study investigators reported the proportion of participants in every category for day 1-15, and day 29, and in addition: <ol style="list-style-type: none"> a. 34/38 in the CP group and 35/43 in the control group were discharged at day 29/end of observation b. Disease progression to mechanical ventilation, ICU admission or death <ul style="list-style-type: none"> • day 15: 0% in CP group versus 14% in control group • day 29: 0% in CP group versus 16.3% in control group 2. Time to first clinical deterioration (HR 0.27, 95% CI 0.06 to 1.25) 3. Time to improvement (HR 0.94, 95% CI 0.59 to 1.50)
<p>Gharbharan 2020</p>	<p>Individuals with moderate to severe disease, hospitalised with either no oxygen (CP 16% and SC 2%), or oxygen by mask or nasal prongs, or noninvasive ventilation or high-flow oxygen, or invasive ventilation (CP 84% and SC 98%) were included (According to WHO clinical progression level: 4-7, as CP arm had 16%</p>	<ol style="list-style-type: none"> 1. Clinical status on 8-point WHO COVID-19 disease severity score at day 15 and day 30 after randomisation 2. Improvement of COVID-19 disease severity (1 point on 8-point WHO score) 	<ol style="list-style-type: none"> 1. Median clinical status on 8-point WHO COVID-19 disease severity score: <ol style="list-style-type: none"> a. Day 15: 3 (IQR: 1 to 6) versus 4 (IQR: 2 to 7) b. Day 30: 2 (IQR: 1 to 3) versus 2 (IQR: 1 to 8)

Table 7. Overview of clinical status and progression of disease (Continued)

	<p>≤ 4 and 84% ≥ 5 and SC arm had 2% ≤ 4 and 98% ≥ 5)</p>		<p>2. Improvement of COVID-19 disease severity:</p> <ol style="list-style-type: none"> day 15: 25/43 versus 25/43 day 30 (data received upon request): 35/43 versus 27/42 <p>3. Further data received upon request:</p> <ol style="list-style-type: none"> liberation from supplemental oxygen (included in Analysis 1.4) liberation from invasive mechanical ventilation (included in Analysis 1.5)
<p>Hamdy Salman 2020</p>	<p>Individuals with moderate illness and/or individuals with severe illness, all receiving received oxygen therapy, but no invasive ventilation or ECMO and having two or more of a four-category illness-severity scale: 1. respiratory frequency ≥ 24/min. (23/30 patients at baseline); 2. blood oxygen saturation ≤ 93% on room air, (19/30 patients at baseline); 3. partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 mmHg, (21/30 patients at baseline); 4. pulmonary infiltrates occupying more than 50% of both lungs (21/30 patients at baseline) were included. (According to WHO clinical progression level: 4-6)</p> <p>Individuals with septic shock or multiple organ failure were excluded.</p>	<p>1. Improvement of two points on a 4-point illness severity scale during the first 5 days after plasma transfusion</p>	<p>1. Study investigators observed a gradual improvement in CP group, but not in the control group</p> <ol style="list-style-type: none"> Incidence of dyspnoea: <ol style="list-style-type: none"> CP group: (day 1: 46.3%; day 2: 33.3%; day 3: 33.3%; day 4: 44%; day 5: 26%) Control group: (day 1: 80%; day 2: 66.3%; day 3: 54.3%; day 4: 66.3%; day 5: 53%) Incidence of hypoxia: <ol style="list-style-type: none"> CP group: (day 1: 40%; day 2: 20%; day 3: 20%; day 4: 26%; day 5: 20%) Control group: (day 1: 53%; day 2: 60%; day 3: 46.3%; day 4: 53.3%; day 5: 53.3%)
<p>Horby 2021</p>	<p>Individuals with moderate illness and/or individuals with severe illness were included. (According to WHO clinical progression level: 4-7, as 5% receiving invasive mechanical ventilation, 87% receiving oxygen only (with or without non-invasive respiratory support) and 8% were receiving no oxygen therapy)</p>	<ol style="list-style-type: none"> Progression to invasive mechanical ventilation or death within 28 days (among those not receiving invasive mechanical ventilation at randomisation) Time to successful cessation of invasive mechanical ventilation (defined as removal of invasive mechanical ventilation within, and survival to, 28 days) Use of renal dialysis or haemofiltration. 	<ol style="list-style-type: none"> Progression to invasive mechanical ventilation or death within 28 days (respective sub-domains included in Analysis 1.1 and Analysis 1.6) Time to successful cessation of invasive mechanical ventilation not reported; number of participants with successful cessation included in Analysis 1.5 Need for renal dialysis included in Analysis 1.12
<p>Li 2020</p>	<p>Individuals with severe illness with respiratory distress and/or hypoxemia or individuals with life-threatening illness having shock, organ failure, or requiring</p>	<ol style="list-style-type: none"> Clinical improvement rate within 28 days: defined as patient discharged alive or reduction of 2 points on a 6- 	<ol style="list-style-type: none"> Clinical improvement within 28 days: 51.9% (27/52) in CP group versus 43.1% (22/51) in control

Table 7. Overview of clinical status and progression of disease (Continued)

	<p>mechanical ventilation were included. (According to WHO 10-point scale: level 6-9)</p> <p>Individuals with severe septic shock or with a partial pressure of arterial oxygen to fraction of inspired oxygen ratio below 100 were excluded.</p>	<p>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)</p> <p>2. Time to clinical improvement</p>	<p>group (OR 1.42, 95% CI 0.65 to 3.09)</p> <p>2. Time to clinical improvement: HR 1.40 (95% CI 0.79 to 2.49)</p>
Ray 2020	<p>Individuals with moderate illness and/or individuals with severe disease having fever or suspected respiratory infection, plus one of the following: respiratory rate > 30 breaths/min, severe respiratory distress, SpO₂ < 90% at room air) with mild ARDS (patients having partial pressure of oxygen in the arterial blood (PaO₂)/fraction of inspired oxygen (FiO₂) ratio of 200-300 mmHg) or moderate ARDS (PaO₂/FiO₂ 100-200 mmHg), not on mechanical ventilation were included. For patients unable to maintain O₂ saturation in blood above 90% with face mask with reservoir, high flow nasal cannula or in some cases MV were deployed.</p> <p>(According to WHO 10-point scale: level 5-7)</p>	<p>No other outcome than mortality or duration of hospital stay assessed</p>	<p>N/A</p>
Simonovich 2020	<p>Individuals with moderate illness with at least one of the following severity criteria: oxygen saturation (SaO₂) below 93% while they were at rest and breathing ambient air, a ratio of the partial pressure of oxygen (PaO₂) to the fraction of inspired oxygen (FiO₂) below 300 mm Hg (PaO₂:FiO₂), or a SOFA or mSOFA score of two or more points above baseline status (scores range from 0 to 24, with higher scores indicating more severe disease)</p> <p>were included. At baseline, more than 90% received receiving oxygen and glucocorticoids at the time of entry into the trial, 64% received low flow nasal cannula, 21.5% venturi or nonrebreather mask, 4.8% high-flow nasal cannula and 0% noninvasive ventilatory support.</p>	<p>1. Clinical status 30 days after intervention, assessed with adapted version of the WHO clinical scale: 1 indicated death, 2 invasive ventilatory support, 3 hospitalised with supplemental oxygen requirement, 4 hospitalised without supplemental oxygen requirement, 5 discharged without full return to baseline physical function, and 6 discharged with full return to baseline physical function.</p> <p>2. Improvement of 2 categories in the ordinal outcome or hospital discharge within 30 days</p>	<p>1. Clinical status: study investigators reported the proportion of participants in every category at day 29, OR 0.83 (95% CI 0.52 to 1.35)</p> <p>2. Time to improvement: 12 days (7–29) in CP group versus 12 (6–ND) in control group (HR 1.0, 95% CI 0.76 to 1.32)</p>

