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 ~~1.01~~3 dated ~~01 June 2020~~<insert date>

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform-entry criteria for REMAP-CAP ~~admitted to participating intensive care units~~ with microbiological testing confirmed COVID-19 infection will be randomized to receive one of two interventions:

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

~~This domain will only enroll patients if the pandemic infection is proven (PISOP) stratum and be analyzed in the Pandemic Statistical Model as outlined from the Pandemic Appendix to Core (PAtC).~~

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

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

This Domain has domain-specific stratum. Sites that participate in this domain must participate in both domain-specific stratum.

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

Stratum	Pandemic infection suspected or proven (PISOP)							Pandemic infection neither suspected nor proven (PINSNP)
Core protocol documents	REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol							REMAP-CAP Core Protocol
Illness Severity State	Moderate State				Severe State			Severe State
Domain-specific stratum	Non-Immune Suppressed stratum	Immune Suppressed stratum			Non-Immune Suppressed stratum	Immune Suppressed stratum		N/A
Domain-specific stratum	N/A	No Prior Monoclonal Antibody stratum	Prior Monoclonal Antibody stratum		N/A	No Prior Monoclonal Antibody stratum	Prior Monoclonal Antibody stratum	N/A
Interventions available in this Domain + State	Not available	No immunoglobulin High titer plasma	No immunoglobulin High titer plasma		Not available	No immunoglobulin High titer plasma	No immunoglobulin High titer plasma	Not available
Interventions submitted for approval at this site	Not available	☐ No immunoglobulin ☐ High titer plasma			Not available	☐ No immunoglobulin ☐ High titer plasma		Not available
Domain offered at this site in these locations	N/A	☐ ICU ☐ Ward	☐ ICU ☐ Ward	☐ ICU ☐ Ward	☐ ICU ☐ Ward	N/A	☐ ICU	N/A

REMAP-CAP: Immunoglobulin Therapy Domain Summary	
Interventions	• No immunoglobulin against COVID-19 (no placebo) • ~~Convalescent~~High titer convalescent plasma ~~(up to 2 units within 48 hours)~~
Unit-of-analysis~~ and~~, Strata and State	~~The default unit-of-analysis for this domain will be the pandemic infection suspected or confirmed (PISOP) stratum. Analysis and Response Adaptive Randomization are applied by PISOP stratum.~~This Domain is analyzed only in the pandemic statistical model. The pandemic statistical model includes patients who are in the pandemic infection suspected or confirmed (PISOP) stratum. Within the stratum the unit-of-analysis is defined by illness severity state at the time of enrollment, defined as either Moderate State or Severe State and by Prior Monoclonal Antibody strata status. Borrowing is permitted between states and strata. Version 3 of this DSA also establishes a new domain-specific stratum, the Immune Suppressed stratum, to define eligibility to patients enrolled using Version 3 but is applied, retrospectively for the purposes of analysis, to patients enrolled using earlier versions of this DSA. Response adaptive randomization will be applied to all PISOP patients, in each illness severity state. Response Adaptive Randomization may be applied differentially according to Prior Monoclonal Antibody strata status.
Evaluable treatment-by-treatment Interactions	~~Treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the Corticosteroid Domain and the COVID-19 Antiviral Therapy Domain.~~ No other interactions will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Deferred Reveal at time of confirmation of infection by microbiological testing.
Inclusions	~~Inclusion criteria are the same as the Platform see Core Protocol Section 7.4.1, and COVID-19~~Patients will be eligible for this domain if: • 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 have elapsed since ICU admission~~ • If in the Severe State, more than 48 hours has elapsed since ICU admission, unless the patient has already been assigned to an intervention in another domain in the Moderate State, in which case exclusion will occur if 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 (~~monoclonal antibody,~~ hyperimmune immunoglobulin, or convalescent plasma) intended to be active against ~~COVID-19~~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 REMAP endpoint: ~~as defined in an operational document specified from the~~ refer to REMAP-CAP Core Protocol + Pandemic Appendix ~~to the~~and REMAP-COVID Core Protocol ~~Section 7.5.1.~~

	Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol ~~Section 7.6.2~~+ Pandemic Appendix and REMAP-COVID Core Protocol 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 • ~~Serious adverse events (SAE) as defined in this appendix~~ • 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 • ~~Venous thromboembolic events at 90 days~~ ~~Domain-specific exploratory outcomes~~ • ~~Percent of subjects who cleared SARS-CoV-2 infection (i.e. all samples (obtained at least in two time points after transfusion) tested negative for SARS-CoV-2 RNA in all respiratory samples or just in blood)~~ • ~~Reduction in SARS-CoV-2 viral load (within the first 3 days; 4 days; 6 days; 9 days; 15 days and 28 days analyzed separately in blood and respiratory samples)~~ • ~~Change in SARS-CoV-2 neutralizing antibody levels (within the first 3 days; 4 days: 6 days; 9 days; 15 days and 28 days)~~

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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
ISIG	International Statistics Interest Group
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 ~~Organisation~~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, Section 1.2 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 (details of the current statistical analysis plan and models) and Simulations Appendix (details of the current simulations of the REMAP), 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 a 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 and Simulations Appendices. 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 International Statistics Interest Group (ISIG) 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~~,~~ (either REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol), DSAs, RSAs, and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

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 <insert date>. This version applies in all regions.

4. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN GOVERNANCE

4.1. Domain members

Chair:

~~Dr~~A/Prof. Lise Estcourt~~*~~

Co-~~chair~~chairs:

~~Dr~~ 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:

~~Dr Jacinta Abraham~~

~~A/~~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~~-Simmonds~~

Dr. Thomas Hills

Dr. David Huang

Prof. Stephen Jolles

Dr. Helen Leavis

Dr. Sheila MacLennan

~~Dr Colin McArthur~~

~~A/~~Prof ~~Zoe McQuilten~~. John Marshall

~~*~~Prof. David Menon

Dr. Susan Morpeth

Mr. Paul Mouncey

A/Prof ~~Alistair Nichol~~. Srinivas Murthy

Mr Gavin Pettigrew

Dr. Nicole ~~Pridee~~Priddee

~~*~~Prof. David Roberts

Prof. Kathy Rowan

Prof. Damian Purcell

Dr. Jon Silversides

Ms ~~Helen Thomas~~. Cara Hudson

Dr. Alan Tinmouth

Dr. Darrell Triulzi

Prof ~~Tim Walsh~~

~~Prof~~. Steve Webb

Prof. Erica Wood

~~*Members who are co-leading the COVID-19 Immunoglobulin Therapy Domain~~

Dr. Ryan Zarychanski

4.2. Contact Details

Chair:

Dr Lise Estcourt

NHS Blood and Transplant

Level 2 John Radcliffe Hospital, Oxford

United Kingdom, OX3 9BQ

Phone: +447823 351936

Email: lise.estcourt@nhsbt.nhs.uk

~~**Co-chair**:~~

~~Dr Manu Shankar-Hari~~

~~Guy's and St Thomas' NHS Foundation Trust, London, UK.~~

~~School of Immunology and Microbial Sciences, King's College London~~

~~United Kingdom~~

~~Phone: +447879470843~~

~~Email: manu.shankar-hari@kcl.ac.uk~~

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 for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair
Lise Estcourt

Date ~~1st June 2020~~<insert date>

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP to test the effectiveness of different strategies for immunoglobulin therapy for patients with acute illness due to microbiological testing-confirmed COVID-19 ~~infection in patients with concomitant severe pneumonia who are admitted to an Intensive Care Unit (ICU).~~.

