Domain-Specific Appendix:

COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

COVID-19 Immunoglobulin Therapy Domain-Specific Appendix Version 4 dated 5th November, 2024

Summary

In this domain, participants meeting platform-entry criteria with microbiological testing confirmed COVID-19 infection will be randomized to receive one of two interventions:

- No immunoglobulin against COVID-19 (no placebo)
- High titer convalescent plasma

At this participating site the following interventions have been selected within this domain:

☐ No immunoglobulin against COVID-19 (no placebo)

☐ High titer convalescent plasma

This domain includes patients aged ≥16 years old. In this region, this domain will be offered to eligible patients aged:

☐ ≥ 16 years and < 18 years old

☐ ≥ 18 years old

This DSA applies to the following states and/or stratum:

Age Stratum	≥ 16 years and < 18 years old		≥ 18 years old	
Illness Severity State	Moderate State	Severe State	Moderate State	Severe State
Domain-specific strata	N/A	N/A	N/A	N/A
Interventions specified in this DSA	• No immunoglobulin for COVID-19 • High-titer convalescent plasma	• No immunoglobulin for COVID-19 • High-titer convalescent plasma	• No immunoglobulin for COVID-19 • High-titer convalescent plasma	• No immunoglobulin for COVID-19 • High-titer convalescent plasma
Interventions submitted for approval in this jurisdiction	☐ No immunoglobulin for COVID-19 ☐ High-titer convalescent plasma	☐ No immunoglobulin for COVID-19 ☐ High-titer convalescent plasma	☐ No immunoglobulin for COVID-19 ☐ High-titer convalescent plasma	☐ No immunoglobulin for COVID-19 ☐ High-titer convalescent plasma

Immunoglobulin Therapy Domain Summary	
Interventions	The following interventions are specified in this domain: • No immunoglobulin against COVID-19 (no placebo) • High titer convalescent plasma
Timing of Reveal	Randomization with Deferred Reveal at time of confirmation of infection by microbiological testing.
Population	This domain will be offered to the following patient categories: • Adolescent and Adult Age Strata • Moderate and Severe Illness Severity States
Domain-Specific Inclusions	Patients will be eligible for this domain if: • Patient is aged ≥ 16 years old • SARS-CoV-2 infection is confirmed by microbiological testing • Patient has an underlying immunodeficiency or has received recent immunosuppressant therapy
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 48 hours has elapsed since commencement of sustained organ failure support in an ICU • Patient has already received treatment with any non-trial prescribed polyclonal antibody therapy (hyperimmune immunoglobulin, or convalescent plasma) intended to be active against SARS-CoV-2 during this hospital admission • More than 14 days have elapsed since hospital admission • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	Criteria that exclude a patient from one or more interventions are: • Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent • Known previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma • Known objection to receiving plasma products will exclude a patient from receiving any plasma components
Outcome measures	Primary endpoint: refer to Core Protocol documents Secondary endpoints: refer to Core Protocol documents Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrolment): • All-cause mortality at 28 days censored at hospital discharge • Confirmed deep venous thrombosis • Confirmed pulmonary embolism • Confirmed ischemic stroke • Confirmed acute myocardial infarction • Other confirmed thrombotic events • Serious Adverse Events (SAE) as defined in Core Protocol documents and qualified in this DSA
Platform Conclusions	The following Platform Conclusions are possible for this domain: • Efficacy of high-titer convalescent plasma intervention compared with 'no convalescent plasma' intervention • Futility of high-titer convalescent plasma intervention compared with 'no convalescent plasma' intervention
Unit-of-analysis, Strata and State	This Domain is analyzed in the Immunoglobulin Statistical Model, which is separate to the Primary Statistical Model for the Platform. This is intended to allow continuity with the pandemic statistical model. Within the Immunoglobulin Statistical Model, the unit-of-analysis for this domain consists of all patients who have received an allocation in this domain, further subdivided by illness severity state at the time of enrollment (defined as either Moderate State or Severe State) and Immune Suppressed Stratum. Borrowing is permitted between states and strata. This

	unit-of-analysis applies retrospectively for the purposes of analysis, to patients enrolled using earlier versions of this DSA. Response adaptive randomization will be not be applied in this domain.
Evaluable treatment-by-treatment Interactions	No other interactions will be evaluated with any other domain.
Nesting	No nesting of interventions active in this DSA.

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1. ABBREVIATIONS

ADE	Antibody-dependent enhancement
CCP	Clinical Characterization Protocol
CRP	C-reactive protein
CVA	Cerebrovascular accident
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
DVT	Deep vein thrombosis
ICNARC	Intensive Care National Audit and Research Centre
ICU	Intensive Care Unit
ITSC	International Trial Steering Committee
MERS-CoV	Middle East respiratory syndrome coronavirus
NHS	National Health Service of the United Kingdom
NHSBT	National Health Service Blood and Transplant
PAtC	Pandemic Appendix to the Core Protocol
PE	Pulmonary Embolism
PISOP	Pandemic Infection Suspected or Proven
PT	Prothrombin time
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Serious Acute Respiratory Syndrome
TACO	Transfusion-Associated Circulatory Overload
TRALI	Transfusion-related acute lung injury
TTI	Transfusion-Associated Circulatory Overload
WHO	World Health Organization

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While, all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see Glossary, Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (principles of statistical analysis and models); a Patient, Pathogen and Disease Appendix to the Core Protocol (PANDA); multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain); and multiple Regions-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions, within each domain, is covered in the relevant DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis Appendix. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the Statistical Design Team and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory

aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the Core Protocol documents, DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website.