Table 7. Overview of clinical status and progression of disease (Continued)

(According to WHO 10-point scale: level 4-6)

Individuals with requirement for mechanical ventilation or multiorgan failure were excluded.

Convalescent plasma versus standard plasma for individuals with moderate to severe disease

Bajpai 2020

All participants received supplemental oxygen at five litre/min with target SpO₂ being ≥ 94%. If saturation remained below 94%, either of high flow oxygen or NIV (via BiPAP) was given.

Individuals presenting with multi-organ failure or on mechanical ventilation or a PaO₂/FiO₂ ratio less than 150 were excluded from the study.

1. Primary outcome: Proportion of participants remaining free of invasive mechanical ventilation in both groups on day seven.
2. Reductions in respiratory rate
3. Improvement in O₂ saturation
4. Reduction in SOFA score
5. Improvement in PaO₂/FiO₂
6. Need for vasopressors

1. Need for IMV on day 7 (included in [Analysis 2.2](#))
2. Median reductions in respiratory rate per min: -14.5 (-18.75 to -13) in CP group vs. -10 (-14 to -9) in control group
3. Median improvement in % O₂ saturation: 10 (8.2 to 11) in CP group versus 7.5 (4.75 to 9.25) in control group
4. Median reduction in SOFA score: -5 (-6.5 to -4.0) in CP group versus -3 (-5.25 to -2.75) in control group
5. Median improvement in PaO₂/FiO₂: 231.15 (183.37 to 245.2) in CO group versus 77.01 (56.93 to 96.20) in control group
6. Need for vasopressors: 3/14 in CP group versus 1/15 in control group

O'Donnell 2021

Individuals with moderate illness and individuals with severe illness, with infiltrates on chest imaging, oxygen saturation ≤ 94% on room air or requirement for supplemental oxygen (including non-invasive positive pressure ventilation or high flow supplemental oxygen), IMV, or extracorporeal membrane oxygenation (ECMO) at the time of screening, were included.

(According to WHO 10-point scale: level 5-9, as 57% (126/223) of participants required supplemental oxygen, 25% (55/223) required high-flow oxygen therapy or non-invasive mechanical ventilation, and 13% (28/223) required IMV or ECMO)

Individuals with a duration of IMV or ECMO ≥ 5 days at time of screening or severe multi-organ failure were excluded.

1. Clinical status at day 28 following randomisation, measured using an ordinal scale based on that recommended by the World Health Organization: 1, not hospitalised with resumption of normal activities; 2, not hospitalised, but unable to resume normal activities; 3, hospitalised, not requiring supplemental oxygen; 4, hospitalised, requiring supplemental oxygen; 5, hospitalised, requiring high-flow oxygen therapy or noninvasive mechanical ventilation; 6, hospitalised, requiring ECMO, IMV, or both; 7, death. Since distinguishing between clinical status 1 and 2 on the ordinal scale was difficult in participants discharged from hospital, these two scores were combined, and a six-point ordinal scale was used

1. Clinical status: study investigators reported the proportion of participants in every category, and the odds of a one-point improvement in clinical status at day 28 (OR 1.5, 95% CI 0.83 to 2.68)

Table 7. Overview of clinical status and progression of disease (Continued)

for all analyses of the primary outcome.

Convalescent plasma versus placebo or standard care alone for individuals with asymptomatic or mild disease

<p>Libster 2020</p>	<p>Individuals of 75 years or older with at least one coexisting condition enrolled and admitted to hospital after screening and RT-PCR testing via home visits.</p> <p>Individuals with severe respiratory disease were excluded.</p>	<ol style="list-style-type: none"> 1. Development of severe respiratory disease: defined as a respiratory rate of 30 breaths per minute or more, an oxygen saturation of less than 93% while the patient was breathing ambient air, or both. 2. Life-threatening respiratory disease and critical systemic illness: <ol style="list-style-type: none"> a. Life-threatening respiratory disease defined as oxygen supplementation at a fraction of inspired oxygen (FiO₂) of 100%, noninvasive or invasive ventilation, admission to an intensive care unit, or any combination of these b. Critical systemic illness defined as respiratory failure with a ratio of the partial pressure of oxygen to FiO₂ ≤ 200 mm Hg, shock, multiple organ dysfunction syndrome, or any combination of these 	<ol style="list-style-type: none"> 1. Development of severe respiratory disease: <ol style="list-style-type: none"> a. 13/80 (16%) in CP group versus 25/80 (31%) in control group (RR 0.52, 95% CI 0.29 to 0.94) b. Median time to development of severe respiratory disease: 15 days (IQR 15 to 15) in CP group versus 15 days (IQR 9 to 15) in control group 2. Development of life-threatening disease and critical illness: 5/80 (6%) in CP group versus 6/80 (8%) in control group
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Abbreviations: BiPAP: bilevel positive airway pressure; CI: confidence interval; CP: convalescent plasma; ECMO: extracorporeal membrane oxygenation; FiO₂: fraction of inspired oxygen; HR: hazard ratio; IMV: invasive mechanical ventilation; IQR: interquartile range; mSOFA: modified sequential organ failure assessment; MV: mechanical ventilation; NIV: non-invasive ventilation; OR: odds ratio; O₂: oxygen; PaO₂: partial pressure of oxygen in the arterial blood; RR: risk ratio; RT-PCR: reverse transcription polymerase chain reaction; SaO₂: oxygen saturation; SOFA: sequential organ failure assessment; SC: standard care; SpO₂: peripheral oxygen saturation; WHO: World Health Organization.