~~This is the version of the COVID-19 Immunoglobulin Therapy Domain that will apply in the United Kingdom and has the version number 1.0. It is anticipated that this domain may also enroll patients in other countries. However, because of differences in nature and supply of product, or timing of availability of product, it is anticipated that differences in the DSA will be necessary. Versions used in~~

other countries, that are derived from this DSA, will be numbered sequentially with a new number after the decimal point (i.e. 1.1, 1.2 etc.) each applying to new countries. A major revision to the DSA will be allocated a new number before the decimal point, i.e. 2.0.

6.2. Domain-specific background

6.2.1. COVID-19 Infection

The first report of infection with COVID-19 occurred in Wuhan, China, in late 2019. Since that time, and as of the time of writing of this DSA, there have been hundreds of thousands of reported cases across the globe, with a range of severity, tens of thousands of deaths, and documented sustained human-to-human transmission. On January 30th 2020, the World Health Organization (WHO) declared this outbreak a Public Health Emergency of International Concern (https://www.who.int/newsroom/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)). Due to previous experience with other novel coronaviruses, such as Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome coronavirus (MERS-CoV), public health agencies have responded aggressively to the urgent need to acquire knowledge regarding this emerging infection. An important component of this urgently needed knowledge includes understanding the effectiveness of alternative treatment strategies in patients with suspected or proven infection. Clinical guidance issued by the WHO indicates that unproven therapies should be administered preferably only within the setting of a clinical trial (https://www.who.int/docs/defaultsource/coronaviruse/clinical-management-of-novel-cov.pdf).

Globally, as of 12th April 2020 there are 1,854,464 confirmed cases, 114,331 deaths and 435,074 patients have recovered from SARS-CoV-2 illness (https://coronavirus.jhu.edu/map.html; Accessed on 12th April 2020). Estimates of the burden of critical illness among patients infected with COVID-19 vary and the corresponding case-fatality estimates are unreliable and differ by resource availability in terms of testing and critical care beds. Nevertheless, it is recognized that fatal critical illness, especially from severe respiratory failure from pneumonitis is high. In reports from China and from Italy (Grasselli et al., 2020, Huang et al., 2020, Remuzzi and Remuzzi, 2020), the proportion of confirmed COVID-19 cases requiring organ support in critical care units varies between 16% to 32% of all hospitalized SARS-CoV-2 illness. Although the overall case fatality rate is estimated as 5.7% (95% confidence intervals 5.5% – 5.9%) for COVID-19 disease (Baud et al., 2020), the 28-day mortality in critically ill patients with COVID-19 disease is approximately 60%, and even higher in those requiring mechanical ventilation (Yang et al., 2020).

~~The corresponding figures in the United Kingdom are 84,279 confirmed cases and 10,612 deaths. In the UK, the critical care case-mix of COVID19 has been reported by the Intensive Care National Audit and Research Centre (ICNARC) (https://www.icnarc.org; Accessed on 12th April 2020). This report contains all confirmed COVID-19 cases reported to ICNARC up to midnight on 10th April 2020 from critical care units participating in the Case Mix Programme (all NHS adult, general intensive care and combined intensive care/high dependency units in England, Wales and Northern Ireland, plus some specialist and non-NHS critical care units). ICNARC has been notified of 4,960 admissions. Amongst these 4,960 admissions, the first 24-hour data to inform the case-mix characteristics such as age, sex, illness severity has been submitted to ICNARC for 4,292 admissions of 3,883 patients. Of the 3,883 patients, 59.0% of patients are mechanically ventilated within 24 hours of admission, 871 patients have died, 818 patients have been discharged alive from critical care. Importantly, 2,194 patients were last reported as still being in critical care. The predictions for all health care systems globally, including the UK, are that the demands on critical care requirements are likely to increase and any intervention that reduces this by accelerating illness resolution, ideally by reducing both mortality and by reducing critical care length of stay are essential.~~

~~Interim recommendations from the WHO for clinical care of infected patients focus upon supportive care, including organ support as needed, prevention of complications, and no specific anti-COVID-19 therapies. The WHO have recommended that any specific therapy targeted to COVID-19 infection should be provided only as part of a research protocol (https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf).~~ 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. REMAP-CAP 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 at www.remapcap.org.

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.

~~6.2.2.~~6.2.3. Convalescent Plasma

Convalescent plasma treatment, containing high titers of polyclonal antibody (Ab), ~~has~~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 ~~1915-1917~~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).

~~Several trials have shown that convalescent plasma had some efficacy in the treatment of SARS-CoV infected patients. Eight observational studies reported improved mortality after SARS-CoV – infected patients received various amounts of convalescent plasma (Mair-Jenkins et al., 2015). For example, a small retrospective case-comparison study (19 vs 21 patients) showed a case fatality rate reduction after convalescent plasma treatment of 23% (95% CI: 6%-42%, p≤0.05) (Soo et al., 2004). Each patient received 200 to 400 ml of convalescent plasma. In a case series of 80 patients treated with 160-640 ml of convalescent plasma 12.5% died compared with the overall SARS-related mortality rate in Hong-Kong of 17% (Cheng et al., 2005). In this limited series, convalescent plasma given before 14 days after the onset of symptoms was associated with better outcome, however such post-hoc analyses are fraught with confounding factors but do suggest early treatment may be more efficacious.~~

~~Convalescent plasma therapy had been given to at least 245 COVID-19 patients in China by the end of February 2020, and, according to a Chinese health official, 91 cases had shown improvement in clinical indicators and symptoms (http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm). There have been three published reports from China (Duan et al., 2020, Shen et al., 2020, Zhang et al., 2020), the largest study showed that 10 patients hospitalized with COVID-19 and given 200ml of convalescent plasma with a neutralizing antibody titer of >1:640 showed significant clinical and radiological improvement and commensurate reduction in C-reactive protein (CRP), liver function tests, viremia and oro-pharyngeal viral load and increases in lymphocyte count (Duan et al., 2020).~~

~~*6.2.2.1. Adverse effects of convalescent plasma*~~

~~Minor side effects have been reported with convalescent plasma, such as fever or chills (Luke et al., 2006), or allergic transfusion reactions~~ 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.

