Domain-Specific Appendix:

Statin Therapy

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

Statin Domain-Specific Appendix Version 1.2 dated 26th August 2020
**Summary**

In this domain of the REMAP-CAP trial, participants meeting the platform entry criteria will be randomized to receive one of two interventions:

- No simvastatin (no placebo)
- Simvastatin

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

- No simvastatin (no placebo)
- Simvastatin

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

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Pandemic infection suspected or proven (PISOP)</th>
<th>Pandemic infection neither suspected nor proven (PINSNP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core protocol documents</td>
<td>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>Moderate State</td>
<td>Severe State</td>
</tr>
<tr>
<td>Interventions available in this Domain + State</td>
<td>No Simvastatin Simvastatin</td>
<td>No Simvastatin Simvastatin</td>
</tr>
<tr>
<td>Interventions submitted for approval at this site</td>
<td>□ No simvastatin □ Simvastatin</td>
<td>□ No simvastatin □ Simvastatin</td>
</tr>
<tr>
<td>Interventions offered at this site in these locations</td>
<td>□ No simvastatin □ Simvastatin</td>
<td>□ No simvastatin □ Simvastatin</td>
</tr>
</tbody>
</table>
## REMAP-CAP: Statin Therapy Domain Summary

| Interventions          | No statin (no placebo)  
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin 80 mg daily for up to 28 days</td>
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</tr>
</tbody>
</table>

### Unit-of-analysis, Strata, and States

This domain is analyzed only in the pandemic statistical model. The pandemic statistical model includes 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. Unit-of-analysis may also be defined by SARS-CoV-2 infection strata. Borrowing is permitted between states and strata. If the SARS-CoV-2 infection strata is applied in analysis, Response Adaptive Randomization will be applied to patients all PISOP patients using probabilities derived from SARS-CoV-2 confirmed stratum.

### Evaluable treatment-by-treatment Interactions

No interactions will be evaluated with any other domain.

### Nesting

None

### Timing of Randomization with Immediate Reveal and Initiation

### Inclusions

Patients are eligible for this domain if:
- COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing

### Domain-Specific Exclusions

Patients will be excluded from this domain if they have any of the following:
- More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of organ failure support)
- Known severe liver disease
- Known hypersensitivity to simvastatin
- Creatinine more than 200 μmol/L (2.26 mg/dL) and not receiving renal replacement therapy
- Current treatment with a medicine that cannot be co-administered with simvastatin
- Current treatment with any statin or treating clinician intends to commence treatment with any statin
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

### Intervention-Specific Exclusions

Patients who are known or suspected to be pregnant or breastfeeding will be excluded from the simvastatin intervention.

### Outcome measures

Primary REMAP endpoint: refer to REMAP-CAP Core Protocol + PATC and REMAP-COVID Core Protocol

Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol + PATC and REMAP-COVID Core Protocol

Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrolment):
- Serious Adverse Events (SAE) as defined in relevant core protocol documents
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1. **ABBREVIATIONS**

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>CAP</td>
<td>Community Acquired Pneumonia</td>
</tr>
<tr>
<td>DSA</td>
<td>Domain-Specific Appendix</td>
</tr>
<tr>
<td>DSWG</td>
<td>Domain-Specific Working Group</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data Safety and Monitoring Board</td>
</tr>
<tr>
<td>HMG-CoA</td>
<td>3-hydroxy-3-methylglutaryl coenzyme A</td>
</tr>
<tr>
<td>HARP-2</td>
<td>Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction-2</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>ISIG</td>
<td>International Statistics Interest Group</td>
</tr>
<tr>
<td>ITSC</td>
<td>International Trial Steering Committee</td>
</tr>
<tr>
<td>LCA</td>
<td>Latent Class Analysis</td>
</tr>
<tr>
<td>PATC</td>
<td>Pandemic Appendix to the Core Protocol</td>
</tr>
<tr>
<td>PEG</td>
<td>Percutaneous EnteroGastric</td>
</tr>
<tr>
<td>PEJ</td>
<td>Percutaneous EnteroJejunal</td>
</tr>
<tr>
<td>PISOP</td>
<td>Pandemic Infection Suspected or Proven</td>
</tr>
<tr>
<td>RAR</td>
<td>Response Adaptive Randomization</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>REMAP</td>
<td>Randomized, Embedded, Multifactorial Adaptive Platform trial</td>
</tr>
<tr>
<td>REMAP-CAP</td>
<td>Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia</td>
</tr>
<tr>
<td>RSA</td>
<td>Region-Specific Appendix</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAILS</td>
<td>Statins for Acutely Injured Lungs from Sepsis trial</td>
</tr>
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2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a ‘modular’ protocol design. While, all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Section 1.2 Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study), a Statistical Analysis Appendix (details of the current statistical analysis plan and models) and Simulations Appendix (details of the current simulations of the REMAP), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Regions-Specific Appendices (RSA) (detailing regional management and governance).

