



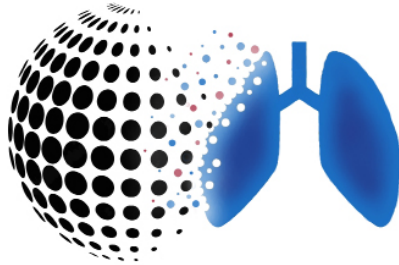
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MEDICAL RESEARCH  
INSTITUTE  
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CCCTG  
Canadian Critical Care  
Trials Group



# REMAP-CAP

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

## 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 2.3 dated 03 August 2020

## Summary

In this domain of the REMAP-CAP trial, participants meeting the platform-entry criteria with microbiological testing confirmed SARS-CoV-2 infection will be randomized to receive one of two interventions:

- No immunoglobulin against SARS-CoV-2
- Convalescent plasma

This DSA applies to the following states and 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
Interventions specified in this DSA	No immunoglobulin against SARS-CoV-2 Convalescent plasma	No immunoglobulin against SARS-CoV-2 Convalescent plasma	Not available
Interventions submitted for approval in this jurisdiction	<input type="checkbox"/> No immunoglobulin against SARS-CoV-2 <input type="checkbox"/> Convalescent plasma	<input type="checkbox"/> No immunoglobulin against SARS-CoV-2 <input type="checkbox"/> Convalescent plasma	Not available
Interventions offered at this site	Ward	ICU	ICU
	<input type="checkbox"/> No immunoglobulin against SARS-CoV-2 <input type="checkbox"/> Convalescent plasma	<input type="checkbox"/> No immunoglobulin against SARS-CoV-2 <input type="checkbox"/> Convalescent plasma	<input type="checkbox"/> No immunoglobulin against SARS-CoV-2 <input type="checkbox"/> Convalescent plasma

<b>REMAP-CAP: Immunoglobulin Therapy Domain Summary</b>	
Interventions	<ul style="list-style-type: none"> <li>No immunoglobulin against COVID-19</li> <li>Convalescent plasma (up to 2 units within 48 hours)</li> </ul>
Unit-of-analysis and Strata and States	The default unit-of-analysis for this domain will be the pandemic infection suspected or confirmed (PISOP) stratum with SARS-CoV-2 infection strata applied. 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. Borrowing is permitted between states. Response Adaptive Randomization will be applied to using probabilities derived from the SARS-CoV-2 confirmed stratum.
Evaluable treatment-by-treatment Interactions	No interaction 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 those specified in the relevant core protocol documents, and <ul style="list-style-type: none"> <li>SARS-CoV-2 infection is confirmed by microbiological testing</li> </ul>
Domain-Specific Exclusions	<p>Patients will be excluded from this domain if they have any of the following:</p> <ul style="list-style-type: none"> <li>If in ICU, more than 48 hours have elapsed since ICU admission</li> <li>Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission</li> <li>Enrolment in a trial evaluating any antibody therapy directed against COVID-19, where the protocol of the trial requires continuation of the treatment assignment specified in that trial</li> <li>More than 14 days have elapsed since hospital admission</li> <li>The treating clinician believes that participation in the domain would not be in the best interests of the patient</li> </ul>
Intervention-Specific Exclusions	<p>Criteria that exclude a patient from one or more interventions are:</p> <ul style="list-style-type: none"> <li>Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent</li> <li>Known previous history of transfusion-related acute lung injury will exclude a patient from receiving convalescent plasma</li> <li>Known objection to receiving plasma products will exclude a patient from receiving any plasma components</li> </ul>
Outcome measures	<p>Primary REMAP endpoint: refer to the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol.</p> <p>Secondary REMAP endpoints refer to the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol</p> <p>Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrolment):</p> <ul style="list-style-type: none"> <li>All-cause mortality at 28 days</li> <li>Confirmed deep venous thrombosis</li> <li>Confirmed pulmonary embolism</li> <li>Confirmed ischemic stroke</li> <li>Confirmed acute myocardial infarction</li> <li>Other confirmed thrombotic events</li> <li>Serious treatment-related adverse events (SAE) as defined in this appendix</li> <li>Serious Adverse Events (SAE) as defined in Core Protocol</li> </ul> <p>Domain-specific exploratory outcomes in a subset of patients</p> <ul style="list-style-type: none"> <li>Percentage of participants who cleared SARS-CoV-2 infection in respiratory samples after transfusion</li> </ul>