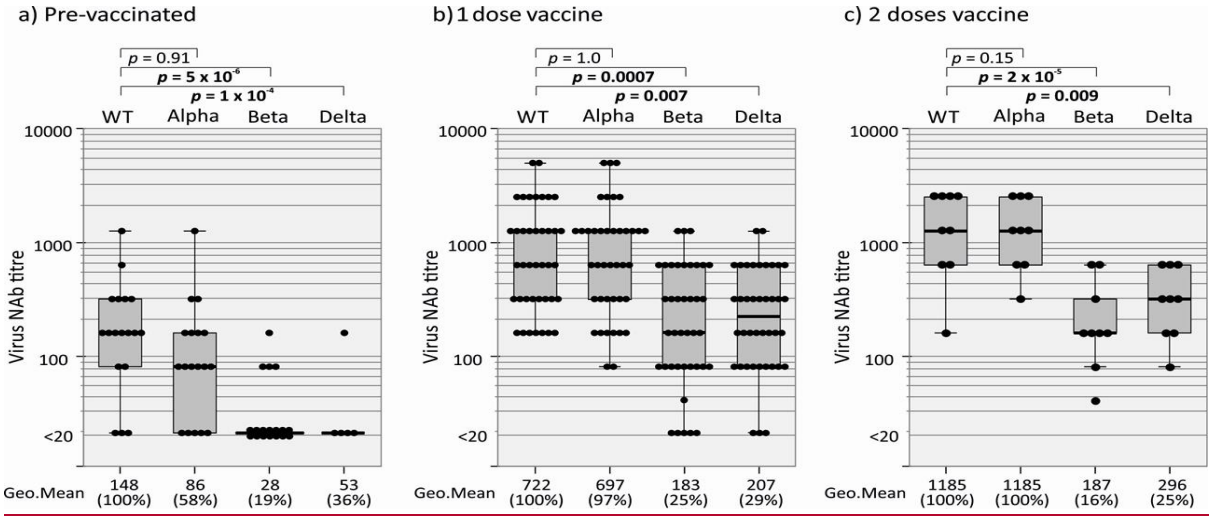


Figure 1. Level of viral neutralization of different viral variants by convalescent plasma a) pre-vaccinated donors, b) after 1 dose of vaccine and c) after two doses of vaccine.

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 REMAP-CAP.

6.2.4.2. Rationale for previous monoclonal antibody therapy stratification

The available monoclonal antibodies were designed using the original wild-type strain and new variants may become resistant to the available monoclonal antibody therapies. This has already happened with the SARS-CoV-2 virus and one monoclonal antibody. Monotherapy with bamlanivimab has had its emergency use authorization (EUA) withdrawn due to development of viral resistance (https://www.fda.gov/media/147629/download). This may mean that monoclonal cocktails (at least two different monoclonal therapies given together) are effective and less likely to lead to resistance than use of a single monoclonal. However, even a monoclonal cocktail could

become ineffective in the future, as shown by the prospective mapping of viral variants that detected a potential mutation (E406W) that could escape neutralization by both components of the Regeneron monoclonal cocktail (http://science.sciencemag.org/content/371/6531/850.abstract). A small non-randomized study showed development of escape mutations after treatment with bamlanivimab and etesevimab monoclonal cocktail in patients with hematological malignancies associated with clinical deterioration (~~Beigel~~Pommeret et al., ~~2019~~2021). ~~More significantly two reports of possible transfusion-related acute lung injury (TRALI) following~~These patients all received convalescent plasma ~~have been documented in one patient with Ebola disease~~therapy after the monoclonal cocktail, and ~~one patient with MERS-CoV, although no anti-HLA~~four out of the five patients survived.

In many locations in which REMAP-CAP recruits there is likely to be prophylaxis or ~~anti-HNA antibodies~~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 ~~identified in donor~~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 as highlighted in the small study above.

As such, we will create a Prior Monoclonal Antibody stratum so that we can generate independent estimates of treatment effect with independent application of statistical triggers, but permitting borrowing between strata. We will also compare the spectrum of viral variants and characterize significant mutations at baseline between those who have received monoclonal therapy and those who have not in selected study sites. Monoclonal therapy is expensive, requires specialized manufacturing units, and it is likely that supply will be constrained. It is therefore a treatment that most low- and middle-income countries cannot afford and will be unable to manufacture locally. Convalescent plasma can be produced in many countries of the world and is much more affordable (~~Chun~~Libster et al., ~~2016, Mora-Rillo et al., 2015~~2021). ~~However, none of the 84 patients in the Ebola randomized controlled trial developed any serious adverse events due to the transfusion (Van Griensven et al., 2016b).~~

~~*6.2.2.2. Antibody Dependent Enhancement*~~

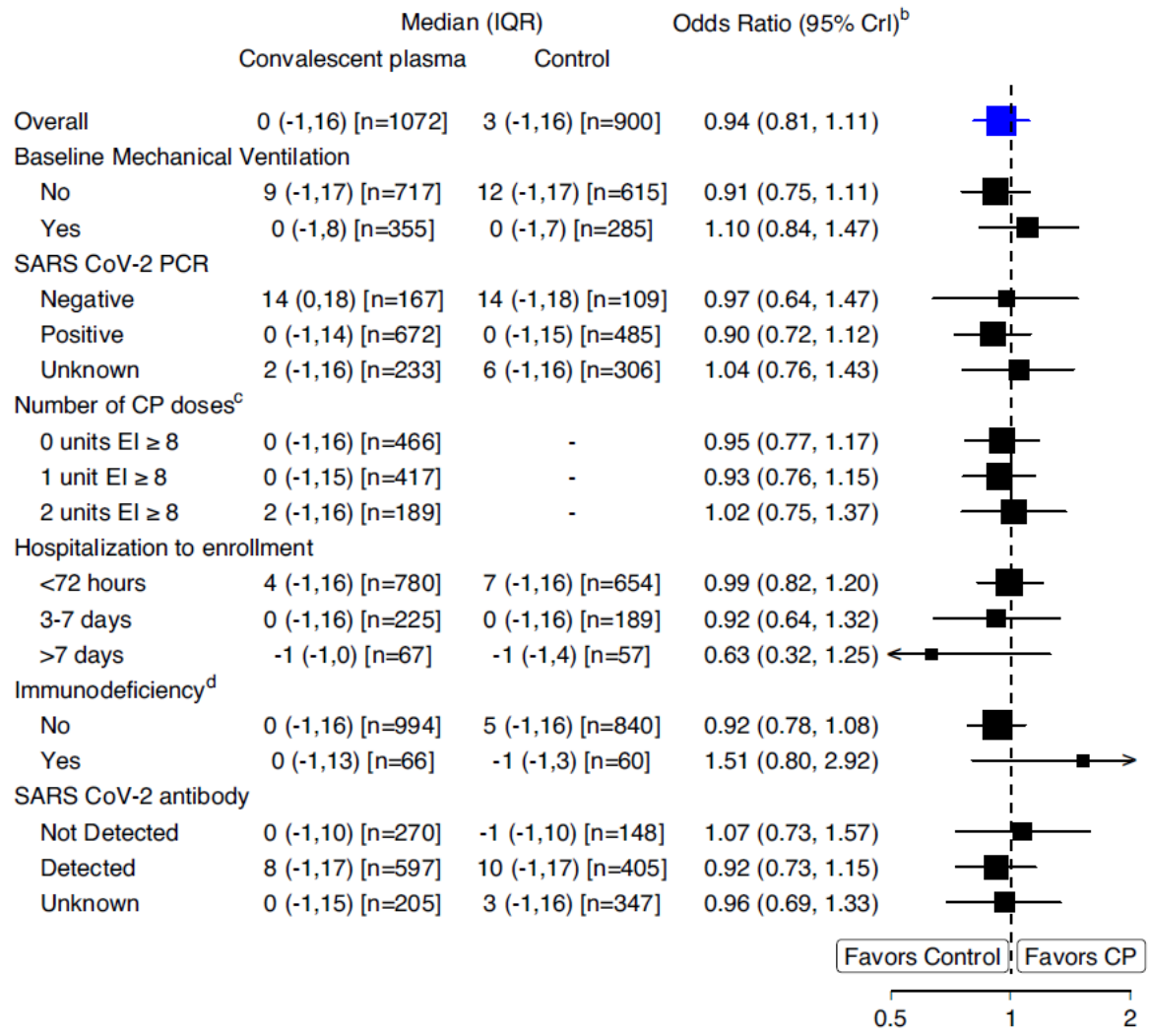
~~Antibody-dependent enhancement (ADE) occurs when antibodies facilitate viral entry into host cells and enhance viral infection in these cells (Wan et al., 2019). Potential toxicity associated with convalescent plasma remains a concern, and this is very relevant to COVID-19 patients who exhibit a spectrum of lung pathology from acute lung injury to acute respiratory disease syndrome and death. In SARS-CoV-associated disease, antibodies may mediate pathology if they target a different serotype of the virus~~ . Therefore, when thinking about whether to use passive immunization therapy consideration needs to be made not just on its effectiveness, but also on its accessibility.

