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# Domain-Specific Appendix: Monoconal Antibody domain

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

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Monoclonal Antibody Domain-Specific Appendix Version 1 dated 29 November 2021

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

- 1.2g casirivimab / 1.2g imdevimab (low dose)
- 4g casirivimab / 4g imdevimab (high dose)

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

☐ 1.2g casirivimab / 1.2g imdevimab (low dose)

☐ 4g casirivimab / 4g imdevimab (high dose)

This DSA applies to the following states and stratum:

<table>
<tr><td>Stratum</td><td colspan="3">Pandemic infection suspected or proven (PISOP)</td><td>Pandemic Infection neither suspected nor proven (PINSNP)</td></tr>
<tr><td>Core protocol documents</td><td colspan="3">REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol</td><td>REMAP-CAP Core Protocol</td></tr>
<tr><td>Illness Severity State</td><td colspan="2">Moderate State</td><td>Severe State</td><td>Severe State</td></tr>
<tr><td>Interventions specified in this DSA</td><td colspan="2">Low dose<br>High dose</td><td>Low dose<br>High dose</td><td>Not available</td></tr>
<tr><td>Interventions submitted for approval in this jurisdiction</td><td colspan="2">☐ Low dose<br>☐ High dose</td><td>☐ Low dose<br>☐ High dose</td><td>Not available</td></tr>
<tr><td rowspan="2">Interventions offered at this site</td><td>Ward</td><td>ICU</td><td>ICU</td><td>ICU</td></tr>
<tr><td>☐ Low dose<br>☐ High dose</td><td>☐ Low dose<br>☐ High dose</td><td>☐ Low dose<br>☐ High Dose</td><td>Not available</td></tr>
</table>

| **REMAP-CAP: Monoclonal Antibody Domain Summary** | |
|---|---|
| Interventions | • 1.2g casirivimab / 1.2g imdevimab (low dose)<br>• 4g casirivimab / 4g imdevimab (high dose) |
| Unit of Analysis, Strata, and State | This domain is analyzed only in the pandemic statistical model. The pandemic statistical model includes only patients who are in the Pandemic Infection Suspected or Proven (PISOP) stratum. Within the stratum the unit-of-analysis is defined by illness severity state at the time of enrollment, defined as either Moderate State or Severe State. Borrowing is permitted between states and strata. Response Adaptive Randomization will not be applied in this domain with fixed randomization proportions at a ratio of 2:1 for low dose compared to high dose. |
| Evaluable treatment-by-treatment Interactions | No interactions wil be evaluated with any other domain. |
| Nesting | None. |
| Timing of Reveal | Randomization with Deferred Reveal. |
| Inclusions | Patients will be eligible for this domain if:<br>• COVID-19 infection has been confirmed by microbiological testing (i.e. PISOP stratum)<br>• Serum antibodies against SARS-CoV-2 (anti-S) are not detected<br>• Patient is eligible for treatment with monoclonal antibody therapy directed against SARS-CoV-2, according to local guidelines |
| Domain-Specific Exclusions | Patients will be excluded from this domain if they have any of the following:<br>• If in the Severe State, more than 48 hours has elapsed since ICU admission, unless the patient has already been assigned a treatment in another domain in the Moderate State in which case exclusion will occur if more 48 hours has elapsed since commencement of sustained organ failure support in an ICU.<br>• Previously received treatment in hospital with any monoclonal antibodies to SARS-CoV-2<br>• Enrolled in another trial of monoclonal antibody therapy on this hospital admission<br>• The treating clinician believes that participation in the domain would not be in the best interests of the patient |
| Intervention-Specific Exclusions | Criteria that exclude a patient from a one or more interventions are:<br>• Known hypersensitivity to an agent (or its excipients) specified as an intervention in this domain will exclude a patient from receiving that agent. |
| Outcome measures | Primary REMAP endpoint: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol<br><br>Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol + Pandemic Appendix and REMAP-COVID Core Protocol<br><br>Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment): |

| | |
|---|---|
| | • Weekly SARS-CoV-2 PCR testing through normal clinical testing routes in hospital, to enable viral genomic sequencing<br>• Serum levels of casirivimab and imdevimab measured at up to 4 time points over 28 days. 6mls of blood at each time point will be collected at the time of other blood sampling for clinical purposes. |

