



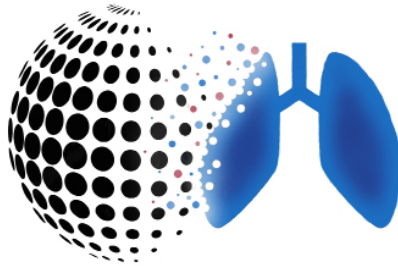
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CCCTG  
Canadian Critical Care  
Trials Group



# 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 1.01 dated 01 June 2020

## 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 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 plasma

<b>REMAP-CAP: Immunoglobulin Therapy Domain Summary</b>	
Interventions	<ul style="list-style-type: none"> <li>No immunoglobulin against COVID-19 (no placebo)</li> <li>Convalescent plasma (up to 2 units within 48 hours)</li> </ul>
Unit-of-analysis and Strata	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.
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 <ul style="list-style-type: none"> <li>COVID-19 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>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>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: as defined in an operational document specified from the Pandemic Appendix to the Core Protocol Section 7.5.1.</p> <p>Secondary REMAP endpoints refer to Core Protocol Section 7.6.2</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>Serious adverse events (SAE) as defined in this appendix</li> <li>Serious Adverse Events (SAE) as defined in Core Protocol</li> <li>Venous thromboembolic events at 90 days</li> </ul> <p>Domain-specific exploratory outcomes</p> <ul style="list-style-type: none"> <li>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)</li> <li>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)</li> <li>Change in SARS-CoV-2 neutralizing antibody levels (within the first 3 days; 4 days; 6 days; 9 days; 15 days and 28 days)</li> </ul>

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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

## 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, 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 1.01: Approved by the COVID-19 Immunoglobulin Therapy DSWG on 1<sup>st</sup> June 2020

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

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

**Chair:**

Dr Lise Estcourt\*

**Co-chair:**

Dr Manu Shankar-Hari\*

**Members:**

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A/Prof Scott Berry

A/Prof Mark Coyne

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\*Prof David Roberts  
Prof Kathy Rowan  
Dr Jon Silversides  
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### **4.3. 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 1<sup>st</sup> June 2020

## **5. BACKGROUND AND RATIONALE**

### **5.1. Domain definition**

This is a domain within the REMAP-CAP to test the effectiveness of different strategies for immunoglobulin therapy for 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.

### **5.2. Domain-specific background**

#### 5.2.1. 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-\(2019-ncov\)](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>).

#### 5.2.2. 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 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%,  $p \leq 0.05$ ) (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](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).

#### *5.2.2.1. 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., 2016b).

#### *5.2.2.2. 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).

#### *5.2.2.3. 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 (TCID<sub>50</sub>) 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.

#### *5.2.2.4. 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).

#### *5.2.2.5. 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 (Beigel et al., 2019, Davey et al., 2019). We are therefore uncertain whether convalescent plasma will be effective for COVID-19 patients and a RCT is required to assess the benefits of convalescent plasma.

#### *5.2.3. 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 in patients who are critically ill 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.

## **6. DOMAIN OBJECTIVES**

The objective of this domain is to determine the effectiveness of Immunoglobulin Therapy for patients with severe CAP who have microbiological testing-confirmed COVID-19.

We hypothesize that the primary end-point specified from the PATC will differ based on the immunoglobulin therapy intervention. The following interventions will be available:

- No immunoglobulin against COVID-19 (no placebo)
- Convalescent plasma

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.

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.

## **7. 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.

### **7.1. Population**

The REMAP enrolls patients with severe pneumonia admitted to ICU (see Core Protocol Section 7.3).

### **7.2. 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 Core Protocol Section 7.4 and PATC). Patients eligible for REMAP may have conditions that exclude them from the COVID-19 Immunoglobulin Therapy Domain.

#### **7.2.1. Domain inclusion criteria**

Patients are eligible for this domain if:

- COVID-19 infection is confirmed by microbiological testing

#### **7.2.2. 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
- 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
- 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

### 7.2.3. 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

## 7.3. Interventions

### 7.3.1. 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 plasma

### 7.3.2. No immunoglobulin against COVID-19 (no placebo)

Patients assigned to this intervention will not receive any preparation of immunoglobulin intended to neutralize COVID-19 during the index hospitalization. Administration of such a preparation is considered a protocol deviation.

### 7.3.3. Convalescent Plasma

#### 7.3.3.1. 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 and the level of antibodies within each unit will be tested.

#### *7.3.3.2. 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. 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.

### **7.4. Concomitant care**

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. 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.

### **7.5. Endpoints**

#### *7.5.1. 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.

#### *7.5.2. Secondary endpoints*

All secondary endpoints as specified from the PATC 7.5.2.