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

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

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change overtime in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).
The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region’s RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the relevant Core Protocol (either REMAP-CAP Core Protocol + Pandemic Appendix or REMAP-COVID Core Protocol), DSAs, RSAs and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. STATIN DOMAIN-SPECIFIC APPENDIX VERSION

The version of the Statin Domain-Specific Appendix is in this document’s header and on the cover page.

3.1. Version history

Version 1.0: Approved by the Statin Domain-Specific Working Group (DSWG) on 7th July 2020

Version 1.1: Approved by the Statin DSWG on 23rd July 2020

Version 1.2: Approved by the Statin DSWG on 26th August 2021

4. STATIN DOMAIN GOVERNANCE

4.1. Domain members

Chair: Prof. Danny McAuley

Members: Prof. Derek Angus
          Prof. Yaseen Arabi
          Dr. Diptesh Aryal
          Dr. Abi Beane
          Prof. Carolyn Calfee
          Dr Rabindrarajan Ebenezer
          A/Prof. Ewan C Goligher

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4.2. Contact Details

Chair: Prof. Danny McAuley

Centre for Experimental Medicine
97 Lisburn Road
Belfast, BT9 7BL
Phone 00447958221745
Email d.f.mcauley@qub.ac.uk
5. STATIN DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

Chair
Danny McAuley

Date 26 August 2021

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP platform to test the effectiveness of simvastatin versus no simvastatin in patients with acute illness due to suspected or proven COVID-19.

6.2. Domain-specific background

6.2.1. Acute Respiratory Failure and ARDS

Acute respiratory failure is a common critical illness and reason for admission to ICUs (Bellani et al., 2016). In the most severe form, acute respiratory distress syndrome (ARDS), non-invasive or invasive ventilatory support is required. The etiology of ARDS is varied and can be classified as non-infectious/infectious or pulmonary/non-pulmonary. Infectious pulmonary causes of ARDS include community acquired pneumonia (CAP) including the recent COVID-19 pandemic where bilateral infiltrates are the most common radiological feature and is associated with acute respiratory failure (Yang et al., 2020, Huang et al., 2020, Shi et al., 2020).

Statins have been proposed as a treatment for ARDS, mediated by an anti-inflammatory mechanism of action. The role of statins in ARDS has not been established, with some studies suggesting a beneficial effect although this was not confirmed in a subsequent phase 3 multicenter trial (McAuley et al., 2014). In critically ill patients with sepsis an observational study has reported statin use was associated with a reduced 30 day and 90-day mortality (Lee et al., 2018). It is acknowledged that prior receipt of statins is different to administration of statins with therapeutic intent when disease has developed and that unadjusted confounding may be responsible for reported associations in observational studies. However, if effective, statin therapy could be a cheap, safe intervention for these patients.
6.2.2. Biological rationale for simvastatin

Statins inhibit the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase resulting in modification of a number of the underlying mechanisms implicated in the development of ARDS (Terblanche et al., 2006). In murine models of acute lung injury, administration of statins results in decreased inflammation and histologic evidence of lung damage (Jacobson et al., 2005). Statins have diverse anti-inflammatory properties and act on epithelial and endothelial function to reduce alveolar capillary permeability and reduce pulmonary edema (Terblanche et al., 2006). In addition, they modulate the inflammatory cascade; regulate inflammatory cell recruitment, activation and apoptosis; and reduce cytokine and protease activity (Craig et al., 2007). A similar reduction in pulmonary and systemic inflammatory responses is observed in a human model of ARDS induced by lipopolysaccharide inhalation (Shyamsundar et al., 2009).