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# 1. ABBREVIATIONS

| | |
|---|---|
| DSA | Domain-Specific Appendix |
| DSMB | Data Safety and Monitoring Board |
| DSWG | Domain-Specific Working Group |
| ICU | Intensive Care Unit |
| ISIG | International Statistics Interest Group |
| ITSC | International Trial Steering Committee |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| nMAB | Neutralising monoclonal antibodies |
| PAtC | Pandemic Appendix to the Core Protocol |
| PCR | Polymerase Chain Reaction |
| PISOP | Pandemic infection is suspected or proven |
| PK | Pharmacokinetic |
| PO | Polyolefin |
| PVC | Polyvinyl chloride |
| RAR | Response Adaptive Randomization |
| RCT | Randomized controlled trial |
| REMAP-CAP | Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia |
| RSA | Region-Specific Appendix |
| SAC | Statistical Analysis Committee |
| SAE | Serious Adverse Event |
| SARS | Severe Acute Respiratory Syndrome |
| 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); 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 Region-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 to a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analytic model will also change over time in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices and an operational document referred to as the Current State. These documents 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. 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).

# 3. MONOCLONAL ANTIBODY DOMAIN-SPECIFIC APPENDIX VERSION

The version of the Monoclonal Antibody Domain-Specific Appendix (DSA) is in this document's header and on the cover page.

## *3.1. Version history*

Version 1: Approved by the monoclonal antibody Domain-Specific Working Group (DSWG) on 29th November 2021

# 4. MONOCLONAL ANTIBODY DOMAIN GOVERNANCE

## *4.1. Domain members*

**Chair:** Prof Anthony Gordon

**Members:**

Dr. Farah Al-Beidh
Prof. Wendy Barclay
Prof. Graham Cooke
Prof. Anthony de-Soyza
Mr. Cameron Green
Dr. Lise Estcourt
Prof. Danny McAuley
Mr. Paul Mouncey
Prof. Andrew Owen

Prof. Najib Rahman

Prof. Kathy Rowan

Prof. Manu Shankar-Hari

Prof. Andrew Ustianowski

Prof. Steve Webb

Dr. Tao You

### *4.2. Contact Details*

**Chair:** Prof Anthony Gordon

Intensive Care Unit, St Mary's Hospital / Imperial College, London W2 1NY

Email: Anthony.gordon@imperial.ac.uk

## 5. MONOCLONAL ANTIBODY DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The Monoclonal Antibody Domain-Specific Working Group have read this appendix and authorize it as the official monoclonal antibody Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee

**Chair**
Prof. Anthony Gordon

Date 29th November, 2021

## 6. BACKGROUND AND RATIONALE

### *6.1. Domain definition*

This is a domain within the REMAP-CAP platform to test the effectiveness of monoclonal antibodies against SARS-CoV2 for patients admitted to hospital with COVID-19.

## 6.2. Domain-specific background

### 6.2.1. COVID-19 infection

#### 6.2.1.1. *Introduction*

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

#### 6.2.1.2. *Clinical trials for COVID-19 infection*

Observational data cannot determine treatment effects reliably due to the risk of systematic bias (Califf et al., 2020). Clinical trials to identify effective COVID-19 treatments are needed and a large number of trials are underway. Early in the pandemic, the WHO provided guidance regarding both trial design and prioritization of candidate therapies. With regards to trial design, the WHO noted that initially there were no treatments with proven efficacy in patients with COVID-19. Therefore, the recommended 'standard of care' comparator was a control group that did not receive an agent intended to be active against COVID-19 infection, its associated immune response, or other complications (https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintnCoV-2020.4-eng.pdf?ua=1). As effective COVID-19 treatments are identified, it is anticipated that 'standard of care', both inside and outside of a clinical trial, will continue to change to incorporate the use of agents with proven efficacy. REMAP-CAP randomizes COVID-19 patients to a range of therapeutic interventions across different domains. Up to date information regarding active and inactive interventions and domains is available at www.remapcap.org.

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

### 6.2.2. Background about monoclonal antibodies

Casirivimab and imdevimab are neutralising monoclonal antibodies (nMAB) used in combination that bind specifically to two different sites on the spike protein of the SARS-CoV-2 virus particle, blocking its entry into the host cell and therefore inhibiting its replication. They are intended to compensate/substitute for endogenous antibodies in those individuals who have yet to mount their own immune response.