Table 8. Adverse events of any grade

Study	Number of participants	Any grade adverse events	
		CP group	Control group
Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease			
<p>Agarwal 2020</p>	<p>227 in CP group and 224 in control group</p>	<ul style="list-style-type: none"> • 0 individuals with grade 3-4 adverse events, included in Analysis 1.14 	<ul style="list-style-type: none"> • 0 individuals with grade 3-4 adverse events, included in Analysis 1.14

Table 8. Adverse events of any grade (Continued)

		<ul style="list-style-type: none"> • 15 individuals with transfusion-related events, within 6 hours of CP transfusion <ul style="list-style-type: none"> ◦ 1 individual with pain at the infusion site ◦ 1 individual with chills ◦ 1 individual with nausea ◦ 1 individual with bradycardia ◦ 1 individual with dizziness ◦ 3 individuals with fever and tachycardia ◦ 2 individuals with dyspnoea ◦ 2 individual with blockage of an intravenous catheter ◦ 3 individuals with mortality as possibly related to convalescent plasma transfusion 	
AlQahtani 2020	20 in CP group and 20 in control group	<ul style="list-style-type: none"> • 0 individuals with grade 3-4 adverse events, included in Analysis 1.14 • 3 transient adverse reactions, but not considered to be related to therapy 	<ul style="list-style-type: none"> • 0 individuals with grade 3-4 adverse events, included in Analysis 1.14
Avendano-Sola 2020	38 in CP group and 43 in control group	<ul style="list-style-type: none"> • 4 individuals with grade 3-4 adverse events, included in Analysis 1.14 • 2 individuals with transfusion-related events: transfusion reactions (injury, poisoning and procedural complications) 	<ul style="list-style-type: none"> • 4 individuals with grade 3-4 adverse events, included in Analysis 1.14
Gharbharan 2020	43 in CP group and 43 in control group	NR	NR
Hamdy Salman 2020	15 in CP group and 15 in control group	<ul style="list-style-type: none"> • 0 individuals with transfusion-related complications 	NR
Horby 2021	in CP group and in control group	<ul style="list-style-type: none"> • Individuals with any adverse events within the first 72 hours after randomisation <ul style="list-style-type: none"> ◦ 1130 individuals with any sudden worsening in respiratory status ◦ 16 individuals with severe allergic reactions ◦ 195 individuals with temperature > 39 °C or ≥ 2 °C rise above baseline ◦ 127 individuals with any sudden hypotension ◦ 87 individuals with clinical haemolysis ◦ 73 individuals with any thrombotic event ◦ 215 individuals with any major cardiac arrhythmia 	<ul style="list-style-type: none"> • Individuals with any adverse events within the first 72 hours after randomisation <ul style="list-style-type: none"> ◦ 1132 individuals with any sudden worsening in respiratory status ◦ 2 individuals with severe allergic reactions ◦ 168 individuals with temperature > 39 °C or ≥ 2 °C rise above baseline ◦ 140 individuals with any sudden hypotension ◦ 66 individuals with clinical haemolysis ◦ 87 individuals with any thrombotic event ◦ 247 individuals with any major cardiac arrhythmia

Table 8. Adverse events of any grade (Continued)

Li 2020	52 in CP group and 51 in control group	<ul style="list-style-type: none"> • 2 individuals with transfusion-related adverse events <ul style="list-style-type: none"> ◦ 1 individual with possible severe transfusion-associated dyspnoea (shortness of breath, cyanosis, and severe dyspnoea) within 6 hours of transfusion ◦ 1 individual with non-severe allergic transfusion reaction and probable non-severe febrile non-haemolytic transfusion reaction (chills and rashes) within 2 hours of transfusion 	NR
Ray 2020	40 in CP group 43 in control group	Reported any grade events in the CP group: <ul style="list-style-type: none"> • 0 individuals with transfusion-related adverse events 	NR
Simonovich 2020	228 in CP group and 105 in control group	<ul style="list-style-type: none"> • 153 individuals with any grade events, included in Analysis 1.13 • 40 individuals with grade 3-4 adverse events, included in Analysis 1.14 • 11 individuals with transfusion-related events: <ul style="list-style-type: none"> ◦ 0 TRALI ◦ 0 TACO ◦ 5 Non-haemolytic febrile reaction ◦ 4 Allergic reaction ◦ 1 Unexplained event ◦ 1 Technical resolution event 	<ul style="list-style-type: none"> • 66 individuals with any grade events, included in Analysis 1.13 • 21 individuals with grade 3-4 adverse events, included in Analysis 1.14 • 2 individuals with transfusion-related events: allergic reactions
Convalescent plasma versus standard plasma for individuals with moderate to severe disease			
Bajpai 2020	14 in CP group and 15 in control group	<ul style="list-style-type: none"> • 1 individual with transfusion-related events: signs of mild urticaria during plasma transfusion 	<ul style="list-style-type: none"> • 1 individual with transfusion-related events: signs of mild urticaria during plasma transfusion
O'Donnell 2021	147 in CP group and 72 in control group	<ul style="list-style-type: none"> • 96 individuals with any adverse events, included in Analysis 2.4 <ul style="list-style-type: none"> ◦ 38 individuals with grade 1 adverse events ◦ 61 individuals with grade 2 adverse events ◦ 27 individuals with grade 3 adverse events ◦ 26 individuals with grade 4 adverse events • 4 individual with probably or definitely transfusion-related events, included worsening anaemia, urticaria, skin rash, and transfusion-associated circulatory overload 	<ul style="list-style-type: none"> • 40 individuals with any adverse events, included in Analysis 2.4 <ul style="list-style-type: none"> ◦ 17 individuals with grade 1 adverse events ◦ 23 individuals with grade 2 adverse events ◦ 17 individuals with grade 3 adverse events ◦ 15 individuals with grade 4 adverse events • 3 individuals with probably or definitely transfusion-related events
Convalescent plasma (no comparison) for individuals with moderate to severe disease			
Joyner 2020	35,322 (20,000 included in safety analysis)	NR	N/A (single-arm study)

Table 8. Adverse events of any grade (Continued)

Convalescent plasma versus placebo or standard of care alone for individuals with asymptomatic or mild disease

Libster 2020	80 in CP group and 80 in control group	<ul style="list-style-type: none"> 0 individuals with solicited adverse events 	<ul style="list-style-type: none"> 0 individuals with solicited adverse events
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Abbreviations: CP: convalescent plasma; NR: not reported; TACO: transfusion-associated circulatory overload; TRALI: transfusion-related acute lung injury.