3. COVID-19 IMMUNOGLOBULIN DOMAIN-SPECIFIC APPENDIX VERSION

The version of the COVID-19 Immunoglobulin Therapy Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) on 19th April 2020

Version 1.01: Approved by the COVID-19 Immunoglobulin Therapy DSWG on 1st June 2020

Version 2.2: Approved by the COVID-19 Immunoglobulin Therapy DSWG on 1st June 2020. This version applied only to sites in Canada.

Version 2.3: Approved by the COVID-19 Immunoglobulin Therapy DSWG on 3rd August 2020. This version applied only to sites in the United States of America.

Version 2.4: Approved by the COVID-19 Immunoglobulin Therapy DSWG on 23rd July 2020. This version applied only to sites in Australia.

Version 2.5: Approved by the COVID-19 Immunoglobulin Therapy DSWG on 3rd August 2020. This version applied only to sites in New Zealand.

Version 3: Approved by the COVID-19 Immunoglobulin Therapy DSWG on 29th November 2021. This version applies in all regions.

Version 3.1: Approved by the COVID-19 Immunoglobulin Therapy DSWG on 5th July 2024. This version applies to both the REMAP-CAP and ASCOT Platforms, which are federated.

Version 4: Approved by the COVID-19 Immunoglobulin Therapy DSWG on 5th November, 2024

4. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN GOVERNANCE

4.1. Domain members

Chair:

A/Prof. Lise Estcourt

Co-chairs:

Dr. Colin McArthur (New Zealand)

A/Prof. Zoe McQuilten (Australia)

A/Prof. Bryan McVerry (United States of America)

Prof. Alistair Nichol (Ireland)

Prof. Manu Shankar-Hari (United Kingdom)

Prof. Alexis Turgeon (Canada)

Members:

Prof. Derek Angus

Dr. Donald Arnold

Dr. Phillipe Begin

A/Prof. Scott Berry

Dr Jeannie Callum

Dr. Richard Charlewood

Dr. Michael Chasse

Prof. Jamie Cooper

A/Prof. Mark Coyne

Dr Thomas Craven

Dr. James Daly

Dr. Lennie Derde

Prof. Dean Fergusson

Prof. Anthony Gordon

Prof. Iain Gosbell

Mr. Cameron Green

Dr. Heli Harvala

Dr. Thomas Hills

Dr. David Huang

Ms. Cara Hudson

Prof. Stephen Jolles

Dr. Helen Leavis

Prof. John Marshall

Prof. David Menon

Dr. Susan Morpeth

Mr. Paul Mouncey

A/Prof. Srinivas Murthy

Mr Gavin Pettigrew

Dr. Nicole Priddee

Prof. David Roberts

Prof. Kathy Rowan

Prof. Damian Purcell

Dr. Jon Silversides

Dr. Alan Tinmouth

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4.2. Contact Details

Chair:

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5. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official COVID-19 Immunoglobulin Therapy Domain-Specific Appendix. Signed on behalf of the committee,

Chair
Lise Estcourt

Date 5th November, 2024

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain to test the effectiveness of different strategies for immunoglobulin therapy for immune compromised patients with microbiological testing-confirmed COVID-19.

6.2. Domain-specific background

6.2.1. COVID-19 Infection

COVID-19 is caused by a novel coronavirus designated SARS-CoV-2. In December 2019, COVID-19 was first reported when a cluster of patients with severe pneumonia of unknown cause was identified in Wuhan, China. SARS-CoV-2 quickly spread across the globe and the WHO declared COVID-19 a pandemic in March 2020 (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf). The spectrum of illness due to SARS-CoV-2 ranges from asymptomatic infection through to severe pneumonia, respiratory distress, multiorgan dysfunction, and death. A substantial proportion of patients admitted to hospital because of COVID-19 require provision of organ failure support in an Intensive Care Unit (ICU) and in-hospital mortality within this group is high (Tan et al., 2021). Early clinical management recommendations focus on supportive care, including organ support as needed and the prevention of complications. Effective treatments are urgently needed. The WHO have recommended that "investigational anti-COVID-19 therapeutics should be used only in approved, randomized, controlled trials" (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf).

6.2.2. Clinical trials for COVID-19

Observational data cannot determine treatment effects reliably due to the risk of systematic bias (Califf et al., 2020). Clinical trials to identify effective COVID-19 treatments are needed and a large number of trials are underway. Early in the pandemic, the WHO provided guidance regarding both trial design and prioritization of candidate therapies.

As effective COVID-19 treatments have been identified, 'standard of care', both inside and outside of a clinical trial, has changed to incorporate the use of agents with proven efficacy. This Platform randomizes COVID-19 patients to a range of therapeutic interventions across different domains. Up to date information regarding active and inactive interventions and domains is available on the trial website.

It is recognized that in patients with COVID-19 the effect of treatments can be different depending on stage or progression and severity of illness (Recovery Collaborative Group et al., 2020). As such, therapies should be evaluated independently in pre-defined patient groups e.g. those who are critically ill, those who are admitted to hospital but are not critically ill, those who have COVID-19 but have not been admitted to hospital, and those who impaired immunity to fight the infection. Among trials that evaluate interventions in patients who are critically ill, it is common for the results of the trial to be different to that which was predicted based on a prior understanding of mechanism of action combined with known mechanism of disease (Landoni et al., 2015, Webb, 2015). This observation reinforces the importance of not necessarily relying on extrapolation of results (both positive and negative) from patients who are not critically ill. It is also possible different disease mechanisms apply at different levels of illness severity and that this may influence the balance between beneficial and adverse effects of a particular intervention, reinforcing the importance of obtaining estimates of treatment effect dependent on the level of illness severity.