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 (~~Wan~~Senefeld et al., ~~2019, Wang et al., 2014~~2021). ~~Furthermore, a novel mechanism~~

~~for ADE where a neutralizing antibody binding to the surface protein of a coronavirus-like viral receptor triggers viral cell entry has been recently proposed. This ADE pathway was shown not only to be antibody dose dependent but also likely mediated by presence of non-neutralizing antibodies (Ricke and Malone, 2020). For these reasons, we plan to collect convalescent plasma at the earliest 28 days after recovery so that antibody response has matured in terms of titer and affinity.~~

~~There is currently no evidence of ADE occurring in the current epidemic, and a small trial of 10 patients in China with COVID-19 treated in a single infusion of 200ml of convalescent plasma showed neither pulmonary injury nor infection enhancement. The high levels of neutralizing antibodies (>1:640), timely transfusion (median time from onset of symptoms to hospital admission and CP transfusion was 6 days (IQR, 2.5–8.5 days) and 16.5 days (IQR 11.0–19.3 days), respectively, and appropriate plasma volume (200ml) were thought to contribute to the absence of side-effects (Duan et al., 2020).~~

~~*6.2.2.3. Collection of Convalescent Plasma*~~

~~NHS Blood and Transplant (NHSBT) has been preparing to collect convalescent plasma from recovered COVID-19 infected patients since this was requested by NHS England in mid-February. These patients are contacted to ask if they are willing to consider blood donation. We are collecting convalescent plasma at least 28 days after their recovery from the infection to maximize the quality and quantity of neutralizing antibodies present in their donations. In addition to the usual donor and donation screening, the first 1,000 donations will be tested for SARS-CoV-2 RNA, SARS-CoV-2 RNA testing will be stopped if there is no evidence of RNA in any of these donations. Neutralizing antibody levels will also be determined in each donation using microneutralization (TCID50) or pseudovirus particle assays or both. However, if an adequate correlation between neutralizing antibody titre and Elisa antibody reactivity is demonstrated, this can replace the test for neutralising antibodies. Only donations containing high levels of neutralizing antibodies will be offered for clinical use (the cut-off level to be defined during the first two weeks of collections; 1:160 previously used for SARS-CoV-1 (Cheng et al., 2005) and MERS-CoV (Arabi et al., 2015)). We will only use male plasma or plasma from female donors who have been tested and are eligible to donate apheresis platelets (Epstein et al., 2020) to reduce the risk of TRALI. Treatment with convalescent plasma with low levels of antibody has been shown to be ineffective in Ebola (Van Griensven et al., 2016a, Van Griensven et al., 2016b).~~

~~The Scottish National Blood Transfusion Service (SNBTS), Welsh Blood Service (WBS), and Northern Ireland Blood Transfusion Service (NIBTS) are instituting similar convalescent plasma production~~

~~policies and they will supply convalescent plasma to hospitals in the devolved nations. There is a UK-wide collaboration to ensure production of convalescent plasma is consistent across all devolved nations. Any British Overseas Territories will also collaborate with the UK Blood Services to ensure a consistent product is produced.~~

~~The Irish Blood Transfusion Service will collect convalescent plasma at least 14 days after donors have recovered from infection, donors have to be nasopharyngeal swab negative prior to donation. The component will otherwise be similar to the component produced in the UK. Samples will be kept to ensure the component is consistent with the UK component.~~

~~The other blood services do not plan to perform SARS-CoV-2 RNA testing if there is no evidence of RNA in any of the initial 1000 donations tested by NHSBT.~~

~~*6.2.2.4. Administration of convalescent plasma*~~

~~Administration of convalescent plasma is more likely to be beneficial early in the course of the disease (up to 10 to 14 days after onset of symptoms) (Chen et al., 2020b).~~

~~*6.2.2.5. Need for a clinical trial*~~

~~Although there is evidence that convalescent plasma can have beneficial effects in patients with severe respiratory viral infections the majority of the evidence is of low quality. Two randomized trials, one of convalescent plasma and one of anti-influenza hyperimmune intravenous immunoglobulin showed no benefits of convalescent plasma~~ 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) (~~Beigel~~Writing Committee for the REMAP-CAP Investigators et al., ~~2019, Davey et al., 2019~~2021). ~~We are therefore uncertain whether~~

In the RECOVERY trial, the incidence of transfusion-related adverse events was again low, 13/5301 patients receiving convalescent plasma ~~will~~had reports submitted to the United Kingdom's Serious Hazards of Transfusion (SHOT) hemovigilance scheme: nine patients with pulmonary reactions (none considered to be ~~effective for COVID-19 patients~~ transfusion-related acute lung injury, including three deaths possibly related to transfusion), and ~~a RCT is required to assess the benefits of convalescent plasma.~~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.