Table 9. Serious adverse events (SAEs)

Study	Number of participants	Serious adverse events	
		CP group	Control group
Convalescent plasma versus placebo or standard care alone for individuals with moderate to severe disease			
Agarwal 2020	227 in CP group and 224 in control group	<ul style="list-style-type: none"> 3 transfusion-related SAEs: deaths could possibly be related to transfusion 	NR
AlQahtani 2020	20 in CP group and 20 in control group	NR	NR
Avendano-Sola 2020	38 in CP group and 43 in control group	<ul style="list-style-type: none"> 6 individuals with SAEs, included in Analysis 1.15 	<ul style="list-style-type: none"> 7 individuals with SAEs, included in Analysis 1.15
Gharbharan 2020	43 in group and 43 in control group	<ul style="list-style-type: none"> 0 individuals with serious transfusion-related adverse events 	NR
Hamdy Salman 2020	15 in group and 15 in control group	NR	NR
Horby 2021	5795 in group and 5763 in control group	<ul style="list-style-type: none"> 13 individuals with transfusion-related serious adverse reactions reported to SHOT: <ul style="list-style-type: none"> 9 patients with pulmonary reactions (including 3 deaths possibly related to transfusion) 4 patients with serious febrile, allergic or hypotensive reactions 	NR
Li 2020	52 in CP group and 51 in control group	NR	NR
Ray 2020	40 in CP group and 40 in control group	NR	NR
Simonovich 2020	228 in CP group and 105 in control group	<ul style="list-style-type: none"> 54 individuals with SAEs, included in Analysis 1.15 	<ul style="list-style-type: none"> 19 individuals with SAEs, included in Analysis 1.15

Table 9. Serious adverse events (SAEs) (Continued)

Convalescent plasma versus standard plasma for individuals with moderate to severe disease			
Bajpai 2020	14 in CP group and 15 in control group	NR	NR
O'Donnell 2021	147 in CP group and 72 in control group	<ul style="list-style-type: none"> 39 individuals with SAEs, included in Analysis 2.5 	<ul style="list-style-type: none"> 26 individuals with SAEs, included in Analysis 2.5
Convalescent plasma (no comparison) for individuals with moderate to severe disease			
Joyner 2020	35,322 (20,000 included in safety analysis)	Total events within 7 days after transfusion: 1282 Within 4 h after transfusion: 146 events reported <ul style="list-style-type: none"> 63 dead (12 possibly, 1 probably, 0 definitely related) 37 TACO (37 potentially, probably, or definitely related) 20 TRALI (20 potentially, probably, or definitely related) 26 severe allergic reaction (26 potentially, probably, or definitely related) Within 7 days after transfusion: additional 1136 events reported <ul style="list-style-type: none"> 87 thrombotic or thromboembolic complication (32 potentially, probably, or definitely related) 406 sustained hypotension (54 potentially, probably, or definitely related) 643 cardiac events (74 potentially, probably, or definitely related) 	N/A (single-arm study)
Convalescent plasma versus placebo or standard of care alone for individuals with mild disease			
Libster 2020	80 in CP group and 80 in control group	<ul style="list-style-type: none"> 0 individuals with solicited adverse events 	<ul style="list-style-type: none"> 0 individuals with solicited adverse events

Abbreviations: CP: convalescent plasma; NR: not reported; TACO: transfusion-associated circulatory overload; TRALI: transfusion-related acute lung injury; SAEs: serious adverse events; SHOT: serious hazards of transfusion.

APPENDICES

Appendix 1. Planned methodology for study designs that are no longer included in this systematic review

Criteria for considering studies for this review

Types of studies

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](#)).

We had further planned to include retrospective controlled NRSIs, in case of insufficient evidence (very low-certainty evidence or no evidence) available from RCTs and prospective controlled NRSIs and to adapt the methods for the inclusion of controlled NRSIs in systematic reviews as specified by the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2019).

In case the evidence that we found from RCTs was at high risk of bias and at critical risk of bias for the controlled NRSIs for safety outcomes, we had planned to also included safety data from prospectively and retrospectively registered non-controlled NRSIs, for example, case series, and followed the methodology as specified in the protocol (Piechotta 2020a).

Data collection and analysis

Assessment of risk of bias in included studies

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) would have 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 would have 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 for previous versions of this review. 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 had planned to assess 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 had planned to make a judgement using one of five response options.

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

Measures of treatment effect

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).

Data synthesis

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

Summary of findings and assessment of the certainty of the evidence

As we had planned to use the ROBINS-I tool to assess risk of bias for controlled NRSIs, we had planned to follow GRADE guidance 18 to rate the certainty in the evidence for controlled NRSIs; starting from high-certainty evidence with the opportunity to downgrade by three points for critical risk of bias (Schünemann 2019).

Appendix 2. Search strategy MEDLINE

- | | |
|----|---|
| # | Searches |
| 1 | Coronavirus Infections/ or Coronavirus/ |
| 2 | SARS-CoV-2/ or COVID-19/ |
| 3 | ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2").tw,kf. |
| 4 | ((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kf. |
| 5 | "severe acute respiratory syndrome coronavirus 2".tw,kf,nm. |
| 6 | (anti-flu* or anti-influenza* or antifu* or antinfluenza*).tw,kf. |
| 7 | or/1-6 |
| 8 | Plasma/ |
| 9 | Immunoglobulins/ |
| 10 | Immunoglobulins, Intravenous/ |
| 11 | Immune Sera/ |
| 12 | ((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. |
| 13 | ((plasma adj1 therap*) or gamma-globulin* or "γ-Globulin" or hyper-Ig).tw,kf. |
| 14 | (hyperimmune* or hyper-immune*).mp. |
| 15 | (high-dos* adj3 (plasma or immunoglobulin* or IVIG* or immune globulin* or globulin* or IgG)).tw,kf. |
| 16 | (plasma adj5 (immun* or antibod* or exchange* or donor* or donat* or transfus* or infus*)).mp. |
| 17 | ((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. |
| 18 | (serum or sera or serotherap* or sero-therap*).tw,kf. |
| 19 | exp Immunization, Passive/ |
| 20 | (passiv* adj3 (antibod* transfer* or immunization* or immunotherap* or immuno-therap* or vaccin*)).tw,kf. |
| 21 | ((immunoglobulin* or immune globulin*) adj2 (therap* or treatment* or neutrali?ing or prevent* or protect* or prophylax*)).tw,kf. |
| 22 | hIVIG.tw,kf. |
| 23 | (XAV-19 or SAB-185 or equine or INM005 or CSL760).tw,kf. |
| 24 | (IGY-110 or IGY110 or GIGA-2050 or GIGA2050).tw,kf. |
| 25 | (GC5131 or 5131A).tw,kf. |
| 26 | ((anti-coronavirus or anticoronavirus) adj1 immunoglobulin*) or ITAC).tw,kf. |
| 27 | ("Hyperimmune anti-COVID-19 IVIG" or C-IVIG or CIVIG).tw,kf. |
| 28 | (equine polyclonal antibod* or EpAbs).tw,kf. |

