Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Convalescent plasma therapy to treat people with coronavirus disease (COVID-19)

Executive summary

- This report aims to identify and summarise evidence that addresses the following question: what is the clinical effectiveness of convalescent plasma therapy for people with COVID-19?
- Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus. Most people infected with the virus will have mild to moderate symptoms that recover without needing special treatment. However, COVID-19 can present as a severe illness.
- Convalescent plasma therapy can be completed by transfusing plasma from people who have recently been infected with SARS-CoV-2 into people who have an active infection and are at risk of negative outcomes. This is done with the aim of promoting passive immunity to protect a person from disease progression until their immune system is able to develop its own antibodies.
- We identified 25 randomised controlled trials that examined the effectiveness of convalescent plasma therapy for people with COVID-19. Ten of these were identified during a living evidence review conducted by the European Network for Health Technology Assessment (EUnetHTA) and are reported in a meta-analysis. Fifteen of these were identified since the EUnetHTA review concluded and their findings are reported alongside the meta-analysis.
- Across a range of outcomes, evidence suggests that convalescent plasma therapy does not provide benefits to people with COVID-19. There may be some benefits if the intervention is used in the early stages of symptoms developing, but these benefits are likely to be negated by vaccination.
- Convalescent plasma therapy was available to some patients as part of the RECOVERY and REMAP-CAP platform trials in the early stages of the pandemic. However, convalescent plasma therapy has not been used in Wales outside of this setting and there is no plan for future use for people with COVID-19.

1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the following question: what is the clinical effectiveness of convalescent plasma therapy for people with COVID-19?

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of published evidence identifying the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The Evidence Appraisal Report has been reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Health problem

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus (NHS England 2022). Most people infected with the virus will have mild to moderate symptoms that recover without needing special treatment. However, COVID-19 can present as a severe illness that has adverse effects on multiple systems of the body and requires hospitalisation, sometimes with escalation to intensive treatment. The most well documented effect is on the lungs, where it can cause a reduction in the ability to transfer oxygen from the air into the blood leading to low blood oxygen levels. Impacts on other organs, including kidneys, heart, liver, and brain, and the circulatory system are less well understood. Older people and those with underlying medical conditions are most at risk of serious illness (NHS England 2022).

3. Health technology

Convalescent plasma from people who have recently been infected by SARS-CoV-2 can contain pathogen-specific neutralising antibodies against SARS-CoV-2 that have been produced by their immune system. By collecting blood donations, convalescent plasma therapy can be completed by transfusing this plasma into people who have an active infection and are at risk of negative outcomes. This is done with the aim of promoting passive immunity to protect a person from disease progression until their immune system is able to develop its own antibodies. Transfusion can occur within varying timing, either in the period immediately after exposure to SARS-CoV-2, when symptoms of COVID-19 first appear, or later when a patient has been hospitalised. Alongside potential benefits, convalescent plasma therapy has known serious adverse events that may cause harm to patients. In particular, there are risks of transfusion-related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), and cytokine storm (Casadevall & Pirofski 2020, Chen et al. 2020, Roback & Guarner 2020).

Convalescent plasma therapy has previously been used in other infectious disease outbreaks, such as severe acute respiratory syndrome (SARS), influenza A (H1N1), avian influenza A (H5N1), and Ebola. Evidence on the effectiveness of convalescent plasma therapy for these diseases is varied with some studies suggesting it may result in earlier discharge and reduced mortality and others suggesting there is a limited impact (Davey et al. 2019, Hung et al. 2011, Hung et al. 2013, Mair-Jenkins et al. 2015, Devasenapathy et al. 2020). Of particular interest for COVID-19, a meta-analysis of studies on use of convalescent plasma therapy for SARS suggests that it can reduce mortality, particularly with early use (Mair-Jenkins et al. 2015).

Convalescent plasma therapy was pursued as a treatment of interest in the early stages of the COVID-19 pandemic. At that time, other options for prevention and treatment were limited and relied largely on varying intensity of respiratory support. Since then, widespread vaccination has reduced the number of people who could benefit from passive immunity due to presence of

vaccine-induced antibodies and guidelines now recommend other effective therapeutics at different stages of the pathway (NICE 2022).

4. Clinical effectiveness

As part of its response to the Covid-19 pandemic, EUnetHTA produced a number of rolling collaborative reviews (RCRs) to provide decision-makers with a timely synthesis of available evidence on the comparative effectiveness of various potential treatments for COVID-19 (EUnetHTA 2020). In 2020-2021, an RCR was produced on convalescent plasma therapy (EUnetHTA 2021). This review (which HTW contributed to) includes all evidence up to May 2022; here we adapt its findings and build upon it by including all available evidence up to February 2022. Sections 9 and 10 report contributors to the review and the full methods used to search for synthesis evidence.

During the EUnetHTA RCR, ten RCTs examining the effectiveness of convalescent plasma therapy for COVID-19 were identified and included in a meta-analysis (Agarwal et al. 2020, AlQahtani et al. 2020, Avendaño-Solà et al. 2020, Bajpai et al. 2020, Gharbharan et al. 2020, RECOVERY Collaborative Group 2021, Li et al. 2020, Libster et al. 2020, Ray et al. 2020, Simonovich et al. 2021). The updated search identified a further 15 RCTs and as these were published after the final version of the EUnetHTA RCR was published, findings are reported but not included in the meta-analysis (Baldeón et al. 2022, Bar et al. 2021, Bégin et al. 2021, Devos et al. 2021, Holm et al. 2021, Kirenga et al. 2021, Körper et al. 2021, Menichetti et al. 2021, O'Donnell et al. 2021, Ortigoza et al. 2022, Pouladzadeh et al. 2021, Sekine et al. 2021, Shoham et al. 2021, Sullivan et al. 2021, Writing Committee for the REMAP-CAP Investigators 2021). Due to the availability of large number of randomised controlled trials (RCTs) with large sample sizes, lower priority evidence was not considered for inclusion. Full characteristics of each of these RCTs are available in Appendix 4.

The majority of studies included populations who had been hospitalised for COVID-19 and had varying severity of COVID-19 progression. Three studies focused on people in the community who had had recent exposure to SARS-CoV-2 or people who had recently developed COVID-19 symptoms. All studies reported some detail on the method of administration of convalescent plasma. However, studies had varying approaches to plasma collection and criteria for required level of neutralising antibody titres. Details of the control arm were often vague and restricted to stating that the comparator was standard care at the relevant trial sites. Studies were completed in a range of countries across each of the WHO regions and across low, middle and high-income settings. The majority recruited participants from multiple centres. Almost all studies had a higher proportion of male participants and the average age of participants was mostly over 50.