This combination has been tested in several clinical trials in different populations at different doses and via different administration routes.

In an interim analysis of 275 non-hospitalised patients with COVID-19 treatment with intravenous casirivimab and imdevimab (combined dose of either 2.4g or 8.0g) resulted in a significant reduction of “medically attended visits”, 3% vs 6% and reduced viral loads (Weinreich et al., 2021a). These effects were more marked in those who had not yet mounted their own immune response. There were no safety concerns.

In the subsequent Phase III part of the trial (Weinreich et al., 2021b), treatment with 2.4 g casirivimab and imdevimab compared to placebo reduced the risk of COVID-19–related hospitalization or death from any cause from 4.6% to 1.3% in unvaccinated patients who underwent randomization concurrently (relative risk reduction, 71.3%; P<0.001).

In a trial of subcutaneous casirivimab and imdevimab (1.2g combined dose) for unvaccinated participants who had been exposed to SARS-CoV-2 infection, treatment with the antibodies led to a significant reduction in symptomatic infection (relative risk reduction, 81.4%; odds ratio, 0.17; P<0.001) (O'Brien et al., 2021). Among the participants who became infected, treatment with the antibodies reduced the duration of symptomatic disease and the duration of a high viral load.

The RECOVERY trial demonstrated a 6% decrease in 28-day mortality at 28-days (24% vs 30%, rate ratio 0·80; 95% CI, 0·70–0·91; p=0·0010) in the pre-specified sub-group of seronegative patients in hospital treated with casirivimab (4g) / imdevimab (4g) 8g combined dose compared with controls (untreated) (https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1). Similarly, among the seronegative patients who were not receiving invasive mechanical ventilation at baseline, treatment with the antibodies was associated with less frequent progression to use of ventilation versus usual care (28% vs 32%; risk ratio 0·87, 95% CI 0·77 to 0·98). There was no benefit seen for any clinical outcomes in seropositive patients. Rates of adverse events were low and generally balanced in treated and control groups. There were 7 suspected serious adverse reactions (3 allergic reactions) reported in the 1792 patients who had these records collected.

In the UK, the MHRA has awarded a Conditional Marketing Authorisation for casirivimab and imdevimab for the prophylaxis and treatment of acute COVID-19 infection at a single dose of 1.2g (600mg of casirivimab / 600mg of imdevimab). In the Summary of Product Characteristics, it is reported that there is a flat dose-response relationship for efficacy at all doses (1.2g, 2.4g and 8g combined intravenous dose), based on viral load and clinical outcomes in the clinical trial COV-2067 (non-hospitalised patients with COVID-19).

A UK-wide commissioning policy has now been published recommending casirivimab and imdevimab at a dose of 2.4g (1.2g/1.2g) in seronegative patients hospitalised due to COVID-19. However, this dose is off-label and also a fraction of the dose tested in RECOVERY, where clinical effectiveness was demonstrated in hospitalised patients.

The recommendation has been made based on evidence from other studies in non-hospitalised patients that suggest that a dose of 2.4g is likely to achieve serum levels in excess of that necessary to neutralise SARS-CoV-2. However, similar pharmacokinetic (PK) studies have not been reported in hospitalized patients, and it should be noted that very large inter-individual variations in casirivimab and imdevimab levels are seen in the existing PK studies. Further variation in serum levels is expected depending on the degree of systemic inflammation present and also due to treatment with intravenous fluids. As patients with COVID-19 are usually admitted to hospital due to severe systemic inflammation and also likely to require intravenous fluid (especially when critically ill) it is crucial to

undertake PK studies in this population to confirm adequate levels to neutralise SARS-CoV-2 are achieved, and provide evidence of clinical effectiveness to support the decision to use casirivimab and imdevimab at this lower dose, in this population. This domain is designed to provide answers to these uncertainties.

### 6.2.3. Intervention strategy for this domain

This domain will test the potential benefits of different doses of the same monoclonal antibody and undertake a pharmacokinetic study.

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

## 7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of of monoclonal antibodies against SARS-CoV2 for patients admitted to hospital with COVID-19.