6.2.3. Clinical trials of statins in ARDS and sepsis

The effect of statins in patients with ARDS was investigated in two large multicenter randomized controlled trials (RCTs). The Statins for Acutely Injured Lungs from Sepsis trial (SAILS), which compared rosuvastatin and placebo, reported no difference in 60-day in-hospital mortality or in ventilator free days to day 28 (National Heart et al., 2014). In the Hydroxymethylglutaryl-CoA Reductase Inhibition with Simvastatin in Acute Lung Injury to Reduce Pulmonary Dysfunction-2 (HARP-2) trial there was no significant difference in ventilator-free days up until day 28, non-pulmonary organ failure–free days or 28-day mortality (McAuley et al., 2014). In patients with sepsis, an RCT reported benefit in the sub-group of patients with prior statin user when compared to statin naive patients demonstrating lower plasma IL-6 levels and improved outcomes in patients randomized to continue rather than cease statin therapy (Kruger et al., 2013) and reduced progression of sepsis to severe sepsis (Patel et al., 2012).

6.2.4. Simvastatin for hyper-inflammatory ARDS phenotype

It has been proposed that a possible explanation for the absence of benefit from statins in some RCTs is divergent treatment effect depending on whether the patient has a hyper- or hypo-inflammatory phenotype (Prescott et al., 2016). In secondary data analyses of five large multi-center trials, using latent class analysis (LCA) two distinct phenotypes, hyper-inflammatory and hypoinflammatory, have been identified (Calfee et al., 2014). Patients with the hyperinflammatory phenotype demonstrate improved survival at both day 28 and day 90 in randomized to simvastatin 80 mg compared to placebo (Calfee et al., 2018). This is a post hoc analysis of a sub-group, but it is
hypothesized that there may be differential, including divergent, treatment effect depending on the inflammatory phenotype at baseline.

6.2.5. Baseline clinical variables used to identify ARDS phenotypes

Biomarkers (e.g. interleukin-8, interleukin-6) that are available only as research assays are key determinants of inflammatory phenotype in the LCA models. As such, values for serum levels of these cytokines are not available in routine clinical practice, which limits their capacity to be applied as a stratification variable, for randomization or analysis or both. An alternative to these research-only biomarkers has been developed using machine-learning models that apply readily-available clinical data and have been to accurately classify patients with respect to their inflammatory ARDS phenotypes (Sinha et al., 2019). The clinical-classifier models offer the opportunity to identify ARDS phenotypes in the studied cohort without measuring specialized biomarkers. A probability cut off of 0.5 using the clinical classifier model to assign inflammatory phenotype, had a sensitivity of 0.8 and specificity of 0.93. This will offer the opportunity to test the efficacy of simvastatin therapy within a strata defined by inflammatory phenotype.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of simvastatin for patients with acute illness due to suspected or proven pandemic infection.

We hypothesize that the probability of occurrence of the primary endpoint specified in the relevant core protocol documents will differ based on the allocation to simvastatin or no simvastatin. The following interventions will be available:

- No simvastatin (no placebo)
- Simvastatin

We hypothesize that the treatment effect of simvastatin is different depending on whether SARS-CoV-2 infection is confirmed to be present or absent.

We hypothesize that the treatment effect of simvastatin is different depending on inflammatory phenotype strata status.

We hypothesize that the treatment effect of simvastatin is different depending on 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 be adaptive, as described in core protocol documents.

8.1. Population

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

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in either the REMAP-CAP Core Protocol + Pandemic Appendix, or the REMAP-COVID Core Protocol. Patients otherwise eligible for REMAP-CAP may have conditions that exclude them from the Statin Domain.

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

8.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

• COVID-19 infection is suspected by the treating clinician or has been confirmed by microbiological testing (i.e. PISOP stratum)

8.2.2. Domain exclusion criteria

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

• More than 48 hours has elapsed since ICU admission (noting that this may be operationalized as more than 48 hours has elapsed since commencement of sustained organ failure support)
• Known severe liver disease
• Known hypersensitivity to simvastatin
• Creatinine more than 200 μmol/L (2.26 mg/dL) and not receiving renal replacement therapy
• Current treatment with a medicine that cannot be co-administered with simvastatin
• Current treatment with any statin or treating clinician intends to commence treatment with any statin
• The treating clinician believes that participation in the domain would not be in the best interests of the patient

Simvastatin co-administration is contraindicated with lopinavir and ritonavir. At REMAP-CAP sites that are not participating in any intervention that includes lopinavir/ritonavir in the COVID-19 antiviral domain, treatment with, or intention to commence lopinavir/ritonavir will be operationalized as an exclusion criteria to this domain. At sites that are participating in the COVID-19 anti-viral domain and include lopinavir/ritonavir as an intervention, the co-administration of lopinavir/ritonavir with simvastatin will be blocked. The statistical consequences of precluding co-administration is outlined in the statistics section.