	<ul style="list-style-type: none"><li>• Reduction in SARS-CoV-2 viral load</li><li>• Change in SARS-CoV-2 neutralizing antibody levels</li></ul>
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SUPERSEDED

## TABLE OF CONTENTS

<b>1.</b>	<b>ABBREVIATIONS</b> .....	<b>7</b>
<b>2.</b>	<b>PROTOCOL APPENDIX STRUCTURE</b> .....	<b>8</b>
<b>3.</b>	<b>COVID-19 IMMUNOGLOBULIN DOMAIN-SPECIFIC APPENDIX VERSION</b> .....	<b>9</b>
3.1.	Version history .....	9
<b>4.</b>	<b>COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN GOVERNANCE</b> .....	<b>9</b>
4.1.	Domain members.....	9
4.2.	Contact Details.....	11
<b>5.</b>	<b>COVID-19 Immunoglobulin therapy DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION</b>	<b>12</b>
<b>6.</b>	<b>BACKGROUND AND RATIONALE</b> .....	<b>12</b>
6.1.	Domain definition .....	12
6.2.	Domain-specific background.....	13
6.2.1.	COVID-19 Infection .....	13
6.2.2.	Convalescent Plasma.....	14
6.2.3.	Intervention Strategy for this domain .....	17
<b>7.</b>	<b>DOMAIN OBJECTIVES</b> .....	<b>18</b>
<b>8.</b>	<b>TRIAL DESIGN</b> .....	<b>18</b>
8.1.	Population.....	18
8.2.	Eligibility criteria.....	19
8.2.1.	Domain inclusion criteria .....	19
8.2.2.	Domain exclusion criteria .....	19
8.2.3.	Intervention exclusion criteria .....	19
8.3.	Interventions.....	20
8.3.1.	Immunoglobulin Therapy Interventions .....	20
8.3.2.	No immunoglobulin against SARS-CoV-2 .....	20
8.3.3.	Convalescent Plasma.....	20
8.3.4.	Discontinuation of study therapy .....	21
8.4.	Concomitant care.....	21
8.5.	Endpoints .....	21
8.5.1.	Primary endpoint .....	21
8.5.2.	Secondary endpoints .....	21
<b>9.</b>	<b>TRIAL CONDUCT</b> .....	<b>22</b>
9.1.	Microbiology .....	22

9.2.	Domain-specific data collection .....	22
9.3.	Criteria for discontinuation .....	23
9.4.	Blinding .....	23
9.4.1.	Blinding .....	23
9.4.2.	Unblinding .....	23
<b>10.</b>	<b>STATISTICAL CONSIDERATIONS.....</b>	<b>23</b>
10.1.	Domain-specific stopping rules.....	23
10.2.	Unit-of-analysis and strata .....	24
10.3.	Timing of revealing of randomization status .....	24
10.4.	Interactions with interventions in other domains .....	24
10.5.	Nesting of interventions .....	25
10.6.	Threshold probability for superiority, effectiveness and inferiority.....	25
10.7.	Threshold odds ratio delta for equivalence or futility .....	25
10.8.	Informative priors .....	25
10.9.	Post-trial Sub-groups.....	25
10.10.	Domain-specific secondary and exploratory analyses.....	26
10.11.	Data sharing .....	26
<b>11.</b>	<b>ETHICAL CONSIDERATIONS.....</b>	<b>26</b>
11.1.	Data Safety and Monitoring Board .....	26
11.2.	Potential domain-specific adverse events .....	27
11.2.1.	Convalescent Plasma.....	27
11.3.	Domain-specific consent issues .....	27
<b>12.</b>	<b>GOVERNANCE ISSUES .....</b>	<b>28</b>
12.1.	Funding of domain .....	28
12.2.	Funding of domain interventions and outcome measures.....	28
12.3.	Domain-specific declarations of interest .....	28
<b>13.</b>	<b>REFERENCES .....</b>	<b>29</b>