~~6.2.3.~~6.2.6. Intervention Strategy for this domain

~~It is intended that this~~This domain of REMAP-CAP ~~will evolve~~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 ~~potentially~~ effective immunoglobulin therapies. WHO guidance notes the flexibility associated with REMAP-CAP as a platform 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 ~~commencement~~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 ~~for two reasons. Firstly, there is relatively limited trial or clinical experience with the administration of immunoglobulin therapies in patients who are critically ill and it is not reasonable to presume that such agents do not cause net harm. Secondly,~~because designs that include only active interventions are not able to ascertain if any option is better or worse than no treatment. ~~If, during the evolution of this domain, there is sufficient evidence of effectiveness of agents or clinical practice changes to include the routine use of such agents or both, the control intervention that specifies that no immunoglobulin therapy is administered will be~~

~~abandoned. Although this domain will commence with a single immunoglobulin therapy, it is intended that additional agents can be added (allowing evaluation of several agents against a common control intervention) as well as allowing introduction of combinations of agents (to evaluate potential synergy). Any~~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. ~~The initial selection of immunoglobulin therapy to be evaluated is convalescent plasma.~~

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~~immunoglobulin therapy for patients with ~~severe CAP who have~~acute illness due to 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 ~~from~~in the ~~PAtC~~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)
- ~~Convalescent~~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 ~~allocation status in the Corticosteroid Domain. This is a treatment-by-treatment interaction between the interventions in the COVID-19 Immunoglobulin Therapy Domain and the Corticosteroid Domain~~whether or not the patient has received any prior treatment with a monoclonal antibody for SARS-CoV-2 infection.

~~We hypothesize that the treatment effect of different immunoglobulin strategies is different depending on allocation status in the COVID-19 Antiviral Therapy Domain. This is a treatment-by-~~

~~treatment interaction between the interventions in the COVID-19 Immunoglobulin Therapy Domain and the COVID-19 Antiviral Therapy Domain.~~

~~Each participating site has the option to opt-in to two or more interventions to be included in the randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the intervention at that site. As long as the 'no immunoglobulin therapy for COVID-19' intervention is retained in the platform it is strongly preferred that this intervention is always included by participating sites and is mandatory so long as there is only a single active intervention within the domain.~~

8. TRIAL DESIGN

This domain will be conducted as part of a REMAP trial ~~(see Core Protocol Section 7).~~. Treatment allocation will be adaptive, as described in the Core Protocol ~~Section 7.5.2 and from the PAtC~~documents.

8.1. Population

The REMAP enrolls patients admitted to hospital with ~~severe pneumonia~~acute illness due to suspected or proven COVID-19, including patients admitted to ICU.

8.1.1. State

This domain is available for patients who have acute illness due to proven pandemic infection in the Moderate State and the Severe State.

8.1.2. Domain-specific strata

Domain-specific strata are applied to patients at the time of assessment for this domain. Sites that participate in this domain must participate in both domain-specific stratum.

8.1.2.1. Prior Monoclonal Antibody strata

Patients in the PISOP stratum who have received any treatment prior to reveal of assignment status for this domain with a monoclonal antibody preparation for SARS-CoV-2 infection during this acute illness will be categorized as members of the Prior Monoclonal Antibody stratum.

Patients in the PISOP stratum who have not received any treatment prior to reveal of assignment status for this domain with a monoclonal antibody preparation for SARS-CoV-2 infection during this acute illness will be categorized as members of the No Prior Monoclonal Antibody stratum.

8.1.2.2. Immune Suppressed stratum

Version 3 of this domain establishes an Immune Suppressed stratum to provide statistical continuity with immune suppressed patients enrolled in earlier versions of this domain (see ~~Core Protocol~~ Section ~~7.3).~~10.1). Only patients in the Immune Suppressed stratum will be recruited using this DSA.

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 ~~(see~~as specified in either the REMAP-CAP Core Protocol ~~Section 7.4 and PAtC).~~+ Pandemic Appendix, or the REMAP-COVID Core Protocol. Patients eligible for REMAP 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:

- ~~COVID-19~~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 ICU admission~~
- If in the Severe State, more than 48 hours has elapsed since ICU admission, unless the patient has already been assigned to an intervention in another domain in the Moderate State, in which case exclusion will occur if 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 (~~monoclonal antibody,~~ hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this ~~hospital admission~~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 ~~convalescent~~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)
- ~~Convalescent~~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.Convalescent Plasma~~

8.3.3.High titer plasma

8.3.3.1. Dosing of ~~convalescent~~ plasma

Patients assigned to receive plasma will receive ~~at least one and not more than~~ 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 ~~and~~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 ~~on the first day of the study.~~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. ~~There must be a minimum of 12 hours between transfusions to allow appropriate assessment of adverse reactions to the initial transfusion.~~ Both transfusions should be given within 48 hours from ~~randomization~~reveal of assignment.

8.4. Concomitant care

Additional ~~agents~~immunoglobulin therapy intended to be active against SARS-CoV-2 infection (such as monoclonal antibodies, hyperimmune globulin or convalescent plasma) should not be administered~~, unless they have become standard of care during the trial. In patients who have received an allocation status in the COVID-19 Antiviral Domain, and have microbiological testing confirmed SARS-CoV-2 infection, continuation of antiviral agent will be as per the COVID-19 Antiviral Domain-Specific Appendix (Section 8.3). .~~

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 ~~an operational document from within the options specified in the PAtC~~the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol.

8.5.2. Secondary endpoints

All secondary endpoints as specified ~~from~~in the ~~PAtC 7.5.2.~~REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol

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
- ~~Serious treatment-related adverse events (see table 1 section 10.1 of this appendix)~~
- 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
- ~~Venous thromboembolic events at 90 days~~

~~Domain-specific exploratory outcomes~~

- ~~Proportion of subjects who cleared SARS-CoV-2 infection (i.e. all samples, obtained for at least two time points after transfusion) tested negative for SARS-CoV-2 RNA, just in lower respiratory sample, in all respiratory tract samples or just in blood)~~
- ~~Reduction in SARS-CoV-2 viral load (within the first 3 days; 4 days; 6 days; 9 days; 15 days and 28 days analyzed separately in blood and respiratory tract samples)~~
- ~~Change in SARS-CoV-2 neutralizing antibody levels (within the first 3 days; 4 days; 6 days; 9 days; 15 days and 28 days)~~

9. TRIAL CONDUCT

9.1. Domain-specific data collection

~~9.1.1.Additional testing for all participants~~

~~A group and screen sample must be processed locally, so that ABO compatible convalescent plasma can be administered.~~

~~Samples to be taken on Study Day 1 prior to administration of convalescent plasma to assess the level of:~~

1) ~~Antibodies and neutralizing antibodies detectable prior to treatment on Day 1 (serum 6ml)~~
2) ~~Testing for virus detectable on an oropharyngeal or nasopharyngeal swab prior to treatment on Study Day 1~~

~~These samples must be sent to the central testing laboratory (see laboratory protocol).~~

~~9.1.2.Additional testing sub-study for convalescent plasma~~

~~There will be additional testing as specified in this protocol for a sub-group of sites.~~