- 29 Flebogamma.tw,kf.
- 30 or/8-29
- 31 7 and 30
- 32 "Covid-19 Serotherapy".px.
- 33 (Flu-IVIG or ((anti-flu* or anti-influenza* or antifu* or antinfluenza*) adj5 plasma)).mp.
- 34 or/31-33
- 35 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
- 36 ((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp.
- 37 or/35-36
- 38 (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
- 39 hi.fs. or case report.mp.
- 40 or/38-39
- 41 37 not 40
- 42 randomized controlled trial.pt.
- 43 controlled clinical trial.pt.
- 44 randomi?ed.ab.
- 45 placebo.ab.
- 46 drug therapy.fs.
- 47 randomly.ab.
- 48 trial.ab.
- 49 groups.ab.
- 50 or/42-49
- 51 exp animals/ not humans/
- 52 50 not 51
- 53 clinical trial, phase iii/
- 54 ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").ti,ab,kw.
- 55 (53 or 54) not 51
- 56 52 or 55
- 57 34 and (41 or 56)
- 58 limit 57 to yr="2019 -Current"

Appendix 3. Search strategy Embase

- # Searches
- 1 coronavirinae/ or coronaviridae/ or coronaviridae infection/
- 2 coronavirus disease 2019/

- 3 Coronavirus infection/
 4 sars-related coronavirus/
 5 "Severe acute respiratory syndrome coronavirus 2"/
 6 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).tw,kw.
 7 ("2019 nCoV" or 2019nCoV or coronavir* or coronovir* or COVID or COVID19 or HCoV* or "nCov 2019" or "SARS CoV2" or "SARS CoV 2" or SARSCoV2 or "SARSCoV 2").tw,kw.
 8 "Severe acute respiratory syndrome coronavirus 2".mp.
 9 (anti-flu* or anti-influenza* or antifu* or antinfluenza*).tw,kw.
 10 or/1-9
 11 Plasma Transfusion/
 12 exp Immunoglobulin/
 13 ((convalesc* or recovered or cured or survivor* or survived or rehabilitat* or virus-positive or virus-neutrali* or virus inactivated or antibody-rich or high-tire* or high-titer*) adj6 (plasma or blood or serum or sera)).mp.
 14 ((plasma adj1 therap*) or gamma-globulin or "y-Globulin" or hyper-Ig).tw,kw.
 15 (plasma adj5 (immun* or antibod* or exchange* or donor* or donat* or transfus* or infus*)).mp.
 16 (hyperimmune* or hyper-immune*).mp.
 17 (high-dos* adj3 (plasma or immunoglobulin* or IVIG* or immune globulin* or globulin* or IgG)).tw,kw.
 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 or serotherap* or sero-therap*).tw,kw.
 20 passive immunization/
 21 (passiv* adj3 (antibod* transfer* or immuni?ation* or immunotherap* or immuno-therap* or immunit* transfer* or vaccin*)).tw,kw.
 22 passive immunit*.tw,kw.
 23 ((immunoglobulin* or immune globulin*) adj2 (therap* or treatment* or neutrali?ing or prevent* or protect* or prophylax*)).tw,kw.
 24 hIVIG.tw,kw.
 25 (CSL760 or INM005 or XAV-19 or SAB-185 or equine).tw,kw.
 26 (IgY-110 or IgY110 or GIGA-2050 or GIGA2050).tw,kw.
 27 (GC5131 or 5131A).tw,kw.
 28 (((anti-coronavirus or anticoronavirus) adj1 immunoglobulin*) or ITAC).tw,kw.
 29 ("Hyperimmune anti-COVID-19 IVIG" or C-IVIG or CIVIG).tw,kw.
 30 (equine polyclonal antibod* or EpAbs).tw,kw.
 31 flebogamma.tw,kw.
 32 or/11-31
 33 (Flu-IVIG or ((anti-flu* or anti-influenza* or antifu* or antinfluenza*) adj5 plasma)).mp.
 34 Clinical study/
 35 (cross sectional adj (study or studies)).tw.

- 36 exp longitudinal study/
 37 exp prospective study/
 38 exp follow up/
 39 cohort*.tw.
 40 exp case control study/
 41 (case* and control*).tw.
 42 or/34-41
 43 Randomized controlled trial/
 44 Controlled clinical study/
 45 random*.ti,ab.
 46 randomization/
 47 intermethod comparison/
 48 placebo.ti,ab.
 49 (compare or compared or comparison).ti.
 50 (open adj label).ti,ab.
 51 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
 52 double blind procedure/
 53 parallel group\$1.ti,ab.
 54 (crossover or cross over).ti,ab.
 55 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant \$1)).ti,ab.
 56 (controlled adj7 (study or design or trial)).ti,ab.
 57 (volunteer or volunteers).ti,ab.
 58 trial.ti.
 59 or/43-58
 60 phase 3 clinical trial/
 61 ("Phase 3" or "phase3" or "phase III" or P3 or "PIII").tw,kw.
 62 or/60-61
 63 (10 and 32) or 33
 64 63 and (42 or 59 or 62)
 65 limit 64 to yr="2019 -Current"

Appendix 4. Search strategy Cochrane COVID-19 Study Register

plasma OR convalesc* OR serum OR sera OR donor* OR donation* OR serotherapy OR "sero-therapy" OR "flu-IVIG" OR antifu* OR "anti-flu" OR hyperimmune* OR hyper-immune* OR IVIG OR immunoglobulin OR "immune-globulin" OR globulin OR "gamma-globulin" OR "γ-Globulin" OR "hyper-Ig" OR immunization OR immunisation OR immunotherap* OR CSL760 OR INM005 OR equine OR "XAV-19" OR "SAB-185" OR hIVIG OR equine OR INOSARS OR "GIGA-2050" or GIGA2050 OR "IGY-110" OR IGY1109 OR "GC5131" OR "5131A" OR ITAC OR "C-IVIG" OR CIVIG OR flebogamma OR EpAbs