## 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 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 relevant 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](http://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 19<sup>th</sup> April 2020
- Version 2: Approved by the COVID-19 Immunoglobulin Therapy Domain-Specific Working Group (DSWG) on 30 June 2020
- Version 2.3 Approved by the United States of America members of the COVID-19 Immunoglobulin Therapy DSWG on 03 August 2020

### **4. COVID-19 IMMUNOGLOBULIN THERAPY DOMAIN GOVERNANCE**

#### ***4.1. Domain members***

**Chair:**

Dr. Lise Estcourt\*

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Dr. Colin McArthur<sup>5</sup>

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Dr. Donald Arnold<sup>2</sup>

Dr. Phillipe Bégin<sup>2</sup>

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Prof. Tim Walsh<sup>1</sup>  
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<sup>1</sup> Members leading the UK COVID-19 Immunoglobulin Therapy Domain

<sup>2</sup> Members leading the Canadian COVID-19 Immunoglobulin Therapy Domain

<sup>3</sup> Members leading the USA COVID-19 Immunoglobulin Therapy Domain

<sup>4</sup> Members leading the Australian COVID-19 Immunoglobulin Therapy Domain

<sup>5</sup> Members leading the New Zealand COVID-19 Immunoglobulin Therapy Domain

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## **4.2. Contact Details**

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

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

**Chair**

Lise Estcourt



**Date**

30 June 2020

**Country lead**

Bryan McVerry



03 August 2020

## 6. BACKGROUND AND RATIONALE

### 6.1. Domain definition

This is a domain within the REMAP-CAP platform to test the effectiveness of different strategies for immunoglobulin therapy for microbiological testing-confirmed SARS-CoV-2 infection in patients with acute illness due to suspected or proven COVID-19.

This is the version of the COVID-19 Immunoglobulin Therapy Domain that will apply in the United States of America and has the version number 2.3. 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 SARS-CoV-2 (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 millions of reported cases across the globe, with hundreds 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-\(2019-ncov\)](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 is to understand the effectiveness of COVID-19 treatments. 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 20 June 2020 there are 8,666,697 confirmed cases, 460,066 deaths and 4,247,527 patients have recovered from SARS-CoV-2 illness (<https://coronavirus.jhu.edu/map.html>; Accessed on 20 June 2020). Estimates of the burden of critical illness among patients infected with COVID-19 vary and the corresponding case-fatality estimates are affected by factors such as health system capacity including the availability of diagnostic 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 for hospitalized patients (Baud et al., 2020), the mortality in critically ill patients with COVID-19 disease, especially those requiring mechanical ventilation, is much higher (Yang et al., 2020).

The corresponding figures in the United States are 4,339,997 confirmed cases and 148,866 deaths (3.4%, [www.cdc.gov](http://www.cdc.gov)). In the US, the critical care case-mix of COVID19 has been projected by The Institute for Health Metrics and Evaluation (IHME, <https://covid19.healthdata.org>; Accessed on 30th

July 2020). IHME projects 14,507 inpatient beds needed for COVID-19 care, of which 5,941 are intensive care unit beds. Of the 5941 ICU patients, 5679 are mechanically ventilated, 903 are projected to die. The predictions for all health care systems globally, including the US, are that the demands on critical care requirements are likely to persist and any intervention that accelerates illness resolution, ideally by reducing both mortality and by reducing critical care length of stay is essential.

Interim guidance 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/publications/i/item/clinical-management-of-covid-19>).

#### 6.2.2. Convalescent Plasma

Convalescent plasma treatment, containing high titers of polyclonal antibody (Ab), has been used 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 (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 of more relevance 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 or 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 infection. Eight observational studies reported improved mortality after patients with SARS-CoV – infection 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 23% (95% CI: 6%-42%,  $p \leq 0.05$ ) reduction in mortality after treatment with 200-400 ml of convalescent plasma, when compared with continuation of high-dose methylprednisolone (Soo et al., 2004). 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.