6.2.3. Convalescent Plasma

Convalescent plasma treatment, containing high titers of polyclonal antibody (Ab), had been used prior to the COVID-19 pandemic to treat severe viral pneumonia. Many studies have been poorly controlled but such series have shown decreased mortality in Spanish Influenza A (H1N1) infections in 1918 - 1920 (Luke et al., 2006, McGuire and Redden, 1918), Influenza A (H1N1)pdm09 infections in 2009/2010 (Hung et al., 2011, Ortiz et al., 2013) and more relevantly to this trial, SARS-CoV infections in 2003 (Cheng et al., 2005, Soo et al., 2004). A systematic review and meta-analysis performed identified 699 treated patients with SARS coronavirus infection and severe influenza and 568 untreated "controls" (Mair-Jenkins et al., 2015) found consistent reports of a reduction in

mortality. Post hoc meta-analysis showed a statistically significant reduction in the pooled odds of mortality following treatment, compared with placebo or no therapy (odds ratio, 0.25; 95% CI:0.14–0.45) (Mair-Jenkins et al., 2015).

Convalescent plasma therapy has been widely used to treat patients with COVID-19, both within clinical trials and through access outside clinical trials, such as the Expanded Access Program in the United States. A systematic review of use of convalescent plasma for patients with COVID-19 included 12 randomized controlled trials and one non-randomized study with 48,509 participants, of whom 41,880 received convalescent plasma (Valk et al., 2020). In patients with moderate to severe COVID-19 disease, convalescent plasma did not reduce all-cause mortality (risk ratio 0.98, 95% CI 0.92 to 1.05) and had little or no impact on clinical improvement. There was only one trial included in asymptomatic or mild disease. The largest trial was the RECOVERY trial, which enrolled 16,287 hospitalized adults with COVID-19 and found no difference in 28-day mortality between those who received convalescent plasma and those who received standard of care (24% vs. 24%, rate ratio 1.00, 95% CI 0.93 to 1.07, p=0.95) (Recovery Collaborative Group, 2021). There was also no difference observed in the prespecified subgroups, including based on days since symptom onset or antibody test result at baseline.

Results from Version 1.0 of the REMAP-CAP Immunoglobulin Domain have now been published (Writing Committee for the REMAP-CAP Investigators et al., 2021). This trial showed that administration of two units of convalescent plasma had a low likelihood of improving organ-support free days in critically ill patients (median number of days alive and free of organ support was 14 (IQR 3 to 18) in convalescent plasma arm and 14 (IQR 7 to 18) in standard of care arm, posterior probability of futility (odds ratio <1.2) was 99.4%).

Taken together, these results suggest for unselected patients, two units of convalescent plasma does not improve outcomes in patients with moderate to severe COVID-19. However, there was a possible benefit in patients with an impaired immune system, 89% posterior probability of superiority. No other trials have assessed the immunosuppressed population in detail.

6.2.4. Rationale for evaluation of high-titer convalescent plasma in immunocompromised patients with COVID-19

6.2.4.1. Availability of high-titer plasma for therapeutic use

Convalescent plasma will be collected from whole blood or via apheresis from vaccinated donors, who have had a previous laboratory confirmed SARS-CoV-2 infection. This is because convalescent

plasma from donors who have been vaccinated have much higher antibody levels and a broader spectrum of response than convalescent donors who have not been vaccinated.

Plasma will contain a minimum neutralizing antibody titer of 1:640 against delta variant (B1.617.2) or the relevant predominant variant within a country or region, as this will allow a titer of 1:100 to be achieved in an average recipient and this level is considered sufficient to neutralize the virus within the recipient. Approximately 30% of vaccinated donors with a previous infection will demonstrate these neutralizing antibody levels.

A surrogate test that equates to this neutralization titer can be used for screening of units. For example, antibody level of 20,000 U/ml determined by Roche Elecsys anti-SARS-CoV-2 Spike assay has been shown to reliably identify units containing a minimum neutralizing antibody titer of 1:640 against delta variant. Euroimmun Spike IgG ELISA (additional 1:100 dilution of sample required): a minimum s/co ratio of 1800 IU/ml (requires use of International Standard). Other surrogate assays may be used to screen plasma donations provided they have been shown to equate to a similar antibody level using an international standard.

It is recommended that plasma or serum sample from each convalescent plasma donation provided for clinical trial is also stored for further testing to allow data comparison between countries.

6.2.4.1.1. Justification for the use of vaccinated plasma of a higher titer

In the REMAP-CAP trial of convalescent plasma, convalescent plasma donors in the UK were selected with the highest quartile of anti-Spike antibody levels and with a corresponding mean neutralizing antibody titers (nAb) against the wild-type virus of ~1:250.

However, the nAb titers against the alpha variant fell by approximately a factor of two, and against the beta and delta variants by x5 and x 3 respectively (Figure 1a). Therefore, much higher nAb titers will be required for future trials.