We hypothesize that the probability of the occurrence of the primary endpoint specified in the relevant core protocol documents will differ based on allocation to monoclonal antibody therapy. The following interventions will be available:

- 1.2g casirivimab / 1.2g imdevimab - combined 2.4g (refered to as low dose)
- 4g casirivimab / 4 g imdevimab - combined 8g (referred to as high dose)

We hypothesize that the treatment effect of monoclonal antibody therapy is different depending on the illness severity state at the time of enrollment.

## 8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will commence with fixed randomization ratios for the initial interventions. This will be in the ratio of 2:1 for low dose vs high dose, in order to maximise the power of the study without using excess high doses of the intervention which is limited in supply, and also balancing time required to reach a conclusion. If

additional interventions are added later, then response adaptive randomization may be introduced, as described in the core protocol documents.

## *8.1. Population*

The REMAP enrolls patients with acute illness due to proven COVID-19 admitted to hospital, including patients admitted to ICU.

### 8.1.1. State

This domain is available for patients who have acute illness due to proven COVID-19 in both the Moderate state and Severe state.

### 8.1.2. Domain-specific strata

Domain-specific strata are not applied to patients at the time of assessment for this domain.

## *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 the REMAP may have conditions that exclude them from this Domain.

### *8.2.1.* Domain inclusion criteria

Patients are eligible for this domain if:

- COVID-19 infection has been confirmed by microbiological testing (i.e. PISOP stratum)
- Serum antibodies against SARS-CoV-2 (anti-S) are not detected
- Patient is eligible for treatment with monoclonal antibody therapy directed against SARS-CoV-2, according to local guidelines

### *8.2.2.* Domain exclusion criteria

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

- If in the Severe State, more than 48 hours has elapsed since ICU admission, unless the patient has already been assigned a treatment in another domain in the Moderate State in which case

exclusion will occur if more 48 hours has elapsed since commencement of sustained organ failure support in an ICU.

- Previously received treatment in hospital with any monoclonal antibodies to SARS-CoV-2
- Enrolled in another trial of monoclonal antibody therapy on this 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. In such cases, patients will be randomly allocated a remaining intervention from among those available at that site.

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 in whom all interventions are contraindicated will be treated according to the current standard of care at the clinician's discretion.

Criteria that exclude a patient from a one or more interventions are:

- Known hypersensitivity to an agent (or its excipients) specified as an intervention in this domain will exclude a patient from receiving that agent.

## *8.3. Interventions*

#### 8.3.1. Monoclonal antibody Domain Interventions

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

- 1.2g casirivimab / 1.2g imdevimab - combined 2.4g (refered to as low dose)
- 4g casirivimab / 4g imdevimab - combined 8g (referred to as high dose)

#### 8.3.2. Low dose casirivimab / imdevimab (ronapreve)

Patients will receive 1.2g of casirivimab and 1.2g of imdevimab via intravenous infusion (combined dose 2.4g). The casirivimab and imdevimab will be injected into a 250ml polyvinyl chloride (PVC) or polyolefin (PO) infusion bag of 0.9% Saline or 5% Dextrose, and infused over 60 minutes. Casirivimab and imdevimab should not be infused concomitantly in the same intravenous line with other medication.

No dose adjustments are needed for patients with kidney or liver dysfunction or receiving renal replacement therapy.

#### 8.3.1. High dose casirivimab / imdevimab (ronapreve)

Patients will receive 4g of casirivimab and 4g of imdevimab, via intravenous infusion (combined dose 8g). The casirivimab and imdevimab will be injected into a 250 ml PVC or PO infusion bag of 0.9% saline or 5% Dextrose, and infused over 60 minutes. Casirivimab and imdevimab should not be infused concomitantly in the same intravenous line with other medication.
No dose adjustments are needed for patients with kidney or liver dysfunction or receiving renal replacement therapy.

#### 8.3.2. Duration of monoclonal antibody therapy

Both low and high doses of casirivimab and imdevimab will be given once only.

#### 8.3.3. Discontinuation of study intervention

The intervention is a single infusion and so there is no need to consider discontinuation. If the patient were thought to be having an infusion-associated reaction during administration, the infusion can be slowed, interrupted or discontinued, and this would not be considered a protocol deviation. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, infusion should be stopped immediately and appropriate medications and/or supportive care initiated.