~~Please see Appendix 1 for schedule of sampling. Sites will opt-in to the additional testing sub-study. We aim for at least 100 participants in each study intervention to be included in the sub-study (maximum 200 participants per study intervention). Full details are included in the Laboratory SOP.~~

~~COVID-19 is characterized by cytokine excess (Chen et al., 2020a). Administration of convalescent plasma will be associated with changes in cytokine profile, which may be the causal mechanism for treatment effects via immunomodulation (Shankar-Hari and Rubenfeld, 2019, Shankar-Hari et al., 2011). Antibody dependent potentiation is an adverse event with convalescent plasma, which requires monitoring (Liu et al., 2019).~~

~~*9.1.2.1. Proposed work*~~

~~The following biological work to assess adverse effects and to explain treatment response will be done at pre-defined time points at baseline and at predefined time points post convalescent plasma administration (Appendix 1).~~

- ~~A multiplexable Th1 / Th2 (including IL-10) cytokine profile (Chen et al., 2020a).~~
- ~~D-dimer and other laboratory markers of disease severity~~
- ~~Whole blood transcriptomic alterations (Blanco-Melo et al., 2020)~~

- ~~Flow cytometric analyses to define the immune status of participants~~
- ~~Genotype by SNP array~~
- ~~Neutralizing and other anti-viral antibody assays.~~
- ~~Viral PCR in respiratory and blood samples (Wölfel et al., 2020)~~
- ~~Sequencing of SARS-CoV-2 from respiratory and blood samples~~

~~9.1.3.Microbiology~~

~~Microbiological testing will be performed as per local practice, including bacterial and viral testing to guide clinical care. Results of these tests will be collected. If sites that are participating in this domain are not participating in the additional sample collection sub-study (section 8.1.2) they are encouraged to also participate in the Clinical Characterization Protocol (CCP) for patients with COVID-19 that has been established by the International Severe Acute Respiratory and Emerging Infectious Consortium (https://isaric.tghn.org/CCP/). This protocol specifies the collection of biological samples from patients with COVID-19. Samples collected in patients who are enrolled in the CCP may be made available to REMAP-CAP investigators to evaluate aspects of host or pathogen biology associated with assignment in this domain. Ethical approval at such sites and agreement from patients to undertake the CCP will be obtained separately.~~

~~9.1.4.Clinical data collection on all participants~~

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

- ~~Routinely collected data on neutrophil count, lymphocyte count, prothrombin time (PT), fibrinogen, CRP (if done for clinical reasons) at baseline~~
- ~~SARS-CoV-2 viral load at baseline (in blood and respiratory samples)~~
- ~~SARS-CoV-2 neutralizing antibody levels at baseline~~
- ~~Serious treatment-related serious adverse events within 24 hours of the treatment, similar serious adverse events reported in both arms unrelated to transfusion in the first 72 hours of the study~~
- 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) ~~up to day 90~~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.

~~9.1.5.Clinical Data collection on participants within the intensive sampling sub-set~~

- ~~Routinely collected data on neutrophil count, lymphocyte count, PT, fibrinogen, CRP (if done for clinical reasons) on days 2, 3, 4, 6, 9, 15, 28~~
- ~~SARS-CoV-2 viral load at day 2, 3, 4, 6, 9, 15 and 28 (in blood and respiratory samples)~~
- ~~SARS-CoV-2 neutralizing antibody levels at day 2, 3, 4, 6, 9, 15 and 28~~
- ~~Blood and respiratory samples will only be collected during inpatient admission, results will be censored at hospital discharge. Blood samples will be taken by fresh venipuncture if there is no indwelling cannula.~~

9.2. Criteria for discontinuation

Refer to ~~Core Protocol Section 8.7~~relevant core protocol documents for criteria for discontinuation of participation in the REMAP-CAP trial.

9.3. Blinding

9.3.1. Blinding

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

9.3.2. Unblinding

Not relevant.

10.STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

~~If~~This domain has adapted as a consequence of a Platform Conclusion ~~of equivalence~~ in the ~~primary endpoint is demonstrated the DSMB~~Severe State and a decision to close recruitment in the Moderate State in response to external evidence, in relation to unselected patients. The domain will recommence with recruitment limited to patients in the ~~ITSC may consider~~Immune Suppressed stratum. The 'no immunoglobulin against COVID-19' intervention is a continuation of ~~randomization~~

~~if clinically relevant differences in secondary endpoints have not been demonstrated~~the same intervention in previous versions of this Domain.

The following Platform Conclusions are possible in the four domain specific units-of-analysis (moderate and ~~it is considered plausible that clinically relevant differences in one or more secondary endpoints may be capable of being demonstrated.~~ severe disease state, crossed by Prior Monoclonal Antibody, all within the Immune-Suppressed stratum)

- Superiority 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 ~~Core Protocol Sections 7.8.6 to 7.8.9~~relevant core protocol documents.

10.2. Unit-of-analysis and strata

~~The default unit-of-analysis, for both analysis of treatment effect and the Response Adaptive Randomization, will be the SARS-CoV-2 infection confirmed stratum, as specified from the PAtC.~~

The population of interest that will be reported as a result of the amendment of this domain are patients in the PISOP stratum who are immune suppressed at the time of the eligibility assessment. Analysis will include 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 PISOP 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 entry criteria, for version 3 (i.e. only patients meeting this stratum definition are recruited using version 3). No new analysis will be reported using patients who do not meet this stratum definition, i.e. patients who are not immune suppressed.

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

This domain is analyzed only in the pandemic statistical model and includes only patients who are in the pandemic suspected or proven stratum, as specified in the REMAP-CAP Pandemic Appendix and corresponding to the eligibility criteria specified in the REMAP-COVID Core Protocol. Within this

stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State and by status with respect to Prior Monoclonal Antibody strata.

Borrowing is permitted between states and strata, i.e. borrowing will occur between the Prior Monoclonal Antibody and the No Prior Monoclonal Antibody stratum and between Moderate and Severe states. The domain will commence with balanced randomization and subsequently Response Adaptive Randomization will be applied to patients in each severity state but not applied according to Prior Monoclonal Antibody strata status. The time at which RAR is applied will be an operational decision of the SAC but RAR will not be applied until at least an additional 100 patients have been recruited

If RAR is applied, the cap on the maximum proportion of patients assigned to an intervention that is specified in core protocol documents may be reduced by the Statistical Analysis Committee (SAC) if needed to reduce the likelihood of sites being unblinded during a period of rapid recruitment. If a reduced cap is applied this will be an operational decision of the SAC, who will inform the DSMB, but blinded trial personnel will not be informed.

The shock strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

The influenza strata will not contribute to unit-of-analysis for this domain, as this strata is not applied in the Pandemic Statistical Model.

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with ~~Immediate Reveal or Randomization with~~ Deferred Reveal ~~if~~to permit confirmation of microbiological diagnosis ~~is~~if results of testing are not known at the time of initial assessment of eligibility (see ~~section 7.8.3.6 in Core Protocol)~~relevant core protocol documents).