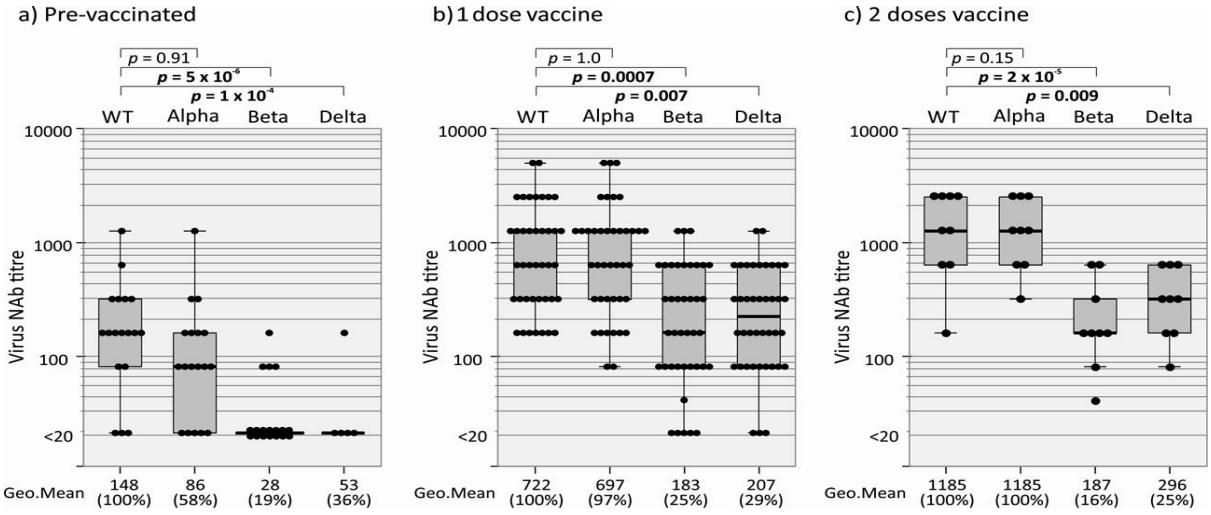


Figure 1. Level of viral neutralization of different viral variants by convalescent plasma a) pre-vaccinated donors, b) after 1 dose of vaccine and c) after two doses of vaccine.

We tested a random sample of our plasma donors, originally infected with wild-type (WT) or alpha variant, for nAb against the alpha, beta and gamma variants, after receiving AstraZeneca (AZ) or Pfizer vaccines. Vaccinated donors with the highest cross-reactive neutralizing antibodies can be readily identified (Figure 1).

A very significant proportion of vaccinated donors achieved very high nAb levels. Donors with a ROCHE Elecsys anti-SARS-CoV-2 spike assay result of >20,000 U/ml have nAb titers against the delta variant with a geometric mean greater than 1:640 (Table 1). There were no significant differences between donors given AZ or Pfizer vaccine.

Table 1. Geometric mean of neutralizing antibody titer for different viral variants (wild type, alpha, beta and delta variant) for differing Roche S IgG ELISA thresholds

		Geometric mean neutralizing antibody titer			
	N	**Wild type**	**Alpha variant (B117)**	**Beta variant (B1.351)**	**Delta variant (B1.617)**
Roche S IgG over 10,000 U/ml	26 (53%)	1627	1627	440	452
Roche S IgG over 15,000 U/ml	19 (39%)	2133	1912	553	574
Roche S IgG over 20,000 U/ml	15 (31%)	2334	2229	611	670

The high titers of cross-reactive neutralizing antibodies in vaccinated donors could allow higher levels of cross-reactive neutralizing antibodies to be achieved in recipients.

A dose of two units each with a volume of 275ml and a mean nAb titer of at least 1:640 would allow a nAb titer of >1:100 against the delta variant to be achieved in a 70kg recipient. The proposed trial would therefore have a realistic chance of testing the efficacy of convalescent plasma in immunocompromised (see later for rationale for evaluation in immunocompromised patients).

As demonstrated, donors with high-titer cross-reactive antibodies could be readily recruited. Moreover, the principle that antibodies derived after natural infection can be significantly boosted against heterologous variants by vaccination suggests donors with high-titer, cross-reactive polyclonal antibody therapy could be sourced as the pandemic evolves. It is therefore feasible to test polyclonal antibody therapy for COVID-19 within this Platform.

6.2.4.2. Rationale for previous monoclonal antibody therapy sub-group

The available monoclonal antibodies were designed using the original wild-type strain and new variants have become resistant to available monoclonal antibody therapies.

In many locations in which this Platform recruits there may be prophylaxis or treatment of patients with monoclonal antibody therapy. In hospitalized patients, this will likely occur in patients who are seronegative and approximately 50% of patients with immunosuppression within the REMAP-CAP trial were seronegative at baseline. The use of monoclonal therapy prior to hospital admission will be in high risk patients, which includes this immunocompromised cohort. It is possible that prior treatment with monoclonal antibody may influence whether there is a treatment effect from high-titer plasma and if high titer convalescent plasma can overcome development of resistant variants.