Limits: treatment and management

Appendix 5. Search strategy PubMed

- #1 "2019 ncov"[Title/Abstract] OR "2019nCoV"[Title/Abstract] OR "corona virus"[Title/Abstract] OR "corona viruses"[Title/Abstract] OR "Coronavirus"[Title/Abstract] OR "coronaviruses"[Title/Abstract] OR "COVID"[Title/Abstract] OR "COVID19"[Title/Abstract] OR "ncov 2019"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "COVID-19"[MeSH Terms] OR "Coronavirus"[MeSH Terms:noexp] OR "SARS-CoV-2"[MeSH Terms] OR "COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]
- #2 ("convalesc*"[Title/Abstract] OR "recovered"[Title/Abstract] OR "cured"[Title/Abstract] OR "rehabilitat*"[Title/Abstract] OR "survivor*"[Title/Abstract] OR "survived"[Title/Abstract] OR "virus-positive"[Title/Abstract] OR "virus neutrali*"[Title/Abstract] OR "virus inactivated"[Title/Abstract] OR "antibod*"[Title/Abstract] OR "high titre*"[Title/Abstract] OR "high titer*"[Title/Abstract]) AND ("plasma"[Title/Abstract] OR "blood"[Title/Abstract] OR "donor*"[Title/Abstract] OR "donat*"[Title/Abstract])
- #3 ("plasma"[Title] AND ("immun*"[Title/Abstract] OR "transfus*"[Title/Abstract] OR "infus*"[Title/Abstract]))
- #4 ("high dos*"[Title/Abstract] AND ("plasma"[Title/Abstract] OR "immunoglobulin*"[Title/Abstract] OR "ivig*"[Title/Abstract] OR "immune globulin*"[Title/Abstract] OR "globulin*"[Title/Abstract] OR "IgG"[Title/Abstract]))
- #5 "serum"[Title] OR "sera"[Title] OR "immunization, passive"[MeSH Terms] OR "hyperimmune"[Title/Abstract] OR "hyperimmunity"[Title/Abstract] OR "serotherap*"[Title/Abstract] OR "sero therap*"[Title/Abstract] OR "therapeutic plasma"[Title/Abstract] OR "plasma therapy"[Title/Abstract] OR "immune plasma"[Title/Abstract] OR "plasma exchange"[Title/Abstract] OR "gamma globulin*"[Title/Abstract] OR "gamma-Globulin"[Title/Abstract] OR "hyper-Ig"[Title/Abstract]
- #6 ("passiv*"[Title/Abstract] AND (("antibod*"[All Fields] AND "transfer*"[All Fields]) OR "immunisation*"[All Fields] OR "vaccin*"[Title/Abstract] OR "immunization*"[All Fields] OR "immunotherap*"[All Fields] OR "immuno therap*"[All Fields] OR "vaccin*"[All Fields]))
- #7 ("immunoglobulin*"[Title] OR "immune globulin*"[Title]) AND ("therap*"[Title/Abstract] OR "treat*"[Title/Abstract] OR "prevent*"[Title/Abstract] OR "protect*"[Title/Abstract] OR "prophylax*"[Title/Abstract]))
- #8 ("equine*"[Title/Abstract] OR "hivig*"[Title/Abstract] OR "c ivig*"[Title/Abstract] OR "XAV-19"[Title/Abstract] OR "5131A"[Title/Abstract] OR "equine polyclonal antibody*"[Title/Abstract] OR "EpAbs"[Title/Abstract] OR "flebogamma*"[Title/Abstract] OR ("anti-coronavirus"[Title/Abstract] OR "anticoronavirus"[Title/Abstract]) AND "immunoglobulin*"[Title/Abstract]))
- #9 (("anti-coronavirus"[Title/Abstract] OR "anticoronavirus"[Title/Abstract]) AND "immunoglobulin*"[Title/Abstract])
- #10 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
- #11 (("anti flu*"[Title/Abstract] OR "anti influenza*"[Title/Abstract] OR "antiflu*"[Title/Abstract] OR "antinfluenza*"[Title/Abstract]) AND ("plasma*"[Title/Abstract])) OR ("flu ivig*"[Title/Abstract])
- #12 #1 AND #10
- #13 #11 OR #12
- #14 ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])
- #15 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
- #16 #13 NOT #14
- #17 #15 AND #16 Filters: from 2020/1/1 - 3000/12/12

Appendix 6. Search strategy - World Health Organization COVID-19 Global literature on coronavirus disease

Advanced search; search fields: title, abstract, subject

Search 1: (plasma OR convalesc* OR serum OR sera OR donor* OR donation* OR serotherapy OR "sero-therapy" OR "flu-IVIG" OR antiflu* OR "anti-flu" OR hyperimmune* OR hyper-immune* OR IVIG) AND (random* OR placebo OR RCT)

Search 2: (immunoglobulin OR immune-globulin OR globulin OR gamma-globulin OR γ -Globulin OR hyper-Ig) AND (random* OR placebo OR RCT)

Search 3: (immunization OR immunisation OR immunotherap*) AND (random* OR placebo OR RCT)

Search 4: (CSL760 OR INM005 OR equine OR "XAV-19" OR "SAB-185" OR hivig) AND (random* OR placebo OR RCT)

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

388

Search 5: (INOSARS OR "GIGA-2050" OR "GIGA2050" OR "IGY-110" OR "IGY1109" OR GC5131 OR 5131A OR ITAC OR C-IVIG OR CIVIG OR flebogamma OR EpAbs) AND (random* OR placebo OR RCT)

Appendix 7. Search strategy - Epistemonikos, L*OVE List Coronavirus disease (COVID-19)

by pico search: population: Covid-19: intervention: passive immunization

Prevention or treatment: passive immunization: convalescent plasma: primary studies: RCTs

Prevention or treatment: passive immunization: Immunoglobulin therapy: primary studies: RCTs

Prevention or treatment: passive immunization: heterologous antibodies: primary studies: RCTs

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

We assessed methodological quality and risk of bias using the 'Risk of bias' assessment criteria for observational studies tool provided by Cochrane Childhood Cancer (see [Table 3](#); [Mulder 2019](#)).