### *8.4. Concomitant care*

Additional agents, other than those specified in the platform, that are intended to provide antibodies against SARS-CoV-2 should not be administered to patients after inclusion in this domain, during this index hospitalization.

All other 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 from in the REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol

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

- Weekly SARS-CoV-2 PCR testing through normal clinical testing routes in hospital, to enable viral genomic sequencing
- Serum levels of casirivimab and imdevimab measured at up to 4 time points over 28 days. 6mls of blood at each time point will be collected at the time of other blood sampling for clinical purposes.

# 9. TRIAL CONDUCT

## *9.1. Microbiology*

Microbiological testing will be performed as per local practice, including bacterial and viral testing to guide clinical care. Additional virology surveillance is likely to be implemented in normal clinical practice to monitor treatment with monoclonal antibody treatment. Results of these tests will be collected but no additional testing is specified in this protocol.

## *9.2. Domain-specific data collection*

No additional domain-specific data will be collected.

## *9.3. Criteria for discontinuation*

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

### *9.4. Blinding*

#### 9.4.1. Blinding

All medication 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:

- Non-inferiority of the low dose casirivimab and imdevimab compared with high dose

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

### *10.2. Sample size*

As drugs supplies are limited, this domain will commence with a planned fixed maximum sample size of 600 patients. A Platform Conclusion can be declared if a statistical trigger occurs prior to reaching the maximum sample size. The proportion of patients enrolled in the Moderate and Severe State will be monitored and if there is substantial imbalance between states, recruitment in one state may be closed prior to the 600 patients maximum sample size being achieved.

Prior to a Platform Conclusion based on one or both of external data or additional study drug supply becoming available the ITSC, in discussion of the DSMB, may choose to increase the maximum sample size including removing the maximum sample size cap.

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

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

stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State.

Borrowing is permitted between states.

RAR will not be applied in this domain with fixed randomization proportions at a ratio of 2:1 for low dose compared to high dose.

At the time of a Platform Conclusion, results will be reported for all randomized patients.

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.

### *10.4. Timing of revealing of randomization status*

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Deferred Reveal.

### *10.5. Interactions with interventions in other domains*

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

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

### *10.6. Nesting of interventions*

Nesting is not applicable in this domain.

### *10.7. Threshold probability for superiority, effectiveness, harm and inferiority*

The threshold probability for statistical triggers for harm, and inferiority specified in the relevant core protocol documents will not be used in this domain.

The threshold odds ratio delta for superiority in this domain is that specified as the default threshold in the relevant core protocol documents. A platform conclusion for superiority is possible in the

domain, but will not result in the stopping of randomization of either of the initial interventions in the domain.

## *10.8. Threshold odds ratio delta for equivalence and futility*

The Platform Conclusion of equivalence and futility will not be evaluated in this domain.
A Platform Conclusion of non-inferiority will be evaluated using an odds ratio delta of 0.35 and a probability threshold of 80%. This odds ratio delta corresponds, approximately, to the magnitude of the treatment effect reported in the RECOVERY trial for 28-day mortality, comparing high dose with control (no treatment) and is also regarded as appropriate in the presence of severe limitation of drug availability. If high dose casirivimab and imdevimab has a posterior probability of more than 80% of not increasing the odds ratio by at least 0.35, then low dose will be declared non-inferior.

Prior to a Platform Conclusion, and based on PK analyses, improved supply of study drug, or other external information the ITSC, in conjunction with the DSMB, may increase the threshold probability or decrease the odds ratio delta. If this occurs, it will be an operational decision communicated to the SAC, via an update to the Current State document, without the requirement to amend this DSA.

It is noted that there is a fixed maximum sample size and if no Platform Conclusion is declared prior to recruiting to the maximum fixed sample size, further recruitment will stop and the posterior probability for superiority, along with the odds ratio and credible intervals, will be reported to allow interpretation for clinical practice, clinical guidelines, and policy.

## *10.9. Informative priors*

This domain will launch with priors that are neutral for main effects.

## *10.10. 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:

- Shock strata
- Receiving invasive mechanical ventilation at baseline
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

# 11.ETHICAL CONSIDERATIONS

## *11.1. Data Safety and Monitoring Board*

The DSMB should be aware that the non-inferiority of low-dose treatment compared with high-dose is the only statistical trigger with respect to the primary endpoints in this domain at the outset.