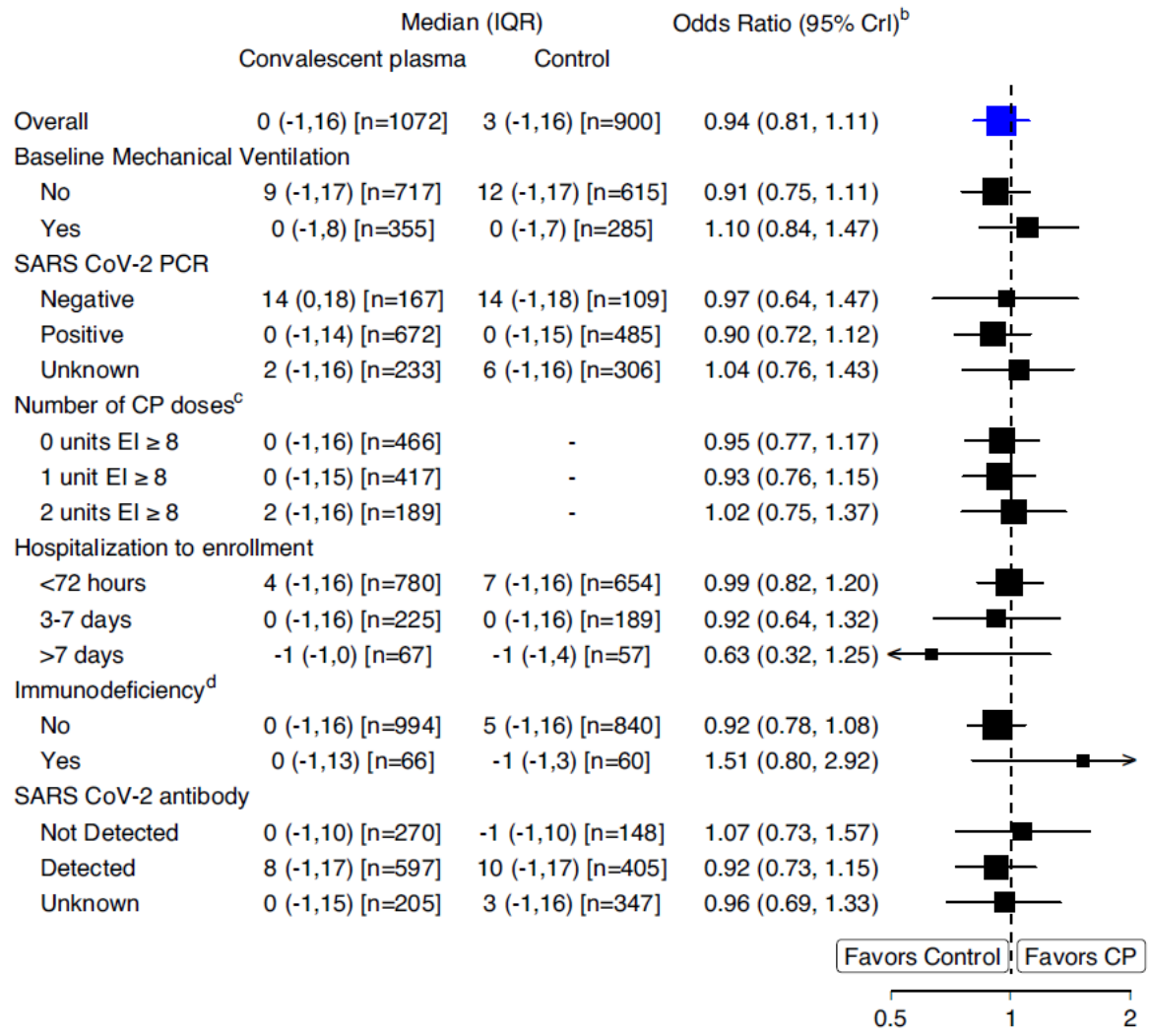
6.2.4.1. Rationale for assessment of viral variants

Patients with immune suppression are known to develop viral variants, especially when they have prolonged carriage of the virus (Corey et al., 2021). Due to this risk, patients with immunosuppression should be swabbed to ensure that viral shedding has ceased. Monitoring of viral variants will be important to ensure that administration of convalescent plasma does not increase the risk of viral variants and enables the virus to be cleared more rapidly. Assessment of viral variants will be an optional sub-study dependent on the feasibility to perform the analyses in different research centers, countries or regions.

6.2.4.2. Rationale for evaluation of high-titer plasma in immune suppressed patients

Although there is no evidence of benefit of convalescent plasma in unselected patient with SARS-CoV-2 infection who has been admitted to hospital, there was evidence of potential benefit in the immunosuppressed patient population derived from data from patients in the Severe state

randomized to Version 1.0 of the Immunoglobulin Domain of REMAP-CAP (Figure 2). Convalescent plasma therapy demonstrated a posterior probability of superiority of 89.8%, and posterior probability of futility of 23.8% (OR < 1.2) for the immunosuppressed subgroup. There was also a 92.9% probability that the OR for the immunosuppressed population was larger than the non-immunosuppressed population (evidence for sub-group difference). Although this evidence is not conclusive that there is a difference, it provides strong support to further investigate the efficacy of convalescent plasma for this sub-group. Due to the small number of participants randomized in the moderate state, an assessment of the intervention in immunosuppressed individuals randomized in the moderate state was unable to be performed, however we assume that a similar effect is likely to be seen. Therefore, moderate patients will be included in this version of the domain.



Abbreviations: CP, convalescent plasma; EI, Euroimmun; OSFD, organ support-free days; PCR, polymerization chain reaction.
[a]Data for sub-group analyses excluded participants who had been randomized within another domain within the moderate stratum and then randomized to the immunoglobulin domain in the severe stratum (excluded 7 participants), maximum of 1980 participants included within the sub-group analyses. The analysis population for subgroup analyses includes 1980 participants where 1972 have known outcomes of OSFD.
[b]An odds ratio > 1 equates to the threshold for superiority to control for the primary outcome. An odds ratio < 1.2 equates to the threshold for futility for the primary outcome.
[c]For the number of convalescent plasma doses administered with a Euroimmun titer ≥ 8, the number of participants analyzed equals total number in the No-CP group (900) plus the number in the intervention group who received those number of convalescent plasma doses.
[d]Immunodeficiency was defined as immunosuppressive treatment or disease (APACHE definition)

Figure 2. Prespecified sub-group analyses of primary outcome (organ-support free days)

Non-randomized studies have suggested benefit of convalescent plasma in immunosuppressed patients, or sub-groups such as patients with hematological malignancies. A review of the literature in April 2021 (Senefeld et al., 2021) identified 75 reports on immunosuppressed patients receiving convalescent plasma, there were 51 case reports and 23 case series, as well as one case-control

study. In this case-control study 143 treated adult patients with hematological malignancies were compared to 823 untreated controls. After adjustment for potential confounding factors, convalescent plasma treatment was associated with improved 30-day mortality (hazard ratio, 0.60; 95% CI, 0.37-0.97). This association remained significant after propensity-score matching (hazard ratio, 0.52; 95% CI, 0.29-0.92) (Thompson et al., 2021). The association with reduced mortality persisted in the subgroup of patients who were admitted to ICU and who required mechanical ventilation.

The RECOVERY trial has shown a benefit of monoclonal therapy in patients who are antibody negative. Passive immune therapy has therefore been shown to be effective in the sub-group of patients who have not developed an antibody response at the time of treatment, if antibody therapy is administered at sufficient dose (Recovery Collaborative Group, 2021).