In general, studies included within this evidence appraisal report appeared to be well designed and conducted. However, there are a number of threats to external validity of the evidence presented here. The majority of the studies were initiated in the early stages of the COVID-19 pandemic when convalescent plasma therapy was seen as a potential treatment that could be implemented without delay. This means that populations within the trials presented here were highly unlikely to have previous exposure to SARS-CoV-2 or have received a COVID-19 vaccination. Further, at the time of study recruitment, there would have been uncertainty regarding the best alternative treatments and standard of care may be sub-optimal compared to current practice. Given these considerations, there is now a less clear rationale for the benefits of convalescent plasma therapy as exposure and vaccination mean only a small minority of people are immunologically naïve and other effective treatments are available.

4.1 All-cause mortality

The EUnetHTA RCR meta-analysis included nine studies reporting on all-cause mortality. There was no difference between convalescent plasma therapy and control treatment (RR = 0.98, 95%CI, 0.92 to 1.05) with moderate certainty of evidence.

Fourteen of the more recent RCTs published findings on all-cause mortality. Of these, 12 reported that mortality was not different for participants who received convalescent plasma therapy compared to standard. One study reported that there were significantly fewer deaths for those receiving CPT, although there appeared to be imbalance between arms at baseline and this may have favourably impacted outcomes for this group. A further study on preventing progression of COVID-19 in a community setting reported few deaths in both arms.

4.2 Discharge from hospital

The EUnetHTA RCR meta-analysis included three studies reporting on the number of patients discharged from hospital during follow-up. There was no difference across arms (RR 1.00, 95%CI 0.95 to 1.05) with a moderate certainty of evidence.

One more recent study also reported on this outcome (Devos et al. 2021). It also reports no difference across arms (HR = 1.06, 95%CI, 0.87 to 1.30)

4.3 Duration of hospitalisation and hospitalisation in intensive care

The EUnetHTA RCR meta-analysis included three studies reporting on duration of hospitalisation and one study reported on duration of hospitalisation in intensive care. They report no difference on duration in hospitalisation (HR 1.08. 95%CI, 0.80 to 1.48) or hospitalisation in ICU (HR 0.94, 95%CI 0.48 to 1.82). Findings on hospitalisation had very low certainty but findings for hospitalisation in ICU had high certainty.

From more recent studies, seven reported on duration of hospitalisation and three reported on duration of hospitalisation in ICU. All of these studies reported no difference for those who received convalescent plasma therapy compared to controls.

4.4 Prevention of COVID-19 and COVID-19 hospitalisation

One study reported on the effectiveness of convalescent plasma therapy for preventing SARS-CoV-2 infection and development of COVID-19 symptoms for individuals receiving intervention as post exposure prophylaxis (Shoham et al. 2021). They report that there was no difference between arms for infection (CPT, 12/81, 14.8%; Control, 13/87, 14.9%), symptomatic infection (CPT, 6/81, 7.4%; Control, 7/87, 8%) or hospitalisation for COVID-19 (CPT, 0/81, 0%; Control, 2/87, 2.3%).

A further study reported on effectiveness of convalescent plasma therapy for preventing progression of COVID-19 for people with symptoms (Sullivan et al. 2021). They report that there were fewer hospitalisations for participants receiving convalescent plasma therapy (RR =0.46; 95%CI, NR to 0.77, p = 0.004). All but one of the participants hospitalised in this trial were unvaccinated.

4.5 SARS-CoV-2 clearance and disease progression after hospitalisation

The EUnetHTA RCR meta-analysis included three studies reporting on SARS-CoV-2 clearance and five studies reporting disease progression, both after hospitalisation. A significantly higher number of people receiving convalescent plasma therapy had SARS-CoV-2 clearance (RR 1.82, 95%CI, 1.19 to 2.77) but there was no difference in disease progression (RR 0.96, 95%CI, 0.88 to 1.21). These findings were both judged to have moderate certainty.

4.6 Adverse events

The EUnetHTA RCR meta-analysis included five studies reporting on adverse events and three studies reporting on serious adverse events. There was a trend towards greater adverse (39.3% vs. 24.5%, RR 1.08, 95%CI 0.91 to 1.28) and serious adverse events (15.4% vs. 8.3%, RR 1.31, 95%CI 0.82 to 2.09) in the convalescent plasma therapy arm but neither difference was statistically significant. These findings were judged to have moderate and high certainty, respectively.

Eight of the more recent RCTs also reported on numbers of severe adverse events. Of those reporting statistics on relative risk, two report no difference and one reports that there were significantly fewer events in the control arm. Other studies reporting proportions appeared to find comparable rates for participants in convalescent plasma therapy and control arms.

Table 1. Convalescent plasma therapy compared to standard care or placebo: outcomes from the EUnetHTA RCR meta-analysis

Outcome	No. of patients		Relative effect (95% CI)	Absolute effect (95% CI)	No. of studies	Certainty of evidence (GRADE)
	CPT	Standard Treatment				
All-cause mortality	1488/6531 (22.8%)	1494/6374 (23.4%)	RR 0.98 (0.92 to 1.05)	5 fewer per 1.000 (from 19 fewer to 12 more)	9	Moderate
SARS-CoV-2 clearance	180/325 (55.4%)	123/323 (38.1%)	RR 1.82 (1.19 to 2.77)	312 more per 1,000 (from 72 more to 674 more)	3	Moderate
Number of patients discharged from hospital	4047/6075 (66.6%)	3944/5919 (66.6%)	RR 1.00 (0.95 to 1.05)	0 fewer per 1.000 (from 33 fewer to 33 more)	3	Moderate
Duration of hospitalisation	NA	NA	HR 1.08 (0.80 to 1.48)	NA	3	Very low
Duration of hospitalisation in intensive care	NA	NA	HR 0.94 (0.48 to 1.82)	NA	1	High
Number of patients with AE	164/417 (39.3%)	73/298 (24.5%)	RR 1.08 (0.91 to 1.28)	20 more per 1.000 (from 22 fewer to 69 more)	5	Moderate
Number of patients with SAE	54/351 (15.4%)	19/228 (8.3%)	RR 1.31 (0.82 to 2.09)	26 more per 1.000 (from 15 fewer to 91 more)	3	High
Disease progression	717/6056 (11.8%)	726/5882 (12.3%)	RR 0.96 (0.88 to 1.21)	5 fewer per 1.000 (from 15 fewer to 7 more)	5	Moderate

AE=Adverse Events; HR=hazard ratio; NA=not applicable; RR=risk ratio; SAE=Serious Adverse Events; SARS-CoV-2 = severe acute respiratory syndrome-related coronavirus

Table 2. Convalescent plasma therapy compared to standard care or placebo: outcomes from individual studies