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

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

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

For patients assigned to any intervention, occurrence of any of the following should be reported as an SAE

- Allergic reaction

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. Risks and benefits of participation*

There is little risk involved through participation in this domain. The low dose is now recommended as standard care in the UK for this population of patients.The high dose has been used in the RECOVERY trial and administered to nearly 5,000 patients without any safety concerns and with clinical benefit seen in seronegative patients.

The additional blood sample for PK analysis are minimal and will be collected when other clinical blood tests are being collected.

## *11.4. Domain-specific consent issues*

Both doses in this domain are “off-label” at the time of writing this document but the low dose is the recommended dose in clinical guidelines and the high dose has been shown to be safe and effective.

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

As all interventions that are available are regarded as being part of the acceptable spectrum of standard care and given the time imperative necessary to evaluate these interventions, entry to the study, for participants who are not competent to consent, is preferred to be via waiver-of-consent or some form of delayed consent.

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

# 12.GOVERNANCE ISSUES

## *12.1. Funding of domain*

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain has received specific funding in the UK from the National Institute for Health Research

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

All monoclonal antibody treatments will be provided by participating hospitals. They will be supplied to hospitals via normal clinical routes but may be donated to the health systems by the manufacturers.

## *12.3. Domain-specific declarations of interest*

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

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# 14. STATISITICAL APPENDIX – NON-INFERIORITY STOPPING RULE OPERATING CHARACTERISTICS

The operating characteristics of the domain-specific stopping rule for non-inferiority were determined through clinical trial simulation. A range of non-inferiority margins and posterior probability thresholds was considered, and the final thresholds were selected to optimize decision-making across several possible scenarios.

To evaluate the characteristics of the non-inferiority stopping rules, we simulated fixed trials with sample sizes from 200 up to 600 patients with 2:1 randomization between low dose and high dose casirivimab and imdevimab (C+I). We simulated primary OSFD outcomes for patients on low dose C+I based on the approximate distribution of OSFD outcomes observed in previous REMAP-CAP severe patients. We assumed hypothetical odds ratio treatment effects of 1, 1.1, 1.2, and 1.5 for high dose C+I relative to low dose C+I. An odds ratio of 1 for high dose versus low dose means that the distribution of OSFD outcomes is the same for the two doses. Odds ratios of 1.1, 1.2, and 1.5 represent minor, moderate, and large benefits on OSFD of high dose C+I relative to low dose.

For each scenario, we simulated 10,000 virtual trials and summarize the outcomes across all trials and potential stopping rules. We evaluated each stopping rule based on the probability of declaring non-inferiority of low dose C+I to high dose C+I and based on the minimum estimated odds ratio that would be sufficient evidence to demonstrate non-inferiority. The figures below summarize the operating characteristics for the final non-inferiority stopping rule.

The first figure below shows the probability of demonstrating non-inferiority versus the total sample size of patients randomized to low dose and high dose C+I. The color of each line represents the assumed odds ratio effect of high dose relative to low dose. With an odds ratio of 1 (no difference between high and low dose), the probability of demonstrating non-inferiority ranges from 60% with a sample size of 200 up to 87% with a sample size of 600. The sample size of 600 represents an upper bound on the probability of demonstrating non-inferiority if there is maximal borrowing of information across the severe and moderate states. The sample size of 200 represents a lower bound on the probability of demonstrating non-inferiority in each state if there is minimal borrowing of information. If the high dose has a minimal odds ratio benefit of 1.1 on OSFD relative to low dose, the probability of demonstrating non-inferiority ranges between the lower bound of 48% to an upper bound of 68%. If high dose is significantly better than low dose with an odds ratio of 1.5, then the probability of demonstrating non-inferiority is approximately 10% or lower based on the sample size and strength of borrowing.

The second figure summarizes the maximum estimated odds ratio that demonstrates non-inferiority of low dose to high dose. With a sample size of 200, the estimated odds ratio for high dose relative to low dose fall below 1.09 to demonstrate non-inferiority of the low dose. With a sample size of 600, the odds ratio must fall below 1.2 to demonstrate non-inferiority of the low dose.