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
- Serious treatment-related adverse events (see table 1 section 10.1 of this appendix)
- Serious Adverse Events (SAE) as defined in Core Protocol
- 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)

## 8. TRIAL CONDUCT

### 8.1. Domain-specific data collection

#### 8.1.1. 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).

#### 8.1.2. 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).

#### 8.1.2.1. 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

#### 8.1.3. 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.

#### 8.1.4. 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
- 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

#### 8.1.5. 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.

### **8.2. Criteria for discontinuation**

Refer to Core Protocol Section 8.7 for criteria for discontinuation of participation in the REMAP-CAP trial.

### **8.3. Blinding**

#### 8.3.1. Blinding

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

#### 8.3.2. Unblinding

Not relevant.

## **9. STATISTICAL CONSIDERATIONS**

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

If a Platform Conclusion of equivalence in the primary endpoint is demonstrated the DSMB and the ITSC may consider continuation of randomization if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered plausible that clinically relevant differences in one or more secondary endpoints may be capable of being demonstrated. 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.

### ***9.2. 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 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.

### ***9.3. 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 section 7.8.3.6 in Core Protocol)

### ***9.4. 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.

### ***9.5. Nesting of interventions***

Nesting is not applicable to this domain

### ***9.6. 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.

### ***9.7. 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).

### ***9.8. 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.

### ***9.9. 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.



- 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 (based on volume of transfusion and titer measurement)
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

### **9.10. Domain-specific secondary and exploratory 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.

## **10. ETHICAL CONSIDERATIONS**

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

The DSMB should be aware that the superiority, inferiority, or equivalence of different interventions with respect to the primary endpoint is 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.

## 10.2. Potential domain-specific adverse events

### 10.2.1. 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	Study Classification
		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	Complete REMAP-CAP SAE form for <u>all</u> events
Fever >2°C rise or >39°C, needing hospital admission or medical intervention	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
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

<b>Hypotension, leading to shock (e.g. acidemia, impairment of vital organ function) without allergic or inflammatory symptoms. Urgent medical intervention required</b>	<b>Within 24 hours of a transfusion and thought to be related</b>	<b>Yes</b>	<b>SAR</b>
	<b>Within first 72 hours of study. Not related to transfusion</b>	<b>No</b>	<b>SAE</b>
<b>Acute serious haemolytic reaction</b>	<b>Within 24 hours of a transfusion</b>	<b>Yes</b>	<b>SAR</b>
	<b>Within first 72 hours of study. Not related to transfusion</b>	<b>No</b>	<b>SAE</b>
<b>Acute lung injury</b>	<b>Within 24 hours of a transfusion</b>	<b>Yes</b>	<b>SAR</b>
	<b>Within first 72 hours of study. Not related to transfusion</b>	<b>No</b>	<b>SAE</b>
<b>Circulatory overload</b>	<b>Within 24 hours of a transfusion</b>	<b>Yes</b>	<b>SAR</b>
	<b>Within first 72 hours of study. Not related to transfusion</b>	<b>No</b>	<b>SAE</b>
<b>Transfusion transmitted infection (TTI) (viral, bacterial or fungal)</b>	<b>During entire study</b>	<b>Yes</b>	<b>SAR</b>
<b>ADE of infection</b>	<b>Within first 72 hours of study</b>	<b>Yes</b>	<b>SAR</b>
<b>Clinically diagnosed arterial thromboembolism (e.g. CVA, MI)</b>	<b>During first 90 days</b>	<b>No</b>	<b>SAE</b>

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.

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 protocol Section 8.13).

### **10.3. 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.

## **11.GOVERNANCE ISSUES**

### **11.1. Funding of domain**

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain will receive any additional domain-specific funding. Initial funding is being provided by NHS Blood and Transplant to enable the domain to start. Further additional funding will be obtained during the life-time of the domain.

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

NHS Blood and Transplant will supply the convalescent plasma for the trial and arrange for distribution to participating sites via its routine distribution system.

### **11.3. 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

### 13.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							Week 4						
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Blood (EDTA) 2ml	*			*																								
Blood (EDTA) 4ml	*	*	*	*		*			*			(*)			*													*
Blood (serum) 6ml	*	*	*	*		*			*			(*)			*													*
PAXgene 2.5ml	*								*																			
Nasopharyngeal <i>or</i> 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, Day 6, Day 9, Day 15 and Day 28 are recommended. Samples can be taken +/- 12 hours of the defined time within the sampling protocol. Additional samples on Day 12 can be submitted.