There are a significant number of people with an impaired immune system who would be eligible to be included within the trial. For example, there are an estimated 500,000 people in England who would fulfill the criteria of immunosuppression according to the APACHE definition (Table 2) (Knaus et al., 1991). This patient population are also those who are less likely to respond to COVID-19 vaccinations (Boyarsky et al., 2021, Agha et al., 2021, Herishanu et al., 2021, Touizer et al., 2021) and are at risk of more severe COVID-19 disease (Belsky et al., 2021).

Table 2. Estimated population of immunosuppressed individuals in England

Immunosuppressed population	Estimated number in England November 2020
Receiving immunosuppressive therapy e.g. rituximab	114,000
Blood cancers	188,000
Other solid cancers receiving chemotherapy	56,000
Lung cancer receiving radical radiotherapy	3,000
Long-term steroids	1,367
Stem cell transplants (within 6 months)	2,000
Stem cell transplants + immunosuppression	681
Solid organ transplants	56,000
Total	**Approx. 500,000**

6.2.5. Safety profile of convalescent plasma

More than 500,000 units of convalescent plasma have been issued for treatment of COVID-19 patients in the United States of America through an expanded access program, and then emergency use authorization (Kamel, 2021). In a convenience sample of 20,000 of these patients, mostly with 'severe' or 'life-threatening' COVID-19, the administration of convalescent plasma was generally safe with a low rate of serious adverse events. Specifically, transfusion reactions (n=89; <1%), thromboembolic or thrombotic events (n=87; <1%), and cardiac events (n=680, ~3%) were uncommon and the majority of thromboembolic/thrombotic (55/87) and cardiac events (562/680) were deemed to be unrelated to the convalescent plasma therapy.

In the REMAP-CAP Immunoglobulin Domain version 1.0, only one transfusion-related adverse event occurred despite over 1000 participants receiving convalescent plasma, an assumed allergic reaction. Venous thrombo-embolic events at 90 days were similar between convalescent plasma and standard of care groups (74/1075 (6.9%) in the convalescent plasma arm and 61/905 (6.7%) in the control arm) (Writing Committee for the REMAP-CAP Investigators et al., 2021).

In the RECOVERY trial, the incidence of transfusion-related adverse events was again low, 13/5301 patients receiving convalescent plasma had reports submitted to the United Kingdom's Serious Hazards of Transfusion (SHOT) hemovigilance scheme: nine patients with pulmonary reactions (none considered to be transfusion-related acute lung injury, including three deaths possibly related to transfusion), and four patients with serious febrile, allergic, or hypotensive reactions (all of whom recovered) (Recovery Collaborative Group, 2021).

No cases of antibody dependent enhancement were reported to SHOT within either the REMAP-CAP or RECOVERY trials.

6.2.6. Intervention Strategy for this domain

This domain has evolved, taking into account evidence derived from the results from the first stage of this domain in REMAP-CAP, other clinical trials, as well as availability of effective immunoglobulin therapies. WHO guidance notes the flexibility associated with adaptive platform trials for the testing of multiple agents, including serial testing of additional interventions (https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf?ua=1).

At the recommencement of this domain a control group is included (i.e. some patients will not receive any polyclonal immunoglobulin therapy that is intended to be active against COVID-19 infection). This is appropriate because designs that include only active interventions are not able to ascertain if any option is better or worse than no treatment. Any further changes to the intervention structure of the domain will be specified using one or more amendments to this DSA with implementation occurring only after ethical approval has been obtained.

If at any stage evidence of harm or definitive evidence of absence of effectiveness in moderately or critically ill patients emerges for any intervention specified in this domain, the ITSC, as advised by the DSWG, may remove an intervention prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to that intervention will occur, so as to contribute additional weight of evidence available in the public domain.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of immunoglobulin therapy for patients with microbiological testing-confirmed COVID-19 who are immuno-suppressed at the time of eligibility.

We hypothesize that the probability of occurrence of the primary end-point specified in the relevant Core Protocol documents will differ based on the immunoglobulin therapy intervention. The following interventions will be available:

- No immunoglobulin against COVID-19 (no placebo)
- High titer convalescent plasma

We hypothesize that the treatment effect of different immunoglobulin strategies is different depending on the illness severity state at the time of enrollment.

We hypothesize that the treatment effect of different immunoglobulin strategies is different depending on whether or not the patient has received any prior treatment with a monoclonal antibody for SARS-CoV-2 infection.

8. TRIAL DESIGN

8.1. Population

8.1.1. Age Strata

This domain is available to patients who are in the Adolescent or Adult Age Strata, as defined in Core Protocol documents. Eligibility within these strata may be further constrained by domain-specific eligibility criteria specified below. Participating sites may choose to offer this domain to patients in one or more of these Age Strata.

8.1.2. State

This domain is available for patients in the Moderate State and the Severe State. These States are defined in Core Protocol documents. Participating sites may choose to offer this domain to patients in one or both of these Illness Severity States.

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in Core Protocol documents. Patients eligible for the Platform may have conditions that exclude them from the COVID-19 Immunoglobulin Therapy Domain.

8.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- Patient is aged ≥ 16 years old
- SARS-CoV-2 infection is confirmed by microbiological testing
- Patient has an underlying immunodeficiency or has received recent immunosuppressant therapy, corresponding to the APACHE II definitions (Knaus et al., 1985) , extended to take into account equivalent forms of immunosuppressant therapy that post-date the APACHE II definitions.

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- More than 48 hours has elapsed since commencement of sustained organ failure support in an ICU
- Patient has already received treatment with any non-trial prescribed polyclonal antibody therapy (hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this acute illness.
- More than 14 days have elapsed since hospital admission
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

8.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons.