10.4. Interactions with interventions in other domains

~~An a priori interaction with the Antibiotic Domain is not able to be evaluated as analysis occurs in different statistical models.~~

~~An *a priori* interaction with the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.~~

~~An *a priori* interaction with the Antiviral Domain is not able to be evaluated as analysis occurs in different statistical models.~~

~~An *a priori* interaction with the COVID-19 Antiviral Domain is considered possible and will be incorporated into the statistical models used to analyze this domain.~~

~~An *a priori* interaction with the COVID-19 Immune Modulation Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.~~

~~An *a priori* interaction with the Corticosteroid Domain is considered possible and will be incorporated into the statistical models used to analyze this domain.~~

~~No interaction is evaluable between the Ventilation Domain and this domain.~~ 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.

10.5. Nesting of interventions

~~Nesting is not applicable to this domain~~

The high titer convalescent plasma (active intervention specified in this DSA and designated P4) will be nested with the (low titer) convalescent plasma intervention (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 stratum. 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.

10.6. Threshold probability for superiority and inferiority

The threshold odds ratio delta for superiority and inferiority in this domain are those specified as the default ~~threshold from the PAtC~~thresholds in the relevant core protocol documents.

10.7. Threshold odds ratio delta for equivalence

~~The threshold odds ratio delta for equivalence in this domain is that specified from the PAtC (Section 7.8.8).~~

The platform conclusion of equivalence will not be evaluated in this domain. The same odds ratio delta as specified in the relevant core protocol documents for equivalence will be used for futility. This will be applied in a one-sided analysis for futility for active interventions specified in this domain.

10.8. Informative priors

~~This domain will launch with priors that are not informative for main effects.~~ 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 10.5. 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:

- ~~Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes pneumonia from blood, pleural fluid, or lower respiratory tract specimen.~~

Primary sub-group analyses

- Receiving invasive mechanical ventilation at baseline
- Patients with ~~undetectable~~detectable virus at baseline ~~(convalescent plasma intervention)~~
- ~~Patients with different levels of neutralizing antibodies at baseline (convalescent plasma intervention)~~
- 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
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

~~Domain-specific secondary and exploratory~~Exploratory sub-group analyses

- ~~All-cause mortality during the first 28 study days will be analyzed using a Kaplan-Meier estimate of survival and analyzed using Cox proportional hazards regression with adjustment for the stratification factors.~~
- ~~Number of SAEs (excluding thrombotic events) from randomization until 72 hours after randomization, per day at risk; described by intervention.~~
- ~~Number of thrombotic events from randomization up to the end of study day 90, per day at risk. These will be analyzed using Poisson regression.~~
- ~~Analyses of the data from the sub-study (exploratory analyses) will be specified in a separate analysis plan.~~
- 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 should be aware that the superiority~~, inferiority,~~ or ~~equivalence~~futility of ~~different interventions~~high titer convalescent plasma with respect to the primary endpoint ~~is~~are possible~~, and~~

if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints, such as all-cause mortality at 28 days.

The DSMB should take into account the public health, as well as clinical significance, of the analyses of this domain and are empowered to discuss results with relevant international and national public health authorities, with rapid dissemination of results to the larger community being the goal.

Safety secondary outcomes will be reported to the DSMB who are empowered to require additional analyses regarding these outcomes as required.

11.2. Potential domain-specific adverse events

11.2.1. Convalescent Plasma

All reportable SAEs listed in this section should be reported to REMAP-CAP in all patients in this domain, irrespective of intervention allocation. In addition, site staff are responsible for reporting all transfusion-related adverse events to their national or regional hemovigilance system (SHOT/SABRE in the UK) according to standard procedures. In Europe this is as required under the regulations of the EU Blood Directive (see section 10.1.1).

Adverse Reactions that are known to be related to transfusion are summarised in the table below together with information on whether they require reporting to the national or regional hemovigilance organisation as well as reporting as SARs:

Table 1: Serious Adverse Reactions and Events (see Appendix 2 for more detailed description)

Reactions	**Timing**	**Needs to be reported to SHOT/SABRE or other national or regional hemovigilance organisation** Call your hospital blood bank to let them know it needs to be reported – they will report to the hemovigilance system and inform you of any other tests that need to be performed	**Study Classification** Complete REMAP-CAP SAE form for ***all*** events
Fever >2°C rise or >39°C, needing hospital	**Within 24 hours of a transfusion and thought to be related**	**Yes**	**SAR**

~~admission or medical intervention~~	~~Within first 72 hours of study. Not related to transfusion~~	~~No~~	~~SAE~~
~~Severe allergic reaction or anaphylaxis (rash, angioedema, bronchospasm, hypotension)~~	~~Within 24 hours of a transfusion and thought to be related~~	~~Yes~~	~~SAR~~
	~~Within first 72 hours of study. Not related to transfusion~~	~~No~~	~~SAE~~
~~Hypotension, leading to shock (e.g. acidemia, impairment of vital organ function) without allergic or inflammatory symptoms. Urgent medical intervention required~~	~~Within 24 hours of a transfusion and thought to be related~~	~~Yes~~	~~SAR~~
	~~Within first 72 hours of study. Not related to transfusion~~	~~No~~	~~SAE~~
~~Acute serious haemolytic reaction~~	~~Within 24 hours of a transfusion~~	~~Yes~~	~~SAR~~
	~~Within first 72 hours of study. Not related to transfusion~~	~~No~~	~~SAE~~
~~Acute lung injury~~	~~Within 24 hours of a transfusion~~	~~Yes~~	~~SAR~~
	~~Within first 72 hours of study. Not related to transfusion~~	~~No~~	~~SAE~~
~~Circulatory overload~~	~~Within 24 hours of a transfusion~~	~~Yes~~	~~SAR~~
	~~Within first 72 hours of study. Not related to transfusion~~	~~No~~	~~SAE~~
~~Transfusion transmitted infection (TTI) (viral, bacterial or fungal)~~	~~During entire study~~	~~Yes~~	~~SAR~~

~~ADE of infection~~	~~Within first 72 hours of study~~	~~Yes~~	~~SAR~~
~~Clinically diagnosed arterial thromboembolism (e.g. CVA, MI)~~	~~During first 90 days~~	~~No~~	~~SAE~~

~~Information from hemovigilance systems (like SABRE/SHOT) will be used by the primary trials team in addition to the trials SAE data. A data-sharing agreement will be set up with SHOT to facilitate this.~~

In this domain occurrence of any of the following will be reported as an SAE:

- 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 ~~Core~~relevant core protocol ~~Section 8.13~~documents).

11.3. Domain-specific consent issues

As noted in the background~~,~~ and endorsed by the WHO, ~~in the absence of evidence of effectiveness of specific treatments for COVID-19,~~ the use of a no treatment control is both appropriate and ethical.

ForClinicians 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.

Entry to the study, for participants who are not competent to consent, either prospective agreement or entry is preferred to be via waiver- of-consent or some form of deferreddelayed consent can be applied, as requiredpermitted by an appropriate ethical review bodylocal requirements.