8.2.3. Intervention exclusion criteria

Patients who are known or suspected to be pregnant or breastfeeding will be excluded from the simvastatin intervention.

8.3. Interventions

8.3.1. Simvastatin Domain 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 simvastatin (no placebo)
• Simvastatin

8.3.2. No simvastatin intervention

Patients randomized to the no intervention group will not receive simvastatin. After randomization, a statin can only be administered for an established clinical indication. Administration of any statin to treat confirmed or suspected COVID-19, up until study day 28, will be considered a protocol deviation.
8.3.3. Simvastatin intervention

8.3.3.1. Dosing

Simvastatin will be administered at a dose of 80 mg once-daily by the enteral route. If the patient has a nasogastric, orogastric, percutaneous enterogastric (PEG), or percutaneous enterojejunal (PEJ) tube, simvastatin can be crushed and mixed with 20ml sterile 0.9% saline and flushed down the tube. To ensure that the feeding tube is not blocked it should be flushed with a further 20 ml sterile 0.9% saline following administration of simvastatin.

The first dose of the study drug will be administered as soon as possible after assignment, ideally within four hours of randomization and subsequent doses will be given each morning starting on the following study day. If for any reason a dose is not administered at the intended time, it should be administered subsequently but not more than 12 hours after the intended time of administration.

There is no dose adjustment for renal failure or during renal replacement therapy but simvastatin must be ceased if there is renal failure that is caused or contributed to by rhabdomyolysis.

If a single dose of amiodarone (intravenous infusion of not more than one hour or any enteral dose) is administered no change is required for simvastatin dose. However, if a patient received more than a single dose of amiodarone, simvastatin dose should be reduced to 20mg daily.

8.3.3.2. Duration of therapy

For patients in the severe state, simvastatin should be ceased at time of first ICU discharge or day 28, whichever comes first. For patients in the moderate state simvastatin should be ceased at time of hospital discharge, first ICU discharge (if admitted to ICU) or day 28, whichever comes first. Continuation after discharge from ICU is not considered a protocol deviation. If the patient is readmitted to ICU prior to the end of study day 28, it is not required to recommence administration of simvastatin. Omission of two or more consecutive doses of simvastatin will be considered a protocol deviation.

8.3.3.3. Monitoring for rhabdomyolysis and abnormal liver function

Liver function tests, serum creatinine kinase, and renal function must be monitored at least once during the first 7 to 14 days after randomization and repeated between study day 21 and 28 if the patient is still receiving simvastatin.
8.3.4. Discontinuation of study drug

Simvastatin should be discontinued if there is development of a serious adverse event (SAE). Simvastatin can also be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

After enrollment, if a patient requires therapy with statin for a proven indication and has been randomized not to receive a statin, a statin can be commenced. If such a patient has been randomized to simvastatin, this should be continued. If an alternative statin is prescribed, simvastatin should be discontinued.

8.4. Simvastatin strategy in patients negative for COVID-19 infection

In patients with suspected COVID-19 infection who receive an allocation status to receive simvastatin but who subsequently test negative for COVID-19 infection after allocation may have treatment ceased unless the treating clinician believes that doing so is not clinically appropriate. This decision should take into account the known or suspected sensitivity for COVID-19 infection.

8.5. Concomitant care

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

8.6. Endpoints

8.6.1. Primary endpoint

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

8.6.2. Secondary endpoints

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

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

- SAE as defined in relevant core protocol documents and qualified in this DSA
9. TRIAL CONDUCT

9.1. Domain-specific data collection

9.1.1. Clinical data collection

Additional domain-specific baseline data will be collected as follows and where available. These variables, in combination with other variables collected at platform-level, are used for the categorization of the hyperinflammatory and hypoinflammatory phenotypes.

- Temperature
- Heart rate
- Systolic blood pressure
- Respiratory rate
- White cell count
- Bicarbonate
- Albumin
- Administration of simvastatin

9.2. Criteria for discontinuation

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

9.3. Blinding

9.3.1. Blinding

Simvastatin will be administered on an open label basis.