Reports on the use of convalescent plasma to treat COVID-19 have emerged from the early stages of the pandemic in China (Duan et al., 2020, Shen et al., 2020, Zhang et al., 2020). The largest study showed that 10 patients hospitalized with COVID-19 each given 200ml of convalescent plasma with a neutralizing antibody titer of >1:640 described an improvement in clinical, laboratory and radiological parameters. However, this study was not adequately controlled or powered to allow robust conclusions (Duan et al., 2020).

Subsequently, the effectiveness of convalescent plasma has been assessed in an open-label, multicenter, randomized clinical trial in China comparing convalescent plasma with standard of care in 103 patients with 'severe' or 'life-threatening' COVID-19 (Li et al., 2020). There was a higher rate of nasopharyngeal SARS-CoV-2 PCR negativity at 72 hours in the convalescent plasma group (87.2% vs 37.5%, OR, 11.39 [95% CI, 3.91-33.18];  $P < 0.001$ ). In patients with 'severe' COVID-19, clinical improvement, defined as either hospital discharge or reduction of 2 points on a 6-point disease severity scale ranging from 6=death to 1=discharge, occurred in 91.3% (21/23) of the convalescent plasma group and 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32];  $P = 0.03$ ). However, this clinical improvement with convalescent plasma was not seen in patients with 'life-threatening' COVID-19. Overall, the secondary outcome of 28-day mortality was not significantly reduced with convalescent plasma treatment (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46];  $P = 0.30$ ).

#### *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 (Beigel et al., 2019). More significantly two reports of possible transfusion-related acute lung injury (TRALI) following convalescent plasma have been documented in one patient with Ebola disease and one patient with MERS-CoV, although no anti-HLA or anti-HNA antibodies were identified in donor plasma (Chun et al., 2016, Mora-Rillo et al., 2015). 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., 2016). Convalescent plasma has now been given to more than 20,000 COVID-19 patients in the United States of America through an expanded access program (Joyner et al., 2020). 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.

#### *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 (Wan et al., 2019, Wang et al., 2014). 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*

Individuals who have documented COVID-19 infections are identified through hospital records with assistance from the local or regional County Health Departments. Recovered individuals will be evaluated in clinic as potential donors for convalescent plasma (CP). US criteria for CP donors has been outlined by the FDA and includes evidence of prior COVID-19 infection, absence of symptoms for a minimum of 14 days (we will be using 21 days for local donors), a negative nasopharyngeal swab by PCR and a positive IgG/ IgA ELISA antibody test (EuroImmun IgG/IgA against the spike protein - S1 domain). A positive result with this assay indicates a titer $\geq$ 100. CP donor samples will be saved to determine maximum titer. Donors must also meet all regular volunteer donor criteria.



We will only use plasma from male donors, non-parous female donors or parous female donors who have tested negative for HLA antibodies.

#### *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., 2020).

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

Thus far, the available literature indicates that convalescent plasma has been used to treat thousands of patients with COVID-19 and that, in this setting, rates of serious adverse effects are low. There is a lack of high-quality evidence to determine whether convalescent plasma is an effective therapy for hospitalized patients with COVID-19 and crucial questions remain unanswered, including whether convalescent plasma reduces mortality in hospitalized patients and whether it improves outcomes in the critically unwell.

#### *6.2.3. Intervention Strategy for this domain*

It is intended that this domain of REMAP-CAP will evolve, taking into account evidence derived from 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 of this domain, a control group is included (i.e. some patients will not receive any 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 and it is not reasonable to presume that such agents do not cause net harm. Secondly, 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 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 critically ill patients emerges for any intervention specified in this domain, the ITSC, as advised by the DSWG, may remove an intervention prior to declaration of a Platform Conclusion. If this occurs, presentation and publication of results that relate to that intervention will occur, so as to contribute additional weight of evidence available in the public domain.