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.

Clinicians are directed to not enrol an individual patient if the treating clinician believes that participation in this domain is not in the best interests of the patient.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5.core protocol documents. This domain will receivehas not received any additional domain-specific funding. Initial but such funding is being provided by NHS Blood and Transplant to enable the domain to start. Further additional funding will, from any source, may be obtained during the life-time of the domain.

12.2. Funding of domain interventions and outcome measures

NHS Blood and TransplantLocal 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

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

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14.APPENDIX 1

For sites that have agreed to participate in the intensive testing sub-study the testing regimen is:

Enrolment / Treatment

	Week 1							Week 2							Week 3					
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Blood (EDTA) 2ml	*	-	-	*	-	-	-	-	-	-	-		-	-	-	-	-	-	-	-
Blood (EDTA) 4ml	*	*	*	*	–	*	–	–	*	–	–	(*)	–	–	*	–	–	–	–	–
Blood (serum) 6ml	*	*	*	*	–	*	–	–	*	–	–	(*)	–	–	*	–	–	–	–	–
PAXgene 2.5ml	*	-	-	-	-	-	-	-	*	-	-		-	-	-	-	-	-	-	-
Nasopharyngeal *or* Oropharyngeal swab	*	*	*	*	–	*	–	–	*	–	–	(*)	–	–	*	–	–	–	–	–

Samples taken from admission up to hospital discharge.

Samples must be taken prior to first and second units of plasma (Days 1 and 2). Follow-up samples at Day 3, Day 4, Da
recommended. Samples can be taken +/- 12 hours of the defined time within the sampling protocol. Additional samp

15.APPENDIX 2

Type of SAE	Diagnostic criteria	Where should cases should be reported
Febrile Acute Transfusion Reaction **Report within 24 hours of a transfusion**	**Severe** A rise in temperature of 2°C or more, and/or rigors, chills, or fever 39°C or over, or other inflammatory symptoms/signs such as myalgia or nausea which precipitate stopping the transfusion, prompt medical review AND/OR directly results in, or prolongs hospital stay	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Febrile Acute Reaction **Report within first 72 hours of the trial**		Must be reported on the REMAP-CAP trial SAE form

Allergic Acute Transfusion Reaction **(Report within 24 hours of a transfusion)**	**Severe** Bronchospasm, stridor, angioedema or circulatory problems which require urgent medical intervention AND/OR, directly result in or prolong hospital stay, or Anaphylaxis (severe, life-threatening, generalized or systemic hypersensitivity reaction with rapidly developing airway AND/OR breathing AND/OR circulation problems, usually associated with skin and mucosal changes)	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Allergic Acute Reaction **(Report within first 72 hours of the trial)**		Must be reported on the REMAP-CAP trial SAE form
Hypotensive Acute Transfusion Reaction **(Report within 24 hours of a transfusion)**	**Severe** Hypotension, as previously defined, leading to shock (e.g. acidemia, impairment of vital organ function) without allergic or inflammatory symptoms. Urgent medical intervention required	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Hypotensive Reaction **(Report within first 72 hours of the trial)**		Must be reported on the REMAP-CAP trial SAE form
Acute Hemolytic Transfusion Reaction (HTR) **(Report within 24 hours of a transfusion)**	Acute HTRs are defined as fever and other symptoms/signs of hemolysis within 24 hours of transfusion; confirmed by fall of Hb AND one or more of the following: • Rise in LDH • Rise in bilirubin • Positive DAT • Positive crossmatch	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Acute hemolytic reaction **(Report within first 72 hours of the trial)**	Defined as fever and other symptoms/signs of hemolysis confirmed by fall of Hb AND one or more of the following: • Rise in LDH • Rise in bilirubin • Positive DAT • Positive crossmatch	Must be reported on the REMAP-CAP trial SAE form
Transfusion-Associated Circulatory Overload (TACO) **(Report within 12 hours of a transfusion)**	*** Required criteria (A and/or B)** **A.** Acute or worsening respiratory compromise and/or **B.** Evidence of acute or worsening pulmonary edema	Patients classified with TACO should have: **at least one required criterion*** with onset during or up to 24 hours after transfusion

	based on: • clinical physical examination, and/or • radiographic chest imaging and/or other noninvasive assessment of cardiac function **Additional criteria** **C.** Evidence for cardiovascular system changes not explained by the patient's underlying medical condition, including development of tachycardia, hypertension, jugular venous distension, enlarged cardiac silhouette and/or peripheral edema **D.** Evidence of fluid overload including any of the following: a positive fluid balance; clinical improvement following diuresis **E.** Supportive result of a relevant biomarker, e.g. an increase of B-type natriuretic peptide levels (BNP) or N-terminal-pro brain natriuretic peptide) NT-pro BNP to greater than 1.5 times baseline value **A total of 3 or more criteria** i.e. *A and/or B, and total of at least 3 (A to E) Acute or worsening respiratory compromise	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Circulatory overload		Must be reported on the REMAP-CAP trial SAE form
Transfusion-associated dyspnea	Respiratory distress within 24 hours of transfusion that does not meet the criteria of TRALI, TACO or allergic reaction. Respiratory distress in such cases should not be explained by the patient's underlying condition	Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Transfusion-Related Acute Lung Injury (TRALI)	Acute dyspnea with hypoxia and bilateral pulmonary infiltrates during or within **six** hours of transfusion, not due to circulatory overload or other likely causes	Suspected TRALI should be reported – further investigations are required to confirm cases Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Acute lung injury	**Timing** Within 1 week of a known clinical insult or new or worsening respiratory symptoms	Must be reported on the REMAP-CAP trial SAE form

	Chest imaging Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules **Origin of edema** Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present **Oxygenation** Mild 200 mm Hg < PaO2/FIO2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H2Oc Moderate 100 mm Hg < PaO2/FIO2 ≤ 200 mm Hg with PEEP ≥ 5 cm H2O Severe PaO2/FIO2 ≤ 100 mm Hg with PEEP ≥ 5 cm H2O	
Transfusion-Transmitted Infections (TTI)	Include as a TTI if, following investigation the recipient had evidence of infection post-transfusion, and there was no evidence of infection prior to transfusion, and no evidence of an alternative source of infection	Suspected TTI should be reported – requires further investigations to confirm the diagnosis Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
Uncommon and new Complications of Transfusion not fitting into any of the other categories	Pathological reaction or adverse effect in temporal association with transfusion which cannot be attributed to already defined side effects and with no risk factor other than transfusion and do not fit under any of the other reportable categories. Including cases of antibody dependent enhancement of infection (ADE)	Suspected ADE should be reported Must be reported on the REMAP-CAP trial SAE form AND Must be reported to the hospital blood bank with details of the patient's trial number
These reactions will be followed up by the national hemovigilance services. (UK hemovigilance system) has agreed to collect detailed information on these patients and we will share data based on the trial number of the participant		