9.3.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The following Platform Conclusions are possible in this domain:
• Superiority of simvastatin compared to no simvastatin

• Futility of simvastatin compared to no simvastatin

10.2. Unit-of-analysis and strata

With respect to strata, the unit-of-analysis, for both analysis of treatment effect and the Response Adaptive Randomization (RAR), will be the PISOP stratum, as specified from PATC and corresponding to the eligibility criteria specified in the REMAP-COVID Core Protocol. Unit of analysis will also be applied according to illness severity state and, as determined by the ITSC and based on an understanding of the sensitivity and availability of testing for COVID-19 infection, the unit-of-analysis may be modified to allow separate analysis of the COVID-19 infection confirmed and not confirmed stratum. This will be an operational decision.

At the time of a Platform Conclusion, results will be reported for all randomized patients, patients in whom COVID-19 infection is confirmed by microbiological testing, microbiological tests do not detect or isolate COVID-19 infection, and testing is not performed.

An additional stratum may be applied to the unit-of-analysis which will determined by the inflammatory phenotype based on clinical variables collected at baseline. The default break-point that is used to categorize patients as either hyper- or hypo-inflammatory phenotype will be 0.5, but the exact value used will be specified in the Operating Characteristics document prior to the first adaptive analysis that includes patients randomized in this domain. The inflammatory phenotype strata will not be applied to the RAR.

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

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Immediate Reveal and Initiation (see relevant core protocol documents).
10.4. **Relationship between the statin domain and the COVID-19 antiviral domain**

The active intervention in this domain cannot be co-administered with any intervention in the COVID-19 antiviral domain that includes lopinavir/ritonavir. The RAR regimen codes that correspond to this combination will be eliminated so that co-administration is not possible. Several statistical consequences of this are acknowledged that occur because of the competitive relationship between the active intervention in this domain (i.e. simvastatin) and interventions in the COVID-19 antiviral domain that include lopinavir/ritonavir.

Firstly, if both simvastatin and lopinavir/ritonavir were superior to no simvastatin and no antiviral active against COVID-19, respectively, and the size of the treatment effect was similar, both drugs are retained within the platform but it is likely that at a longer duration will be required for superiority to be demonstrated, compared to a study design that included only one of the agents. Secondly, if the treatment effect of one of the interventions is larger than the other, the less effective agent will be eliminated from the platform. This could occur even if the less effective agent was more effective than standard of care. Thirdly, if both drugs are ineffective, there will be no impact on the statistical model.

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

An *a priori* interaction with the Antibiotic Domain of REMAP-CAP is not able to be evaluated as analysis occurs in different statistical models.

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

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

An *a priori* interaction with the COVID-19 Antiviral Therapy 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 Therapeutic Anticoagulation Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.
An *a priori* interaction with the Vitamin C Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

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

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

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

**10.6. Nesting of interventions**

Nesting is not applicable to this domain.

**10.7. Threshold odds ratio delta for equivalence**

The threshold odds ratio for equivalence in this domain is that specified in relevant core Protocol documents.

**10.8. Post-trial Sub-groups**

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

- Baseline C-Reactive Protein
- Baseline ferritin
- Ventilatory status at baseline
- Inflammatory phenotype

Inflammatory phenotype is specified as a domain-specific strata for the analysis of this domain. However, as the strata was not applied in the primary efficacy model this variable will be evaluated as a post-trial sub-group. This sub-group will be applied if the frequency distribution of the inflammatory phenotypes allows.

- All remaining potentially evaluable treatment-by-treatment interactions with other domains and treatment-by-strata interactions
11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority, efficacy, inferiority, futility, or equivalence of different interventions with respect to the primary endpoints are possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints.

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

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

- Elevated Creatine Kinase more than 10 times the upper limit of normal
- Alanine Transaminase or Aspartate Transaminase or both more than 8 times the upper limit of normal

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

11.3. Domain-specific consent issues

As noted in the Background, and endorsed by the World Health Organization, 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 of confirming agreement to participate in this (and other) domains of the platform.

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

12. GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the core protocol documents. This domain has not received any additional domain-specific funding may be obtained during the life-time of the domain.

12.2. Funding of domain interventions and outcome measures

Simvastatin will be provided by the participating hospitals on the basis that it is a generic drug that is unlikely to be of significant cost burden.

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.
13. REFERENCES


blind placebo-controlled trial of 40 mg/day of atorvastatin in reducing the severity of sepsis in ward patients (ASEPSIS Trial). *Crit Care*, 16, R231.