Outcome	Evidence source	Absolute effect	Relative effect
All-cause mortality	Bar et al. (2021)	Control: 10/39 (25.6%) CPT: 2/40 (5%)	OR = 0.156 (95%CI, 0.015 to 0.814) Favours CPT
	Bégin et al. (2021)	Control: 63/307 (20.5%) CPT: 141/614 (23.0%)	RR = 1.12 (95%CI, 0.86 to 1.46, p = 0.40) Favours neither
	Devos et al. (2021)	NR	HR = 0.99 (95%CI, 0.52 to 1.88) Favours neither
	Holm et al. (2021)	Control: 3/14 (21.4%) CPT: 2/17 (11.8%)	OR = 0.49 (95%CI, 0.08 to 2.79, p = 0.64) Favours neither
	Kirenga et al. (2021)	Control: 8/67 (11.9%) CPT: 10/69 (14.5%)	NR (p = 0.661) Favours neither
	Körper et al. (2021)	Control: 8/52 (15.4%) CPT: 7/53 (13.2%)	NR (p = 0.79) Favours neither
	Menichetti et al. (2021)	Control: 19/240 (7.9%) CPT: 14/231 (6.1%)	NR (p = 0.43) Favours neither
	O'Donnell et al. (2021)	Control: 18/73 (24.6%) CPT: 19/150 (12.6%)	OR = 0.47 (95%CI, 0.21 to 1.06, p = 0.068) Favours neither
	Pouladzadeh et al. (2021)	NR	aOR = 0.31 (95% CI 0.01–10.07, p = 0.505) Favours neither
	Sekine et al. (2021)	Control: 13/80 (16.3%) CPT: 18/80 (22.5%)	RR = 1.38 (95%CI, 0.73 to 2.63, p = 0.321) Favours neither
	Sullivan et al. (2021)	Control: 3/589 (0.5%) CPT: 0/592 (0%)	NR
	Writing Committee for the REMAP-CAP Investigators (2021)	Control: 347/904 (38.4%) CPT: 401/1075 (37.3%)	aOR = 1.04 (95%CI, 0.85 to 1.27)[1] Favours neither
	Baldeón et al. (2022)	Control: 12/95 (12.6%) CPT: 7/63 (11.1%)	RR = 1.00 (95%CI, 0.39 to 2.56) Favours neither
	Ortigoza et al. (2022)	Control: 59/462 (15.4%) CPT: 71/462 (12.8%)	OR = 0.86 (95%CrI, 0.60 to 1.25) Favours neither
Hospital admission	Shoham et al. (2021)	Control: 2/87 (2.3%) CPT: 0/81 (0%)	NR
	Sullivan et al. (2021)	Control: 37/589 (6.3%) CPT: 17/592 (22.5%)	RR =0.46 (95%CI, NR to 0.77, p = 0.004) Favours CPT

Outcome	Evidence source	Absolute effect	Relative effect
Number of patients discharged from hospital	Devos et al. (2021)	NR	HR = 1.06 (95%CI, 0.87 to 1.30) Favours neither
Duration of hospitalisation (days)	Holm et al. (2021)	Control: median, 8 CPT: median, 13	MeD = -5 (p = 0.21) Favours neither
	Körper et al. (2021)	Control: median, 51 CPT: median, 31	MeD = -20 (p = 0.24) Favours neither
	Menichetti et al. (2021)	Control: median, 13 CPT: median, 12	MeD = -1 (p = 0.73) Favours neither
	O'Donnell et al. (2021)	Control: median, 8 CPT: median, 9	HR = 1.02 (95%CI, 0.75 to 1.38, p = 0.913) Favours neither
	Pouladzadeh et al. (2021)	NR	HR = 0.37 (95%CI, 0.02–6.84, p = 0.502)
	Sekine et al. (2021)	Control: median, 8 CPT: median, 10	NR
	Writing Committee for the REMAP-CAP Investigators (2021)	NR	aHR = 0.96 (95%CrI, 0.80 to 1.13) Favours neither
Duration of hospitalisation in intensive care (days)	Bégin et al. (2021)	Control: mean, 3.7 CPT: mean, 4.3	MD = 0.7 (95%CI, -0.3 to 1.7, p = 0.22) Favours neither
	Körper et al. (2021)	Control: median, 42 CPT: median, 29	MD = -13 (p = 0.39) Favours neither
	Writing Committee for the REMAP-CAP Investigators (2021)	NR	aHR = 0.94 (95%CrI, 0.85 to 1.04) Favours neither
Number of patients with SAE	Bar et al. (2021)	Control: 15/39 (38.5%) CPT: 12/40 (30%%)	OR = 0.69 (95%CI, 0.24 to 0.1.93) Favours neither
	Bégin et al. (2021)	Control: 81/307 (26.4%) CPT: 205/614 (33.4%)	RR = 1.27 (95%CI, 1.02 to 1.57, p = 0.03) Favours control
	Devos et al. (2021)	Control: 36/163 (22.1%) CPT: 66/320 (20.6%)	NR
	Holm et al. (2021)	Control: 0/14 (0%) CPT: 0/17 (0%)	NA
	Körper et al. (2021)	Control: 25/52 (48.1%) CPT: 22/53 (41.5%)	NR
	O'Donnell et al. (2021)	Control: 36/72 (36.1%) CPT: 39/147 (26.5%)	NR
	Sekine et al. (2021)	Control: 44/80 (54.3%) CPT: 50/80 (63.3%)	RR = 1.14 (95%CI, 0.88 to 1.48, p = 0.34) Favours neither

Outcome	Evidence source	Absolute effect	Relative effect
	Writing Committee for the REMAP-CAP Investigators (2021)	Control: 12/905 (1.3%) CPT: 32/1075 (3%)	NR

[1] adjusted odds ratio reported as survival

CI = confidence interval; CPT = convalescent plasma therapy; CrI = credible interval; HR = hazard ratio; MeD = median difference; MD = mean difference; NR = not reported; NA = not applicable; OR = odds ratio; RR = risk ratio; SAE = serious adverse events

4.7 Ongoing trials

The EUnetHTA RCR reported on all ongoing trials registered in the Cochrane COVID-19 Study Registry, ClinicalTrials.gov, ISRCTN, and the EU Clinical Trials Register. On publication of the final RCR in May 2021, there were 106 ongoing trials. Details of these ongoing trials can be found in Table 4.10 to 4.33 in the EUnetHTA RCR. A number of the ongoing trials recorded in EUnetHTA RCR are now published and included in this EAR and due to the number of trials now published on convalescent plasma therapy and consistent null findings, it is likely that a large number of the remaining trials will go unpublished.

5. Economic evaluation

No economic evaluations of convalescent plasma therapy were identified in the literature and there was no value in de-novo analyses being completed due to evidence demonstrating that convalescent plasma did not lead to benefits for patients.