Patients who are eligible for only a single intervention at a site (i.e. all other interventions are contraindicated) are not eligible for this domain. Patients who are not eligible for this domain will be treated according to the current standard of care at the clinician's discretion. Criteria that exclude a patient from one or more interventions are:

- Known hypersensitivity/allergy to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
- Known previous history of transfusion-related acute lung injury will exclude a patient from receiving high titer plasma
- Known objection to receiving plasma products will exclude a patient from receiving any plasma components

8.3. Interventions

8.3.1. Immunoglobulin Therapy Interventions

Patients will be randomly assigned to receive one of the following open-label strategies. All interventions will be commenced immediately after allocation status is revealed.

- No immunoglobulin against COVID-19 (no placebo)
- High titer convalescent plasma

8.3.2. No immunoglobulin against COVID-19 (no placebo)

Patients assigned to this intervention will not receive any preparation of polyclonal immunoglobulin intended to neutralize COVID-19 during the index hospitalization. Administration of such a preparation is considered a protocol deviation. Administration of a monoclonal antibody preparation is permitted prior to time of reveal of assigned treatment.

8.3.3. High titer plasma

8.3.3.1. Dosing of plasma

Patients assigned to receive plasma will receive two adult units of ABO compatible convalescent plasma (total volume 550ml ± 150ml) within 48 hours of randomization. Convalescent plasma must be high titer plasma (as outlined above) derived from whole blood or via apheresis from vaccinated donors who have also had a natural infection. Volume of convalescent plasma administered will be recorded and where available the level of antibodies within each unit will be tested. Plasma or serum sample from each convalescent plasma donation provided for the clinical trial should be stored for further testing to allow comparison of data between countries.

8.3.3.2. Duration of administration of convalescent plasma

Those receiving plasma will receive a unit of ABO compatible convalescent plasma as soon as possible after assignment is revealed. If the patient has no serious adverse reactions to the transfusion the second unit of convalescent plasma will be given. Both transfusions should be given within 48 hours from reveal of assignment.

8.4. Concomitant care

Additional immunoglobulin therapy intended to be active against SARS-CoV-2 infection (such as monoclonal antibodies, hyperimmune globulin or convalescent plasma) should not be administered.

All treatment that is not specified by assignment within the platform will be determined by the treating clinician.

8.5. Endpoints

8.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome specified in the relevant Core Protocol documents.

8.5.2.Secondary endpoints

All secondary endpoints as specified in the relevant Core Protocol Documents.

The domain-specific secondary outcome measures (occurring during the index hospitalization, censored at 90 days after enrollment) will be:

- All-cause mortality at 28 days censored at hospital discharge
- Confirmed deep venous thrombosis
- Confirmed pulmonary embolism
- Confirmed ischemic stroke
- Confirmed acute myocardial infarction
- Other confirmed thrombotic events
- Serious Adverse Events (SAE) as defined in Core Protocol documents and qualified in this DSA

9. TRIAL CONDUCT

9.1. Domain-specific data collection

Additional domain-specific data will be collected on all participants:

- SARS-CoV-2 antibody status at baseline
- Cause of immunosuppression at baseline
- Transfusion-transmitted infection occurring at any time during the study
- Serious clinically diagnosed arterial (e.g. myocardial infarction (MI), cerebrovascular accident (CVA), mesenteric arterial thrombosis) or venous thrombotic events (e.g. deep vein thrombosis (DVT), pulmonary embolism (PE), portal or mesenteric venous thrombosis, or cortical venous sinus thrombosis) occurring during the index hospitalization censored at day 90 after enrolment.
- Viral variants. Method of viral testing and analysis will vary from country to country and will be within country-specific testing guidance document.

9.2. Criteria for discontinuation

Refer to relevant core protocol documents for criteria for discontinuation of participation in the trial.

9.3. Blinding

All interventions will be administered on an open-label basis.

10.STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

This domain has adapted as a consequence of having reached a Platform Conclusion in the Severe State and a decision to close recruitment in the Moderate State in response to external evidence, in relation to unselected patients (January, 2021). The domain subsequently recommenced with recruitment limited to patients in the Immune Suppressed stratum. The 'no immunoglobulin against COVID-19' intervention is a continuation of the same intervention in previous versions of this Domain.

This domain will be analyzed in a separate statistical model. This model will include all participants who have received an allocation in the Immunoglobulin Domain. The Primary Endpoint for this model is as defined in Core Protocol documents.

A decision to integrate this domain into the Primary Statistical Model may occur as an operational decision. If this occurs, the unit of analysis will be specified to be Illness Severity State (defined as Moderate or Severe State), SARS-CoV-2 Infection Confirmed Stratum, and Immune Suppressed Strata. Statistical Triggers will be as specified in this DSA and defined in Core Protocol documents.

The following Platform Conclusions are possible in the two domain specific units-of-analysis (Moderate and Severe Illness Severity State, within the Immune-Suppressed stratum).

- Efficacy of high titer plasma compared to no immunoglobulin
- Futility of high titer plasma compared to no immunoglobulin

In all other respects the stopping rules for this domain are those outlined in the relevant core protocol documents.

10.2. Unit-of-analysis and strata

The population of interest that will be reported as a result of the amendment of this domain are patients who have received an allocation in the Immunoglobulin Domain, including patients who have already been recruited and treated with convalescent plasma, as specified in earlier versions of

this DSA. So as to achieve continuity with the initial phase of this domain, a stratum is defined as comprising patients who are immune suppressed. This stratum definition will be applied retrospectively to patients enrolled using earlier versions of this domain and applied prospectively, operationalized as eligibility criteria, for Version 3 of this DSA onwards (i.e., only patients meeting this stratum definition are recruited using this version of the DSA).

All patients recruited using versions of this DSA prior to Version 3 are classified as members of the No Prior Monoclonal Antibody sub-group. Administration of a monoclonal antibody directed against SARS-CoV-2 was an exclusion criteria in all earlier versions of this DSA.