## **7. DOMAIN OBJECTIVES**

The objective of this domain is to determine the effectiveness of Immunoglobulin Therapy for patients who are eligible for the platform and who have microbiological testing-confirmed COVID-19.

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

- No immunoglobulin against SARS-CoV-2
- Convalescent plasma

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 the REMAP-CAP trial. Treatment allocation will be adaptive, as described in either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol.

### ***8.1. Population***

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

## **8.2. Eligibility criteria**

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol. Patients eligible for REMAP-CAP 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:

- SARS-CoV-2 infection is confirmed by microbiological testing

### 8.2.2. Domain exclusion criteria

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

- If currently in ICU, more than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of sustained organ failure support)
- Patient has already received treatment with any non-trial prescribed antibody therapy (monoclonal antibody, hyperimmune immunoglobulin, or convalescent plasma) intended to be active against COVID-19 during this hospital admission
- Enrolment in a trial evaluating any antibody therapy directed against COVID-19, where the protocol of the trial requires continuation of the assignment specified in that trial
- 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 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
- Convalescent plasma

If the domain evolves to comprise 3 or more interventions, it is required that all sites will participate in the 'No immunoglobulin against COVID-19' intervention, and each site has the option to opt-in to one or more of the remaining interventions based on local practice and availability of the intervention.

#### 8.3.2. No immunoglobulin against SARS-CoV-2

Patients assigned to this intervention will not receive any preparation of immunoglobulin intended to neutralize SARS-CoV-2 during the index hospitalization. Administration of such a preparation is considered a protocol deviation.

#### 8.3.3. Convalescent 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  $\pm$  150ml) within 48 hours of randomization. Volume of convalescent plasma administered will be recorded and where available the level of antibodies within each unit will be tested.

##### 8.3.3.2. Duration of administration of convalescent plasma

Patients will be randomized to receive ABO compatible convalescent plasma plus standard care upon admission to the hospital or standard care alone. Those receiving convalescent plasma will

receive a up to two adult units of convalescent plasma (minimum 200mL each) supply permitting as early as possible following randomization. The antibody titer of the plasma will be tested in each unit as well as documenting the volume transfused.

#### 8.3.4. Discontinuation of study therapy

An immunoglobulin for SARS-CoV-2 infection should be discontinued if there is development of an SAE. Immunoglobulin therapy can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

### **8.4. Concomitant care**

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). Additional agents intended to be active against SARS-CoV-2 infection should not be administered, unless they have become standard of care during the trial or specified in another trial protocol. All treatment that is not specified by assignment within the platform will be determined by the treating clinician.

### **8.5. Endpoints**

#### 8.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome specified in the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol.

#### 8.5.2. Secondary endpoints

All secondary endpoints as specified in the 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
- Confirmed deep vein thrombosis
- Confirmed pulmonary embolus
- Confirmed ischemic cerebrovascular event
- Confirmed acute myocardial infarction

- Other confirmed thrombotic events
- Serious treatment-related adverse events (see section 11.2 of this appendix)
- Serious Adverse Events (SAE) as defined in core protocol documents and qualified in this appendix.

Domain-specific exploratory outcomes in a subset of patients:

- Percentage of participants who cleared SARS-CoV-2 infection in respiratory samples after transfusion
- Reduction in SARS-CoV-2 viral load
- Change in SARS-CoV-2 neutralizing antibody levels

## **9. TRIAL CONDUCT**

### ***9.1. 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 and any additional testing, which may differ between locations, is specified below.

Sites that are participating in this domain 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.

### ***9.2. Domain-specific data collection***

Additional domain-specific data will be collected for the index hospitalization:

- Administration of immunoglobulin therapies
- Neutralizing antibody titer of trial immunoglobulin therapies (where available)
- Deep vein thrombosis
- Pulmonary embolism
- Ischemic cerebrovascular events

- Peak troponin
- Acute myocardial infarction (using fourth international definition)

Type and cross-match will be performed locally for all participants so that ABO compatible convalescent plasma can be administered.