6. Organisational issues

In the early stages of the COVID-19 pandemic, convalescent plasma therapy was available to some patients as part of the RECOVERY and REMAP-CAP platform trials with a number of hospitals in Wales participating as trial sites. After the RECOVERY and REMAP-CAP trials published findings showing no benefit compared to usual care, it was agreed that convalescent plasma collection would be suspended in Wales and convalescent plasma therapy would not continue outside of the research setting. As such, convalescent plasma therapy is not currently in use for people with COVID-19 in Wales.

7. Conclusions

The aim of this EAR was to examine the clinical effectiveness of convalescent plasma therapy for people with COVID-19. Evidence is available from a large number of RCTs and the availability of the EUnetHTA RCR allowed some of this data to be presented within a meta-analysis.

The evidence demonstrates that use of convalescent plasma therapy does not lead to improved outcomes for people with COVID-19 who are hospitalised across a range of measures. This is despite some evidence that convalescent plasma therapy may lead to earlier clearance of the virus. Studies with people in the community who have recently been exposed to the virus or are in the early stages of COVID-19 provide some evidence that it may reduce hospitalisation. However, the absolute reduction in events is limited and very few deaths occurred in these trials. As trials were initiated in the early stages of the pandemic, these results reflect outcomes for people who were not vaccinated. With the wide rollout of vaccine programmes, most people now have some level of pre-existing to SARS-CoV-2 and this undermines the rationale of using convalescent plasma to provide passive immunity. In support of this notion, trials of early use of convalescent plasma therapy did not observe any hospitalisations of people who were vaccinated and the benefits for early use suggested by these trials may not be present in populations with widespread vaccination.

Use of convalescent plasma therapy was seen as a potential treatment early in the pandemic, particularly while there was uncertainty around the time needed to develop vaccines and other therapeutics. However, there is now strong evidence that it does not provide benefit to patients

with COVID-19. These findings should provide caution for assumptions about the benefits of use of convalescent plasma for other viruses and in future pandemics.

8. Contributors

This topic was selected as part of EUnetHTA programme of rolling collaborative reviews (RCR) on COVID-19 treatments. HTW led the authoring team with support for searching and extracting data from Department of Epidemiology Lazio Regional Health Service (DEPLazio) and Norwegian Institute of Public Health (NIPHNO). The RCR programme was project managed by Zorginstituut Nederland (ZIN) and Austrian Institute for Health Technology Assessment (AIHTA).

The HTW staff researchers involved in writing this report were:

- J Washington, Information Specialist – literature search and information management
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- T Winfield, Senior Health Economist – project set-up

The EUnetHTA RCR team advised on methodology throughout the scoping and development of the RCR reports and the HTW Assessment Group advised on methodology prior to the RCR being published as an Evidence Appraisal Report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

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10. Evidence review methods

We searched for evidence that could be used to answer the review question: what is the clinical effectiveness of convalescent plasma therapy for people with COVID-19?

The criteria used to select evidence for the appraisal are outlined in Appendix 1. These criteria are based on those used during the EUnetHTA RCR programme and have been updated with input from the HTW Assessment Group. In particular, the RCR programme included RCTs for effectiveness outcomes, as well as observational studies for safety outcomes. This evidence appraisal review reports the highest priority evidence available for effectiveness and safety outcomes and due to the presence of a number of RCTs, observational studies are not included here.

The search strategy and inclusion criteria were adapted throughout the course of the RCR programme and development of this evidence appraisal report. Up to the final search of the RCR programme (3rd May 2021), a monthly search of MEDLINE, PubMed, and EMBASE databases was completed by DEPLazio. They also searched medRxiv.org, bioRxiv.org, and arXiv.org for preprints, as well as relevant websites (e.g. World Health Organisation, Imperial College London, London School of Hygiene and Tropical Medicine, Eurosurveillance, Cochrane Covid-19 Study Register. Relevant researchers were also contacted. Four authors independently screened the references retrieved by the search, selected the studies, and extracted the data, using a predefined data-extraction sheet. The same reviewers discussed any uncertainty regarding study eligibility and data extraction until consensus was reached. Two authors independently assessed the risk of bias of the included studies with the Cochrane risk of bias tool (Sterne et al. 2019) . Three authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to evaluate the strength of evidence.

Prior to publication of this evidence appraisal report, HTW completed a final search of MEDLINE, PubMed, and EMBASE databases on February 22nd 2022. A single author then screened the references retrieved by the search, selected the studies, and extracted data. The same author also used the Cochrane tool to assess risk of bias (Sterne et al. 2019) and used the GRADE approach (Schünemann et al. 2013) to identify and report any issues with certainty of the evidence. Appendix 2 gives details of the search strategy used for MEDLINE. Search strategies for other databases are available on request. Appendix 3 summarises the selection of articles for inclusion in the review.

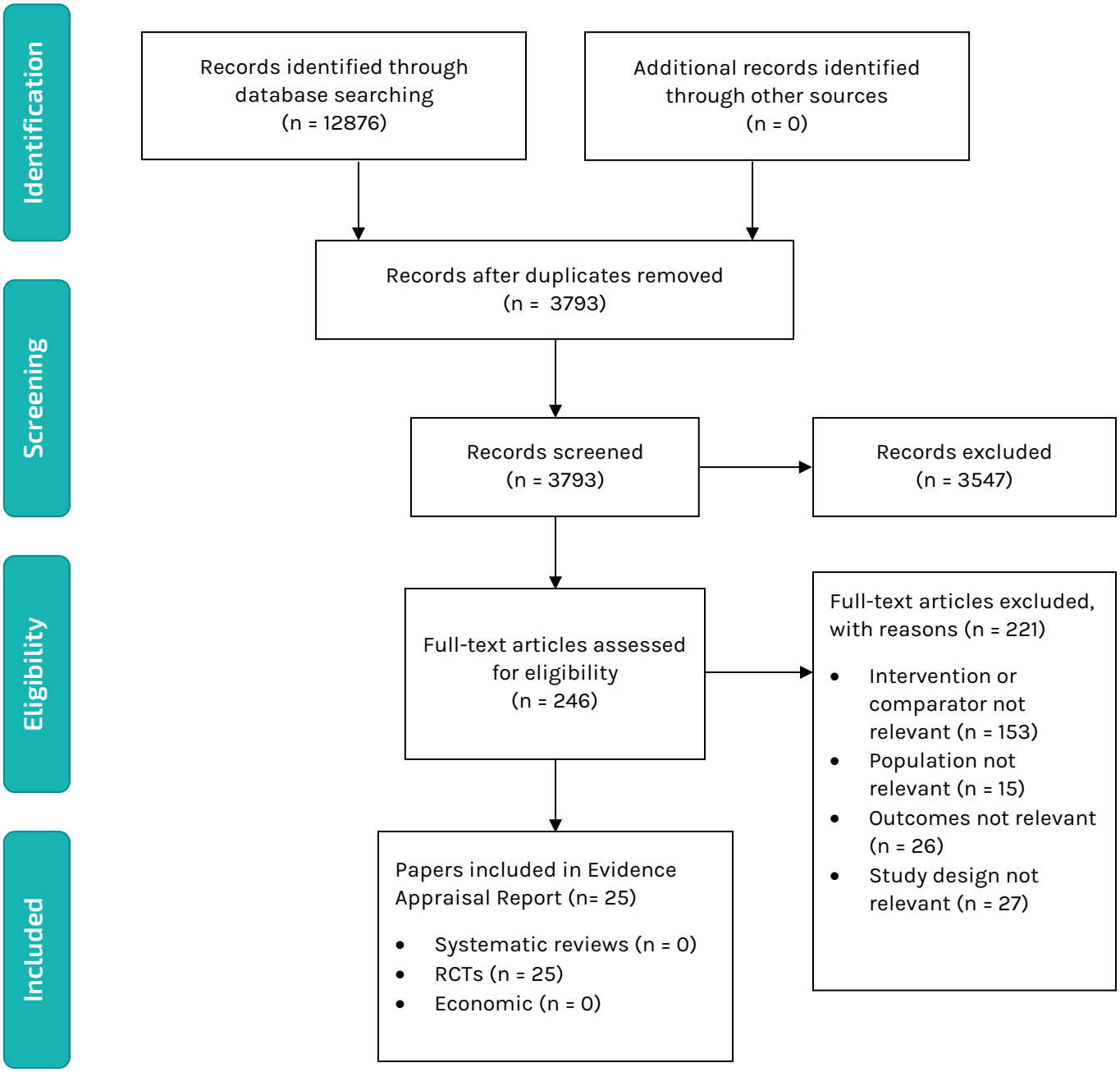
Appendix 1. Inclusion criteria for evidence included in the review