The unit-of-analysis for this domain consists of all patients who have received an allocation in this domain, and is further stratified by illness severity state at time of enrollment (defined as either Moderate State or Severe State) and Immune Suppressed Strata.

Borrowing is permitted between States, i.e. borrowing will occur between Moderate and Severe states.

10.3. Application of Response-Adaptive Randomization

Response Adaptive Randomization will not be applied to this domain.

10.4. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Deferred Reveal to permit confirmation of microbiological diagnosis if results of testing are not known at the time of initial assessment of eligibility (see relevant core protocol documents).

10.5. Interactions with interventions in other domains

Interactions with all other domains are either not evaluable or not considered possible and will not be incorporated into the statistical model or models in which this domain is evaluated.

If an interaction is specified with a future domain, it is sufficient for the interaction to be specified only in the DSA of such a future domain.

10.6. Nesting of interventions

The high titer convalescent plasma (active intervention specified in this DSA and designated the intervention code 'P4') will be nested with the (low titer) convalescent plasma intervention (intervention code 'P2' and the active intervention in earlier versions of this DSA approved in regions other than the United States) in the Immune Suppressed and Non-Immune Suppressed Strata. Nesting high titer plasma with low titer plasma in the Immune Suppressed strata effectively borrows information from the previous immune suppressed patients randomized to convalescent plasma. Nesting high titer plasma with low titer plasma in the Non-Immune Suppressed strata is intended to reduce the amount of information borrowed from the previous positive result. This nesting structure can be interpreted as an informative prior for high titer plasma that is a weighted average of the low titer plasma effect in immune suppressed and Non-Immune Suppressed strata.

Following any Platform Conclusion in this domain, a sensitivity analysis will be conducted that is restricted to patients randomized concurrently to P1 and P4 interventions.

10.7. Threshold probability for efficacy and futility

The threshold odds ratio delta for efficacy and futility in this domain are those specified as the default thresholds in the relevant Core Protocol documents.

10.8. Informative priors

This domain will launch without the mathematical application of priors that are not informative for main effects. However, the application of nesting between the 'P2' intervention applied in earlier versions of this DSA and the 'P4' intervention specified in this DSA has the same effect as would be achieved by the formal application of a prior that was informative. As such, the domain will be re-launched with a hierarchical prior for high titer convalescent plasma as outlined in Section 10.6. The hyperprior distributions for this hierarchy will be non-informative.

If new immunoglobulin agents are added to the domain, consideration will be given to the use of informative priors at the time of amendment of the DSA.

10.9. Post-trial Sub-groups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The a priori patient sub-groups of interest are:

Primary sub-group analyses

- Dose of neutralizing antibodies received (based on volume of transfusion and titer measurement)
- SARS-CoV-2 antibody status at baseline
- COVID-19 vaccination status at baseline
- Prior monoclonal antibody therapy active against SARS-CoV-2 at baseline
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

Exploratory sub-group analyses

- Patients known to have received B-cell depleting therapy (anti-CD20, BTKI, CAR-T cell therapy) at baseline
- Patients with known hematological malignancy at baseline
- Patients known to have received a solid organ transplant at baseline

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB is convened under the guidance provided in the Core Protocol and DSMB Charter. The statistical triggers that apply to this domain are specified in this DSA. If requested by the DSMB, domain-specific safety secondary endpoints will be provided to the DSMB as part of the regular safety reports.

11.2. Potential domain-specific adverse events

The occurrence of the following should be screened for and reported as SAEs for all patients in this domain, irrespective of intervention allocation:

- Severe allergic reaction or anaphylaxis
- Transfusion-associated Acute Lung Injury (TRALI)
- Transfusion-associated Circulatory Overload (TACO)
- Transfusion-associated Dyspnea (TAD)
- Acute serious hemolytic reaction, defined a fever and other symptoms/signs or hemolysis within 24 hours of transfusion, confirmed by a fall in hemoglobin AND one or more of the following:

- Rise in lactate dehydrogenase (LDH)
- Rise in bilirubin
- Positive direct antiglobulin test (DAT)
- Positive crossmatch

These are reactions that are based on the definitions used and reported to the local, regional or national hemovigilance system at each participating site. Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant core protocol documents).

11.3. Domain risk assessment

Participating sites will have reviewed the interventions in this domain and their clinical appropriateness for evaluation in this population. Enrolment in this domain will only occur if the treating clinician believes participation is not contrary to the best interests of the patient. The risks and benefits of participation will be outlined in local consent documentation.

11.4. Domain-specific consent issues

In the absence of evidence of effectiveness of any interventions specified in this DSA or alternative intervention that lies within this domain, the use of a no treatment control is both appropriate and ethical.

Clinicians may choose not to enroll individual patients if they feel that participation is not in the patient's best interests, and safety criteria are used to exclude patients from this domain for appropriate clinical reasons.

For patients who are not competent to consent, and in accordance with local jurisdictional requirements, where permitted entry into this domain is preferred to be via waiver-of-consent or some form of delayed consent. In any jurisdiction in which prospective agreement is necessary, reveal of assignment status will only occur after prospective agreement has been obtained.

During a pandemic, visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods for confirming agreement to participate in this (and other) domains of the platform.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for this Platform are specified in the Core Protocol documents. This domain has received funding in Australia from the Australian Medical Research Future Fund.

12.2. Funding of domain interventions and outcome measures

Local blood services will supply the convalescent plasma for sites participating in the trial in each region and arrange for distribution to participating sites via its routine distribution system.

12.3. Domain-specific declarations of interest

A registry of interests for all members of the International Trial Steering Committee is maintained on the website. These are updated periodically and publicly accessible on the study website.

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