Samples will be taken on Day 1 prior to administration of convalescent plasma to assess the level of antibodies and neutralizing antibodies detectable prior to treatment on Day 1 (6 mL plasma).

Patients may be enrolled in a separate biosampling registry and subsequently blood will be sampled on days 5 and 10 after randomization (plasma 6ml) to assess the level of antibodies and neutralizing antibodies detectable.

Samples will be obtained by research personnel or from excess blood form the central lab sent for clinical testing purposes.

### **9.3. Criteria for discontinuation**

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

### **9.4. Blinding**

#### 9.4.1. Blinding

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

#### 9.4.2. Unblinding

Not relevant.

## **10. STATISTICAL CONSIDERATIONS**

### **10.1. Domain-specific stopping rules**

The following Platform Conclusions are possible in this domain:

- Superiority of convalescent plasma compared to no immunoglobulin against SARS-CoV-2
- Futility of convalescent plasma compared to no immunoglobulin against SARS-CoV-2

Additional Platform Conclusions may be possible if further interventions are added to the domain.

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

### **10.2. Unit-of-analysis and strata**

This domain is analyzed only in the pandemic statistical model and includes only patients who are SARS-CoV-2 infection confirmed. 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. Borrowing is permitted between states and strata. Response Adaptive Randomization will be applied in each illness severity state, using probabilities derived from the SARS-CoV-2 confirmed stratum.

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.

### **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 confirmation of microbiological diagnosis is not known at the time of initial assessment of eligibility (see 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 Influenza 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 not considered possible and will not 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 not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the COVID-19 Statin 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 Vitamin C Domain is either not considered possible and will not be incorporated into the statistical model used to evaluate this domain in the pandemic statistical model or is not able to be evaluated for PINSNP patients as analysis occurs in different statistical models.

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

#### **10.5. Nesting of interventions**

Nesting is not applicable to this domain

#### **10.6. Threshold probability for superiority, effectiveness and inferiority**

The threshold odds ratio delta for superiority, effectiveness and inferiority in this domain are those specified in the relevant core protocol documents

#### **10.7. Threshold odds ratio delta for equivalence or futility**

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 of an active intervention.

#### **10.8. Informative priors**

This domain will launch with priors that are not informative for main effects. 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. Data for post-trial sub-group analysis may not be available from all regions or for all patients in a region. 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.
- Receiving invasive mechanical ventilation at baseline
- Patients with undetectable virus at baseline (convalescent plasma intervention)
- Patients with different levels of neutralizing antibodies at baseline (convalescent plasma intervention)
- Dose of neutralizing antibodies received (convalescent plasma intervention, based on volume of transfusion and titer measurement, where available)
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

#### **10.10. Domain-specific secondary and exploratory analyses**

- 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 acute hospitalization, per day at risk. These will be analyzed using Poisson regression.
- Analyses of the data from any country-specific sub-studies will be specified in separate analysis plans.

#### **10.11. Data sharing**

Not applicable.

### **11. ETHICAL CONSIDERATIONS**

#### **11.1. Data Safety and Monitoring Board**

The DSMB should be aware that the superiority, effectiveness, inferiority, futility or equivalence of different interventions with respect to the primary endpoints 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 are required.

## **11.2. Potential domain-specific adverse events**

### 11.2.1. Convalescent Plasma

The following possible treatment-related adverse events should be reported 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 regional blood bank

- Severe allergic reaction or anaphylaxis
- Transfusion-associated Acute Lung Injury (TRALI)
- Transfusion-associated Circulatory Overload (TACO)
- Complications of transfusion not fitting into other transfusion reaction categories

Other SAEs should be reported only where, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant core protocol documents).

## **11.3. Domain-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.

For patients who are not competent to consent, either prospective agreement or entry via waiver of consent or some form of deferred consent can be applied, as required by an appropriate ethical review body.

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 documents. This domain will receive additional domain-specific funding.

### **12.2. Funding of domain interventions and outcome measures**

Regional blood banks will supply the convalescent plasma for the trial and arrange for distribution to participating hospitals via its routine blood product 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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SUPERSEDED