	Inclusion criteria
Population	People with SARS-CoV-2 caused COVID-19
Intervention	Convalescent plasma therapy
Comparison/ Comparators	Any active treatment, placebo, or usual care
Outcome measures	Effectiveness outcomes (e.g. all-cause mortality, clinical progression, viral burden, admission to hospital, admission to intensive care) Safety outcomes (e.g. adverse events, withdrawals due to adverse events, deaths)
Study design	The following study types were prioritised, in the order listed: Randomised controlled trials Non-randomised controlled trials Single-arm trials We will only include evidence for "lower priority" evidence where outcomes for each condition/symptom of interest are not reported by a "higher priority" source or where "lower priority" evidence relates to an intervention assessed to be of high potential. We will also search for economic evaluations or original research that can form the basis of an assessment of costs/cost comparison and for qualitative studies that provide information on patient or organisational issues.
Search limits	None
Other factors	Where evidence allows, we will report outcomes separately according to disease severity (e.g. mild, moderate, severe)

Appendix 2. MEDLINE search strategy

Ovid MEDLINE(R) ALL <1946 to February 09, 2022>		
DEPlazio search strategy (for all RCRs)		
1	exp coronavirus/	123640
2	((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.	4240
3	(coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw.	238096
4	(((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw.	818
5	((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw.	400
6	"severe acute respiratory syndrome*".ti,ab,kw.	29908
7	or/1-6	249017
8	randomized controlled trial.pt.	558338
9	controlled clinical trial.pt.	94693
10	random*.ab.	1253392
11	placebo.ab.	225542
12	clinical trials as topic.sh.	199143
13	random allocation.sh.	106583
14	trial.ti.	256444
15	or/8-14	1778188
16	exp animals/ not humans.sh.	4956807
17	15 not 16	1601147
18	7 and 17	10428
19	limit 18 to yr="2019 -Current"	9815
HTW CPT search strategy		
20	((convales* or hyperimmun* or hyper-immun* or titer* or titre*) adj3 (plasma* or serum or sera or blood)).tw,kf.	20354
Set combination and date restriction		
21	19 and 20	287
22	(202105* or 202106* or 202107* or 202108* or 202109* or 20211* or 2022*).dt.	1196215
23	21 and 22	106

Appendix 3. Flow diagram outlining selection of relevant evidence sources



Appendix 4. Study characteristics

Characteristics of randomised controlled trials comparing convalescent plasma therapy to standard care, standard plasma, fresh frozen standard plasma, or saline

Table A1. Gharbharan et al. (2020), Li et al. (2020), Agarwal et al. (2020), AlQahtani et al. (2020), Avendaño-Solà et al. (2020), Simonovich et al. (2021)

Author, year	Gharbharan et al. (2020)	Li et al. (2020)	Agarwal et al. (2020)	AlQahtani et al. (2020)	Avendaño-Solà et al. (2020)	Simonovich et al. (2021)
Trial ID, name	NCT04342182 ConCOVID	ChiCTR2000029757	CTRI/2020/04/024775 PLACID	NCT04356534	NCT04345523	NCT04383535 PlasmAr
Sponsor	Erasmus Medical Center	China-Japan friendship hospital	Indian Council Of Medical Research	Royal College of Surgeons in Ireland – Medical University of Bahrain	Instituto de Salud Carlos III	Hospital Italiano de Buenos Aires
Single/multicentre, country, setting	Multicentre; Netherlands; Hospital	Multicentre; China; Hospital	Multicentre; India; Hospital	Singe centre; Bahrain; Hospital	Multicentre; Spain; Hospital	Multicentre; Argentina; Hospital
Patient population	Total (n = 86) CPT (n=43) Mean age = 61 Female = 23% Control (n=43) Mean age = 63 Female = 33%	Total (n = 103) CPT (n=52) Mean age = 70 Female = 48.1% Control (n=51) Mean age = 69 Female = 35.3%	Total (n = 464) CPT (n=235) Mean age = 52 Female = 25.0% Control (n=229) Mean age = 52 Female = 23%	Total (n = 40) CPT (n=20) Mean age = 50.7 Female = 25.0% Control (n=20) Mean age = 52.6 Female = 15%	Total (n = 81) CPT (n=38) Mean age = 60.5 Female = 47.4% Control (n=43) Mean age = 58.0 Female = 44.2%	Total (n = 333) CPT (n=228) Mean age = 62.5 Female = 29.4% Control (n=105) Mean age = 62 Female = 39.0%
Inclusion criteria	RT-PCR confirmed COVID-19 diagnosis; aged 18 years or older	PCR confirmed COVID-19 diagnosis; imaging confirmed pneumonia; aged 18 years or older; severe or life threatening condition	RT-PCR confirmed COVID-19 diagnosis; aged 18 years or older; moderate illness defined by oxygen saturation	PCR confirmed COVID-19 diagnosis; imaging confirmed pneumonia; aged 18 years or older; hypoxia requiring oxygen therapy	PCR confirmed COVID-19 diagnosis; aged 18 years or older; hospitalised without mechanical ventilation or high flow oxygen	qRT-PCR confirmed COVID-19 diagnosis; imaging confirmed pneumonia; modified SOFA score of 2 or more