'Risk of bias' assessment of Joyner 2020

Domain	Assessed outcomes	Authors' judgement	Support for judgement
Representative study group (selection bias)	Adverse events	Low	Large population size, prospective study, interim analysis of safety data for 20,000 participants (out of 35,322 participants)
Outcome detectors blinded to intervention (detection bias)	Adverse events	Low	Assessment of outcome probably not biased through awareness of intervention
Complete outcome assessment/follow-up (attrition bias)	Adverse events	Low	Interim results; serious adverse events assessed over 7 days after transfusion
Well-defined study group (reporting bias)	Adverse events	Low	Study population and intervention well described
Well-defined outcome (reporting bias)	Adverse events	Low	Interim results for 20,000 participants; assessed and reported for all participants
Well-defined risk estimates (analyses)	Adverse events	Low	Quote: "cumulative incidence of each of a series of SAEs [serious adverse events] was summarised using a point estimate and 95% score confidence interval (CI)"
Important prognostic factors or follow-up taken adequately into account (confounding)	Adverse events	Low	Not adjusted, but confounding unlikely

WHAT'S NEW

Date	Event	Description
19 March 2021	New citation required and conclusions have changed	High certainty in the evidence for some of the prioritised outcomes

Date	Event	Description
17 March 2021	New search has been performed	12 RCTs and one NRSI included

HISTORY

Review first published: Issue 5, 2020

Date	Event	Description
30 August 2020	New citation required and conclusions have changed	Additional safety data included (more than 20,000 participants)
30 August 2020	New search has been performed	Two RCTs, eight controlled NRSIs and nine non-controlled NRSIs included
3 June 2020	New citation required and conclusions have changed	We included results from one RCT and three controlled NRSIs and added further safety data from non-controlled NRSIs.
31 May 2020	New search has been performed	We included eight new studies.

CONTRIBUTIONS OF AUTHORS

VP: methodological expertise, study selection, data extraction and assessment, conception and writing of the manuscript

CI: methodological expertise, study selection, data extraction and assessment, writing of the manuscript

KLC: clinical expertise, study selection, data extraction and assessment, conception and writing of the manuscript

SJV: clinical expertise, study selection, data extraction and assessment, conception and writing of the manuscript

CK: clinical expertise, study selection, and advice

ED: study selection, data extraction and assessment, writing of the manuscript

IM: development of the search strategy

EMW: clinical expertise and advice

AL: clinical expertise and advice

DJR: clinical expertise and advice

ZM: clinical expertise and advice

CS-O: clinical expertise and advice

LJE: clinical expertise, and conception and writing of the manuscript

NS: methodological expertise, study selection, data extraction and assessment, conception and writing of the manuscript

DECLARATIONS OF INTEREST

VP: none known

CI: 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: is receiving a PhD scholarship from the not-for-profit Sanquin blood bank.

CK: none known

ED: none known

IM: none known

EMW: I have received funding support from Australian Medical Research Future Fund for a trial of convalescent plasma. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

AL: none known

DJR: investigator on the REMAP-CAP and RECOVERY trial. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

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

CS-O: is a member of the BEST Collaborative Clinical Study Group and Associate Editor for *Transfusion Medicine* Journal. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

LJE: co-lead of the COVID-19 immunoglobulin domain of the REMAP-CAP trial and investigator on the RECOVERY trial. I was not involved in bias assessment, data extraction or interpretation, but served as a content expert.

NS: none known

SOURCES OF SUPPORT

Internal sources

- Sanquin Blood Supply, Netherlands
 - Center for Clinical Transfusion Research
- University Hospital of Cologne, Germany
 - Cochrane Cancer, Department I of Internal Medicine
- Monash University, Australia
 - Transfusion Research Unit, Department of Epidemiology and Preventive Medicine
- NHS Blood and Transplant, UK
 - NHS Blood and Transplant
- Leukaemia Foundation and HSANZ, Australia
 - Haematology Society of Australia and New Zealand (HSANZ)

External sources

- European Union's Horizon 2020 research and innovation programme, Belgium
 - SUPPORTing high-quality evaluation of covid-19 convalescent plasma throughout EUROPE (Support-E)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this section, we do not only report the differences between the protocol and the current review version but the changes between each published version of the review. The summary of amendments are also provided in [Table 1](#).

Types of studies

Differences between first and second published review version

([Valk 2020](#) to [Piechotta 2020b](#))

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 2020a](#)). 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.

Differences between second and third published review version

([Piechotta 2020b](#) to [Chai 2020](#))

We decided to include registered non-controlled NRSIs only to minimise selection bias.

Differences between third published review version and current version

([Chai 2020](#) to current version)

Originally we had planned to include different study designs in a top down approach: randomised controlled trials, prospective and retrospective controlled non-randomised studies of interventions (NRSIs), and prospective and retrospective registered non-controlled NRSIs. We had planned to include the next lower level in case we had low or very low certainty in the evidence of higher-quality studies.

However, because large-scale or expanded access studies could still provide valuable information on the safety of convalescent plasma or hyperimmune immunoglobulins, we decided to include prospectively registered single-arm studies, even if upcoming RCTs report safety data for both groups. We decided to consider prospectively registered single-arm studies only for safety data, and if 500 or more participants were included.

Types of participants

Differences between third published review version and current version

([Chai 2020](#) to current version)

After discussion with different attending physicians and clinical experts, we decided to perform separate analyses for populations with ambulatory mild disease and for hospitalised participants with moderate to severe disease, according to the latest WHO clinical progression score (<https://revman.cochrane.org/#/660020041013463556/dashboard/htmlCompare/3.7.55/3.6#REF-WHO-2020e>). We discussed that patient and study characteristics were not homogenous enough to be combined and outcomes of interest differ.

Types of intervention

Differences between first and second published review version

([Valk 2020](#) to [Piechotta 2020b](#))

We added standard immunoglobulin as an eligible control treatment.

Types of outcome measures

Differences between protocol and first published review version

([Piechotta 2020a](#) to [Valk 2020](#))

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 the fourth bullet point: 'plus high-flow oxygen', to differentiate from the third bullet point. After revision, it read:

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

Differences between first and second published review version

([Valk 2020](#) to [Piechotta 2020b](#))

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

Differences between second and third published review version

([Piechotta 2020b](#) to [Chai 2020](#))

We renamed the outcome 'time to death' as 'mortality (time to event)'. This did not change the outcome measurement we are interested in.

We revised the secondary outcome 'Improvement of clinical symptoms' according to the revised outcome measure set for COVID-19 clinical research (COMET 2020). Instead of defining cut-offs ourselves, we refer to the recommended standardised scales. It read:

- Improvement of clinical symptoms, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020e), WHO Ordinal Scale for Clinical Improvement (WHO 2020f)) at up to 7 days, 8 to 15 days, 16 to 30 days.