## 14.APPENDIX 2

Type of SAE	Diagnostic criteria	Where should cases should be reported
<b>Febrile Acute Transfusion Reaction</b>  <b>Report within 24 hours of a transfusion</b>	<b>Severe</b> 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
<b>Febrile Acute Reaction</b>  <b>Report within first 72 hours of the trial</b>		Must be reported on the REMAP-CAP trial SAE form
<b>Allergic Acute Transfusion Reaction</b>  <b>(Report within 24 hours of a transfusion)</b>	<b>Severe</b> 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
<b>Allergic Acute Reaction</b>  <b>(Report within first 72 hours of the trial)</b>		Must be reported on the REMAP-CAP trial SAE form
<b>Hypotensive Acute Transfusion Reaction</b>  <b>(Report within 24 hours of a transfusion)</b>	<b>Severe</b> 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

<p><b>Hypotensive Reaction</b>  (Report within first 72 hours of the trial)</p>		<p>Must be reported on the REMAP-CAP trial SAE form</p>
<p><b>Acute Hemolytic Transfusion Reaction (HTR)</b>  (Report within 24 hours of a transfusion)</p>	<p>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:</p> <ul style="list-style-type: none"> <li>• Rise in LDH</li> <li>• Rise in bilirubin</li> <li>• Positive DAT</li> <li>• Positive crossmatch</li> </ul>	<p>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</p>
<p><b>Acute hemolytic reaction</b>  (Report within first 72 hours of the trial)</p>	<p>Defined as fever and other symptoms/signs of hemolysis confirmed by fall of Hb AND one or more of the following:</p> <ul style="list-style-type: none"> <li>• Rise in LDH</li> <li>• Rise in bilirubin</li> <li>• Positive DAT</li> <li>• Positive crossmatch</li> </ul>	<p>Must be reported on the REMAP-CAP trial SAE form</p>
<p><b>Transfusion-Associated Circulatory Overload (TACO)</b>  (Report within 12 hours of a transfusion)</p>	<p><b>* Required criteria (A and/or B)</b>  <b>A.</b> Acute or worsening respiratory compromise and/or <b>B.</b> Evidence of acute or worsening pulmonary edema based on:</p> <ul style="list-style-type: none"> <li>• clinical physical examination, and/or</li> <li>• radiographic chest imaging and/or other noninvasive assessment of cardiac function</li> </ul> <p><b>Additional criteria</b> <b>C.</b> Evidence for cardiovascular system changes not explained by the patient’s underlying medical condition, including development of tachycardia,</p>	<p>Patients classified with TACO should have:  <b>at least one required criterion*</b> with onset during or up to 24 hours after transfusion</p> <p>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</p>
<p><b>Circulatory overload</b></p>		<p>Must be reported on the REMAP-CAP trial SAE form</p>

	<p>hypertension, jugular venous distension, enlarged cardiac silhouette and/or peripheral edema  <b>D.</b> Evidence of fluid overload including any of the following:                      a positive fluid balance; clinical improvement following diuresis  <b>E.</b> 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</p> <p><b>A total of 3 or more criteria</b> i.e. *A and/or B, and total of at least 3 (A to E) Acute or worsening respiratory compromise</p>	
<p><b>Transfusion-associated dyspnea</b></p>	<p>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</p>	<p>Must be reported on the REMAP-CAP trial SAE form</p> <p>AND</p> <p>Must be reported to the hospital blood bank with details of the patient’s trial number</p>
<p><b>Transfusion-Related Acute Lung Injury (TRALI)</b></p>	<p>Acute dyspnea with hypoxia and bilateral pulmonary infiltrates during or within <b>six</b> hours of transfusion, not due to circulatory overload or other likely causes</p>	<p>Suspected TRALI should be reported – further investigations are required to confirm cases</p> <p>Must be reported on the REMAP-CAP trial SAE form</p> <p>AND</p> <p>Must be reported to the hospital blood bank with details of the patient’s trial number</p>
<p><b>Acute lung injury</b></p>	<p><b>Timing</b> Within 1 week of a known clinical insult or new or worsening respiratory symptoms  <b>Chest imaging</b> Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules  <b>Origin of edema</b> Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude</p>	<p>Must be reported on the REMAP-CAP trial SAE form</p>

	<p>hydrostatic edema if no risk factor present</p> <p><b>Oxygenation</b></p> <p>Mild 200 mm Hg &lt; PaO<sub>2</sub>/FIO<sub>2</sub> ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H<sub>2</sub>O</p> <p>Moderate 100 mm Hg &lt; PaO<sub>2</sub>/FIO<sub>2</sub> ≤ 200 mm Hg with PEEP ≥ 5 cm H<sub>2</sub>O</p> <p>Severe PaO<sub>2</sub>/FIO<sub>2</sub> ≤ 100 mm Hg with PEEP ≥ 5 cm H<sub>2</sub>O</p>	
<b>Transfusion-Transmitted Infections (TTI)</b>	<p>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</p>	<p>Suspected TTI should be reported – requires further investigations to confirm the diagnosis</p> <p>Must be reported on the REMAP-CAP trial SAE form</p> <p>AND</p> <p>Must be reported to the hospital blood bank with details of the patient’s trial number</p>
<b>Uncommon and new Complications of Transfusion not fitting into any of the other categories</b>	<p>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)</p>	<p>Suspected ADE should be reported</p> <p>Must be reported on the REMAP-CAP trial SAE form</p> <p>AND</p> <p>Must be reported to the hospital blood bank with details of the patient’s trial number</p>
<p>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</p>		