Author, year	Gharbharan et al. (2020)	Li et al. (2020)	Agarwal et al. (2020)	AlQahtani et al. (2020)	Avendaño-Solà et al. (2020)	Simonovich et al. (2021)
Exclusion criteria	IgA deficiency; on mechanical ventilation for >96 hours	Women who were pregnant or lactating; receiving other experimental treatments; immunoglobulin allergy; life expectancy <24 hrs; severe congestive heart failure or comorbidity with increased risk of thrombosis	Women who were pregnant or lactating; known hypersensitivty to blood products or conditions precluding tranfusion; receiving other experimental treatments	Receiving ventilator support; history of allergic reaction to blood interventions; those with autoimmune disease	More than 12 days since onset of symptoms; receiving other experimental treatments, progression to death imminent or inevitable, allergy to blood interventions; stage 4 chronic kidney disease	Women at reproductive age having unprotected sex or pregnant; breastfeeding; receiving other experimental treatments; history of allergic reaction to blood interventions; use of systemic corticosteroids
Intervention	Convalescent plasma therapy (300 ml) with current standard of care	Convalescent plasma therapy (4-13 ml/kg at rate of 10 ml for first 15 minutes and 100 ml per hour thereafter with adjustment for volume and tolerance) with standard standard	Convalescent plasma therapy (400 ml given as 200 ml doses over 2 hrs and 24 hrs apart) with best standard care	Convalescent plasma therapy (400 ml given as 200 ml over 2 hrs over 2 days, rate adjusted if risk of fluid overload) with standard supportive care	Convalescent plasma therapy (single unit of 250-300 ml) with standard of care	Convalescent plasma therapy (10-15 ml/kg at rate of 5-10 ml/kg/h; mean IgB antibodies 1:3200) with standard of care
Comparator(s)	Current standard of care	Standard treatment (including antiviral, antibacterial, steroids, human immunoglobulin, Chinese herbal, and other medications)	Best standard care	Standard supportive treatment (including antiviral, tocilizumab, antibacterial agents)	Standard of care for treatment of COVID-19	Placebo (normal saline solution) with standard of care (including antiviral agents and glucocorticoids)
Follow-up (days, months)	60-days after admission	28-days post transfusion	28-days post transfusion	28-days (timing of recruitment and transfusion not reported)	29-days post transfusion	30 days post-transfusion

Table A2. Libster et al. (2020), Ray et al. (2020), Bajpai et al. (2020), RECOVERY Collaborative Group (2021), Bar et al. (2021)

Author, year	Libster et al. (2020)	Ray et al. (2020)	Bajpai et al. (2020)	RECOVERY Collaborative Group (2021)	Bar et al. (2021)
Trial ID, name	NCT04479163	CTRI/2020/05/025209	NCT04346446	NCT04381936 RECOVERY	NCT04397757 PennCCP2
Sponsor	Fundacion INFANT	Council of Scientific and Industrial Research (India)	Institute of Liver and Biliary Sciences	University of Oxford	University of Pennsylvania
Single/multicentre, country, setting	Multicentre; Argentina; Hospital	Multicentre; India; Hospital	Singe centre; India; Hospital	Multicentre; UK; Hospital	Two centres; USA; hospital
Patient population	Total (n = 160) CPT (n=80) Mean age = 76.4 Female = 68% Control (n=80) Mean age = 77.9 Female = 58%	Total (n = 80) Mean age = 61.36 Female = 29% CPT (n=40) Control (n=43)	Total (n = 29) CPT (n=14) Mean age = 48.1 Female = 21.4% Control (n=15) Mean age = 48.3 Female = 26.7%	Total (n=11558) CPT (n=5795) Mean age = 63.6 Female = 37% Control (n=5763) Mean age = 63.4 Female = 34%	Total (n = 79) CPT (n= 40) Median age = 61 to 74 Female = 61.5% Control (n=39) Median age = 61 to 74 Female = 47.5%
Inclusion criteria	RT-PCR confirmed COVID; aged 75 years and over; or between 65 and 74 years with at least one comorbidity/risk factor for poor outcomes	RT-PCR confirmed COVID with severe disease	PCR confirmed COVID-19 diagnosis; severe condition	Hospitalised patients with clinically suspected or laboratory-confirmed SARS-COV-2 infection.	RT-PCR–confirmed SARS-CoV-2 infection; radiographic documentation of pneumonia; abnormal respiratory status
Exclusion criteria	Already presenting with severe respiratory disease	Pregnant or breastfeeding women; aged under 18; participation in other clinical trial; condition precluding blood tranfusion; not on mechanical ventilation	Under 18 or over 65 years of age; comorbid conditions; multi-organ failure or mechanical ventilation; morbid obesity; pregnant women; life expectancy <24 hrs; known history of allergy to blood interventions	Medical history that may put them at significant risk for the trial (i.e. contraindication to one of the active drugs in the platform trial); advance directive or behaviour indicating they did not wish to participate, if lacking capacity	Contraindication to transfusion, were participating in other clinical trials of investigational COVID-19 therapy; clinical suspicion that the etiology of acute illness was primarily due to a condition other than COVID-19; ABO-compatible CPT was unavailable

Author, year,	Libster et al. (2020)	Ray et al. (2020)	Bajpai et al. (2020)	RECOVERY Collaborative Group (2021)	Bar et al. (2021)
Intervention	Convalescent plasma (250 ml with titer above 1:1000)	Convalescent plasma (given as two doses of 200ml on two consecutive days)	Convalescent plasma therapy (500 ml in two doses on consecutive days) with standard of care	Convalescent plasma (high titre plasma given as two units of 275mls +/- 75 mls)	Convalescent plasma (2 units of locally sourced plasma)
Comparator(s)	Placebo (saline) with standard of care	Standard of care	Fresh frozen plasma from random donor (500 ml in two doses on consecutive days) with standard of care	Usual care	Standard care
Follow-up (days, months)	25 days	30 days	28-days post transfusion	28 days	28 days

Table A3. Bégin et al. (2021), Devos et al. (2021), Holm et al. (2021), Kirenga et al. (2021), Körper et al. (2021)