We added the outcome 'virological response assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days' because this was suggested during the peer review of the last version of this review.

Differences between third published review version and current version

(Chai 2020 to current version)

We divided efficacy outcomes for hospitalised individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease and ambulatory managed individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease, according to WHO clinical progression scale (WHO 2020e).

For individuals with a confirmed diagnosis of SARS-CoV-2 infection and asymptomatic or mild disease, we added the outcomes admission to hospital, development of moderate to severe clinical COVID-19 symptoms, time to symptom onset, and any grade adverse events; and length of hospital stay, for subgroup of participants being hospitalised in the course of disease.

We revised and redefined outcomes for individuals with a confirmed diagnosis of COVID-19 and moderate to severe disease after discussion with intensive care specialists and the German guideline panel for inpatient therapy of people with COVID-19. We summarised different outcome measures for all-cause mortality below one outcome, added sub-outcomes for clinical improvement, and added clinical worsening to better reflect the course of disease and to detect group differences. We also added the outcome need for dialysis, and extended the definition of quality of life to also include fatigue and functional independence;

We renamed the outcome 'time to discharge from hospital' to 'Duration of hospitalisation, or time to discharge from hospital' to clarify that we are interested in both, continuous and time-to-event data. We renamed the outcome 'virological response' to 'viral clearance' to clarify that we are interested in test-negativity and not in changes of viral load.

Electronic searches

Differences between protocol and first published review version

(Piechotta 2020a to Valk 2020)

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.

Differences between first and second published review version

(Valk 2020 to Piechotta 2020b)

We decided to exclude individual study registries from the search strategy, because they are already included in the Cochrane COVID-19 Study Register, which is updated Monday to Friday and to also 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.

Differences between third published review version and current version

(Chai 2020 to current version)

In the list of databases The Living Overview of Evidence (L*OVE) Covid-19 provided from Epistemonikos is included due its variety of sources it contains (since September 2020) and the WHO COVID-19 global literature on coronavirus disease was added because it integrates the CDC database (since October 2020).

New identified search terms like the MeSH term Immunization, Passive exploded and these search strings (passiv* adj3 (antibod* transfer* or immunization* or immunotherap* or immuno-therap*).tw,kf.; ((immunoglobulin* or immune globulin*) adj2 (therap* or treat*).tw,kf.; (INM005 or CSL760).tw,kf.; (XAV-19 or SAB-185 or h1VIG or equine).tw,kf. were searched from November 2020. Due to the availability of more studies, the searches were focused on nonRCTs and RCTs with adequate study filters (since December 2020). At the beginning of 2021, new MeSH or EMTREE terms were inserted in Medline and Embase, so the whole search strategies were revised and new search terms like IGY-110 or GIGA-2050 or GC5131 or 5131A or INOSARS were added. The search string (passive adj2 vaccin*).tw,kf. and new terms for hyperimmune like equine polyclonal antibodies (EpAbs), hyperimmune anti-COVID-19 IVIG (C-IVIG), anti-coronavirus immunoglobulin (ITAC), flebogamma were included in February 2021.

Data extraction and management

Differences between protocol and first published review version

(Piechotta 2020a to Valk 2020)

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](#)).

Differences between first and second published review version

(Valk 2020 to Piechotta 2020b)

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.

Differences between second and third published review version

(Piechotta 2020b to Chai 2020)

Measures of treatment effect

We had planned to use the Excel tool of the purpose-built method based on the Parmar and Tierney approach (<https://revman.cochrane.org/#/660020041013463556/dashboard/htmlCompare/3.6/2.11#REF-Parmar-1998>; <https://revman.cochrane.org/#/660020041013463556/dashboard/htmlCompare/3.6/2.11#REF-Tierney-2007>), to estimate hazard ratios (HRs) with the reported data, if HRs were not available. We were able to read off mortality data from the Kaplan-Meier curve provided by <https://revman.cochrane.org/#/660020041013463556/dashboard/htmlCompare/3.6/2.11#STD-Gharbharan-2020> per day. Because we did not have the rights to edit the Excel tool to add a greater number of time intervals, we could not use the Excel tool. We therefore used a digitising software (<https://revman.cochrane.org/#/660020041013463556/dashboard/htmlCompare/3.6/2.11#REF-GetData-Graph-Digitizer>) to estimate the HR for <https://revman.cochrane.org/#/660020041013463556/dashboard/htmlCompare/3.6/2.11#STD-Gharbharan-2020>.

Assessment of risk of bias in included studies

Randomised controlled trials

The Risk of Bias 2.0 (RoB 2) tool is meanwhile available in RevMan web. We therefore decided to revert to our originally planned methodology for risk of bias assessment in randomised controlled trials, and used RoB 2.0 for any assessments.

Differences between third published review version and current version

(Chai 2020 to current version)

Subgroup analysis and investigation of heterogeneity

We had planned to add subgroup analyses for the following characteristics in this update of the review.

- Duration since symptom onset
- Level of antibody titre in donors
- Level of antibody titre in recipients at baseline
- SARS-CoV-2 variants

Considering the currently available evidence, we decided to add these subgroups, because their role in the effectiveness of convalescent plasma is currently discussed and needs to be further investigated.

Summary of findings and assessment of the certainty of the evidence

Differences between protocol and first published review version

(Piechotta 2020a to Valk 2020)

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, as none of the included studies reported any deaths during their study periods, 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.

Differences between first and second published review version

(Valk 2020 to Piechotta 2020b)

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.

Differences between third published review version and current version

(Chai 2020 to current version)

We decided to include two 'Summary of findings' tables, one for each population.

We amended the outcomes for inclusion into the summary of findings table, in accordance with redefining the types of outcome measures. We summarised the outcome all-cause mortality and provide a hierarchy of outcome measures that we would consider for inclusion in the summary of findings table. We added clinical worsening, in addition to clinical improvement, to better reflect the course of disease, and also provide a hierarchy for sub-outcomes of all-cause mortality.

INDEX TERMS**Medical Subject Headings (MeSH)**

Bias; Cause of Death; COVID-19 [mortality] [*therapy]; Immunization, Passive [adverse effects] [methods] [mortality] [statistics & numerical data]; Non-Randomized Controlled Trials as Topic [statistics & numerical data]; Pandemics; Randomized Controlled Trials as Topic [statistics & numerical data]; Respiration, Artificial [statistics & numerical data]; Treatment Outcome; Ventilator Weaning [statistics & numerical data]

MeSH check words

Humans