Author, year	Bégin et al. (2021)	Devos et al. (2021)	Holm et al. (2021)	Kirenga et al. (2021)	Körper et al. (2021)
Trial ID, name	NCT04348656 CONCOR-1	NCT04429854 DAWn-plasma	NCT04600440	NCT04542941 COVIDIT	NCT04433910 CAPSID
Sponsor	Hamilton Health Sciences Corporation	Universitaire Ziekenhuizen Leuven	Skåne University Hospital	Makerere University	Deutsches Rotes Kreuz DRK-Blutspendedienst Baden-Wurttemberg-Hessen
Single/multicentre, country, setting	Multicentre; Canada, United States, Brazil; Hospital	Multicentre; Belgium; Hospital	Single centre; Sweden; Hospital	Single centre; Uganda; Hospital	Multicentre; Germany; Hospital
Patient population	Total (n = 938) CPT (n = 625) Mean age = 67 Female = 41% Control (n = 313) Mean age = 67 Female = 41%	Total (n = 483) CPT (n=320) Mean age = 62 Female = 21.6% Control (n=163) Mean age = 62 Female = 20.7%	Total (n = 31) CPT (n=17) Mean age = 80 Female = 35% Control (n=14) Mean age = 65 Female = 43%	Total (n = 136) CPT (n=69) Median age = 48 Female = 20.4% Control (n=67) Median age = 53 Female = 26.9%	Total (n = 106) CPT (n=53) Median age = 59 Female = 20.8% Control (n=52) Median age = 62 Female = 32.7%
Inclusion criteria	Eligible participants were (1) ≥16 years of age in Canada or ≥18 years of age in the United States and Brazil; (2) admitted to the hospital ward with confirmed COVID-19; (3) required supplemental oxygen	Adult (⩾18 years) hospitalised patients with laboratory or radiologically confirmed COVID-19	RT-PCR confirmed COVID; need for supplemental oxygen treatment	SARS- CoV-2 confirmed by positive RT- PCR	(a) SARS-CoV-2 infection confirmed by PCR (bronchoalveolar lavage, sputum, nasal and/or pharyngeal swab); (b) age ≥18 years and ≤75 years; (c) severe disease defined by at least 1 of the following: (i) respiratory rate ≥30 breaths/min under ambient air, (ii) requirement of any type of respiratory support (defined as supplemental oxygen, noninvasive or

Author, year	Bégin et al. (2021)	Devos et al. (2021)	Holm et al. (2021)	Kirenga et al. (2021)	Körper et al. (2021)
					invasive ventilation, or ECMO), (iii) need of treatment on ICU
Exclusion criteria	(1) more than 12 d from the onset of respiratory symptoms; (2) imminent or current intubation; (3) a contraindication to plasma transfusion; or (4) a plan for no active treatment.	Receiving mechanical ventilation upon assessment or a therapy restriction code excluding mechanical ventilation and/or endotracheal intubation; pregnancy or lactation, a documented previous grade 3 allergic reaction to plasma transfusions and treatment with rituximab or another anti-CD20 monoclonal antibody during the past year	Age below 18, a habitual oxygen saturation below 94%, inability to give informed consent and severe immunosuppression	Prior diagnosis of IgA deficiency	Opinion that death is imminent; presence of other signfiicant comorbidities, including COPD, chronic heart failure NYHA 3 or more.
Intervention	Convalescent plasma (one or two units of apheresis plasma amounting to approximately 500 ml from one or two donors)	Convalescent plasma (two units, 200 to 250 mL with a second administration of two units 24 to 36 hrs later)	Convalescent plasma (100-250 mL of CPT administered intravenously during 30 min on three consecutive days)	Convalescent plasma (Plasma administered at 1.4 to 2 mL per minute with second aliquot after 3 hrs)	Convalescent plasma (One transfusion unit each of CPT was given on days 1, 3, and 5)
Comparator(s)	Standard of care	Standard of care	Standard of care	Standard of care	Standard of care (with cross-over to CPT at day 14 if COVID-19 progressed)
Follow-up (days, months)	30 days	30 days	28 days	28 days	60 days

Table A4. Menichetti et al. (2021), O'Donnell et al. (2021), Pouladzadeh et al. (2021), Sekine et al. (2021), Shoham et al. (2021)

Author, year	Menichetti et al. (2021)	O'Donnell et al. (2021)	Pouladzadeh et al. (2021)	Sekine et al. (2021)	Shoham et al. (2021)
Trial ID, name	NCT04716556 TSUNAMI	NCT04359810	IRCT20200310046736N1	NCT04547660 PLACOVID	NCT04323800 CSSC-001
Sponsor	Istituto Superiore di Sanità	Columbia University	Ahvaz Jundishapur University of Medical Sciences	Hospital de Clínicas de Porto Alegre	Johns Hopkins University
Single/multicentre, country, setting	Multicentre; Italy; Hospital	Multicentre; United States, Brazil; Hospital	Single centre; Iran; hospital	Single centre; Brazil; Hospital	Multicentre; United States; Community
Patient population	Total (n = 473) CPT (n=232) Median age = 65 Female = 35.2% Control (n=241) Mean age = 63 Female = 36.1%	Total (n = 223) CPT (n=150) Mode age = under 60 Female = 36% Control (n=73) Mode age = under 60 Female = 30%	Total (n = 60) CPT (n=30) Mode age = over 50 Female = 46.7% Control (n=30) Mode age = over 50 Female = 43.3%	Total (n = 160) CPT (n=80) Mean age = 59.0 Female = 38.8% Control (n=80) Mean age = 62.0 Female = 45%	Total (n = 180) CPT (n=87) Median age = 48 Female = 47.1% Control (n=93) Median age = 46 Female = 43%
Inclusion criteria	RT-PCR confirmed COVID-19, radiologically confirmed pneumonia within no more than 10 days from onset of symptoms and partial pressure of oxygen–to–fraction of inspired oxygen (PaO2/FiO2) ratio between 200 and 350mmHg at baseline	Hospitalized patients aged 18 years or older with evidence of SARS-CoV-2 infection by PCR of nasopharyngeal, oropharyngeal swab or tracheal aspirate sample within 14 days of randomization, with infiltrates on chest imaging and oxygen saturation less than or equal to 94% on room air or requirement for supplemental oxygen (including noninvasive positive pressure	PCR and CT scan confirmed COVID-19, severity WHO score of 4 or above, blood oxygen saturation below 93%, no hypersensitivity to plasma administration	⩾18 years, had a positive reverse transcriptase (RT)-PCR for SARS-CoV-2, had <15 days since initial symptom onset and had severe respiratory disease, as defined by the presence of at least one of the following: respiratory rate >30 breaths·min-1 in room air; oxygen saturation ≤93% in room air; PaO2/FiO2 ratio ≤300; need for supplemental O2 to maintain O2 saturation>	Aged ≥18 years who had a close contact exposure to a person with confirmed COVID-19 in the previous 120 hours and did not have SARS-CoV-2 vaccination

Author, year	Menichetti et al. (2021)	O'Donnell et al. (2021)	Pouladzadeh et al. (2021)	Sekine et al. (2021)	Shoham et al. (2021)
		ventilation or high flow supplemental oxygen), IMV, or extracorporeal membrane oxygenation (ECMO) at the time of screening		95%; need for therapy with supplemental 02 by high flow catheter or non-invasive ventilation or invasive mechanical ventilation	
Exclusion criteria	Pregnant and lactating women, patients with known hypersensitivity to blood products, recipients of immunoglobulin in the past 30 days, patients with conditions precluding infusion of blood products, participants in any other clinical trials, and patients requiring noninvasive or invasive mechanical ventilation as well as patients receiving treatment with interleukin (IL) 1, IL 6, or Janus kinase inhibitors at the time of randomization	Participation in another clinical trial of antiviral agent(s) for COVID-19; receipt of any antiviral agent with possible activity against SARS-CoV-2 within 24 hours of randomization; duration of IMV or ECMO 5 days or longer at time of screening; severe multiorgan failure; history of prior reactions to transfusion blood products.	Not reported	Impossibility for any reason to perform the first plasma infusion within 14 days of the onset of symptoms; use of immunosuppressive drugs for other non-COVID-19 underlying diseases in the 30 days before enrolment; pregnancy; history of serious adverse reactions such as transfusion anaphylaxis; disagreement of attending physician; and participation in other interventional randomised clinical trials	Past or active SARS-CoV-2 infection
Intervention	Convalescent plasma (volume infused was 200mL, given over a period of 2.0 hours daily from 1 to a maximum of 3 infusions)	Convalescent plasma (a single unit of plasma (~200–250 milliliters) was transfused over approximately 2 hours)	Convalescent plasma (500 ml on admission day with further unit if no improvement after 24 hours)	Convalescent plasma (two infusions 48 h apart of 300 mL)	Convalescent plasma (1 unit of 200-250 ml)

Author, year	Menichetti et al. (2021)	O'Donnell et al. (2021)	Pouladzadeh et al. (2021)	Sekine et al. (2021)	Shoham et al. (2021)
Comparator(s)	Standard treatment remdesivir (intravenous [IV], 200mg on the first day and 100mg once daily from day 2 to day 5), glucocorticoids (IV dexamethasone 6mg daily or equivalent), and low–molecular weight heparin (subcutaneous enoxaparin, 40-60mg daily or intermediate/high dose in selected cases), according to the AIFA recommendations	Control plasma (oldest available plasma at study site collected prior to Feb 20, 2020)	Standard treatment	Standard of care	Control plasma (collected prior to January 1, 2020 and seronegaitve for SARS-CoV-2)
Follow-up (days, months)	30 days	28 days	2 months	28 days	90 days

Table A5. Sullivan et al. (2021), Writing Committee for the REMAP-CAP Investigators (2021), Baldeón et al. (2022), Ortigoza et al. (2022)

Author, year	Sullivan et al. (2021)	Writing Committee for the REMAP-CAP Investigators (2021)	Baldeón et al. (2022)	Ortigoza et al. (2022)
Trial ID, name	NCT04373460 CSSC-004	NCT02735707 REMAP-CAP	ISRCTN85216856	NCT04364737
Sponsor	Johns Hopkins University	UMC Utrecht	Universidad Tecnolgica Equinoccial	NYU Langone Health
Single/multicentre, country, setting	Multicentre; United States; Community	Multicentre; Australia, Canada, UK, US; Hospital	Multicentre; Ecuador; Hospital	Multicentre; United States; Hospital
Patient population	Total (n = 1181) CPT (n=592) Median age = 42 Female = 54.6% Control (n=589) Median age = 44 Female = 59.8%	Total (n = 1987) CPT (n=1078) Median age = 61 Female = 32.6% Control (n=909) Median age = 61 Female = 32.0%	Total (n = 158) CPT (n=63) Mean age = 56.3 Female = 33.3% Control (n=95) Median age = 55.0 Female = 31.6%	Total (n = 941) CPT (n=468) Median age = 62 Female = 39.3% Control (n=473) Median age = 64 Female = 42.5%
Inclusion criteria	Age >18 years; COVID-19 and within 8 days of symptom onset	8 years or older with confirmed SARS-CoV-2 infection admitted to the hospital and classified as moderately or severely ill	≥18 years of age; from both sexes; COVID-19 diagnosis based on: any molecular testing-polymerase chain reaction (RT-PCR), clinical diagnosis or lung imaging tests; patients with impairment of previously normal lung function defined with a SaO2 <90% at 0.5FiO2 and/or with an increased O2 need in the previous 24 h upon admission	18 years or older hospitalized for 3 days or less or with symptoms of respiratory illness for 7 days or less (to include patients with presumably early phases of disease) who required noninvasive oxygen supplementation and had a positive nasopharyngeal SARSCoV-2 reverse-transcriptase polymerase-chain-reaction test

Author, year	Sullivan et al. (2021)	Writing Committee for the REMAP-CAP Investigators (2021)	Baldeón et al. (2022)	Ortigoza et al. (2022)
Exclusion criteria	Prior COVID-19 hospitalization or planned hospitalization within 24 hours of enrollment, prior transfusion reactions, inability to comply with the protocol transfusion or follow up, or mAb receipt before enrollment	Presumption that death was imminent; lack of commitment to full support or participation in this trial within the prior 90 days. Immunoglobulin domain–specific exclusion criteria included: known hypersensitivity to convalescent plasma; objection to receiving plasma products; previous history of transfusion-related acute lung injury; and more than 48 hours had elapsed since ICU admission or 14 days since hospital admission	Pregnant or lactating; had diagnosis of cancer, HIV infection, superimposed systemic infections, liver failure, renal failure, chronic obstructive pulmonary disease, pulmonary fibrosis, and restrictive pulmonary pathologies; had been receiving immunosuppressants for a different condition than SARS-CoV-2 infection; were participating in any other clinical trial; patients with history of previous blood/derivate transfusion	Receipt of pooled immunoglobulin in the preceding 30 days, contraindication to transfusion, invasive mechanical ventilation or extracorporeal membrane oxygenation, volume overload, considered unlikely to survive past 72 hours based on investigator assessment, and receipt of a COVID-19 vaccine
Intervention	Convalescent plasma (250 mL over one hour)	Convalescent plasma (high titre 550mL ± 150mL within 48hours of randomisation)	Convalescent plasma (5 ml/kg body weight was administered with 10 mL in first 10 minutes followed by 100 mL/hr)	Convalescent plamsa (One unit of CCP (approximately 250 mL) was infused within 24 hours of randomization at a rate of less than or equal to 500 mL/h)
Comparator(s)	Control plasma (donated in 2019, or tested seronegative for SARS-CoV-2)	Standard care	Control plasma	Placebo (saline
Follow-up (days, months)	28 days	90 days	28 days	28 days