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

# PANDEMIC APPENDIX TO THE CORE PROTOCOL

REMAP-CAP Pandemic Appendix to the Core Protocol Version 1.1 dated 12th February, 2020

## Summary

**Background**: REMAP-CAP is an adaptive platform trial that evaluates multiple aspects of care of patients who are admitted to an Intensive Care Unit with severe Community Acquired Pneumonia. It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as severe Community Acquired Pneumonia with concomitant admission to an Intensive Care Unit. Previous pandemics and more localized outbreaks of respiratory emerging infections have resulted in severe Community Acquired Pneumonia and admission to an Intensive Care Unit[1-3]. A pandemic of respiratory infection is much more likely to be caused by a virus than a bacterium. Differences in trial design may be required for influenza, viruses which are known to result in periodic but unpredictable pandemics, in comparison with other viruses, such as Coronaviruses that may also have pandemic potential.

Previous pandemics and outbreaks of emerging infectious diseases have outlined the urgent need for evidence, preferably from Randomized Clinical Trials, to guide best treatment. However, there are substantial challenges associated with being able to organize such trials when the time of onset of a pandemic and its exact nature are unpredictable[4-6]. As an adaptive platform trial that enrolls patients during the interpandemic period, REMAP-CAP is ideally positioned to adapt, in the event of a respiratory pandemic, to evaluate existing potential as well as novel treatment approaches.

The precise nature of a respiratory pandemic cannot be known in advance. The Pandemic Appendix to the Core Protocol lists potential adaptations to trial design and management that are generic, in that they will occur irrespective of the nature of the pandemic, as well as adaptations that are possible, depending on the nature of the pandemic, and the process for determining which adaptations will be applied.

The objective of the Pandemic Appendix to the Core Protocol is to describe the adaptations to the Core Protocol that would apply during a pandemic, including how analyses of domains already operative during the interpandemic period as well as domains that are pandemic-specific, will be integrated during a pandemic. This includes scientific, as well as governance and logistic aspects.

**Aim**: The primary objective of the REMAP during a pandemic is to identify the effect of a range of interventions to improve outcome for patients with severe Community Acquired Pneumonia, as defined by the pandemic primary end-point.

**Methods:** The methods that will be utilized during a pandemic are those in the Core Protocol but with potential for changes to the primary end-point, frequency and process for adaptive analyses,

and determination of which domains will be analyzed using a statistical model that includes data from patients with proven or suspected pandemic infection. During a pandemic, patients who are neither suspected nor proven to have pandemic infection and for certain pre-existing domains, will continue to be analyzed using the statistical model that is outlined in the Core Protocol that was operating during the pre-pandemic period. Depending on the characteristics of a pandemic, one or more interpandemic domains may be analyzed within the pandemic statistical model and one or more pandemic-specific domains may be commenced for patients with suspected or proven pandemic infection.

**Lay description**

REMAP-CAP is a global trial examining the best treatments for community-acquired pneumonia. In the setting of a pandemic that causes pneumonia, some key aspects of the study will be changed to integrate new interventions into the trial, evaluate existing interventions within the trial specifically in patients with pandemic infection, alter trial governance, and provide time-critical data for public health. This will allow the platform to identify which treatments work best for patients during a pandemic.

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# 1. ABBREVIATIONS

| | |
|---|---|
| CAP | Community-Acquired Pneumonia |
| CRF | Case Report Form |
| DSA | Domain-Specific Appendix |
| DSMB | Data Safety and Monitoring Board |
| ICU | Intensive Care Unit |
| ISIG | International Statistics Interest Group |
| ITSC | International Trial Steering Committee |
| MERS-CoV | Middle-Eastern Respiratory Syndrome Coronavirus |
| NAI | Neuraminidase inhibitors |
| PAtC | Pandemic Appendix to the Core Protocol |
| PINSNP | Pandemic infection is neither suspected nor proven |
| PISOP | Pandemic infection is either suspected or proven |
| PWG | Pandemic Working Group |
| RAR | Response Adaptive Randomization |
| REMAP | Randomized, Embedded, Multifactorial, Adaptive Platform trial |
| REMAP-CAP | Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia |
| RCC | Regional Coordinating Center |
| RCT | Randomized Controlled Trial |
| RSA | Region Specific Appendix |
| SAC | Statistical Analysis Committee |
| 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), multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), a Registry Appendix, this Pandemic Appendix to the Core Protocol, 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, because the analysis model will change over time in accordance with the domain and intervention trial adaptations, but this information is contained in the Statistical Analysis Appendix. 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 an 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.

# 3. PANDEMIC APPENDIX TO THE CORE PROTOCOL VERSION

The version of the Pandemic Appendix to the Core Protocol is in this document's header and on the cover page.

## 3.1. Version History

Version 1:        Approved by the Pandemic Working Group on 31st January, 2020

Version 1.1:      Approved by the Pandemic Working Group on 12th February, 2020

# 4. PANDEMIC APPENDIX TO THE CORE PROTOCOL GOVERNANCE

The study administration structure is outlined in the Core Protocol. As outlined in the Core Protocol, a Pandemic Working Group (PWG) is established and works in conjunction with the International Trial Steering Committee (ITSC), to take responsibility for the Pandemic Appendix to the Core Protocol (PAtC) and to advise on operational aspects following emergence of a pandemic.

## 4.1. Pandemic Working Group

The responsibility of the PWG is to maintain and update this PAtC and to advise the ITSC regarding application of the PAtC during a pandemic. The PWG will liaise with individuals and organizations that are external to REMAP-CAP as required. Membership of the PWG is flexible. The core membership is listed but additional members can be added at any time and as required.

**Chair:**              The Chair of the ITSC will Chair the Pandemic Working Group

**Members:**            Prof. Derek Angus

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                        Prof. Richard Beasley

                        A/Prof. Scott Berry

                        Prof. Frank Brunkhorst

                        Dr. Lennie Derde

                        Dr. Robert Fowler

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Prof. Steve Webb

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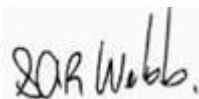
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# 5.  PANDEMIC WORKING GROUP AUTHORISATION

The Pandemic Working Group have read the appendix and authorize it as the official Pandemic Appendix to the Core Protocol for the study entitled REMAP-CAP. Signed on behalf of the committee,

**Chair**                                                                      Date
                                                                                          12th February, 2020
Steve Webb

# 6. BACKGROUND AND RATIONALE

## 6.1. Introduction

It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as severe Community Acquired Pneumonia (CAP) with concomitant admission to an Intensive Care Unit (ICU). Previous pandemics and more localized outbreaks of respiratory emerging infections have resulted in severe CAP and ICU admission[1-3]. A pandemic of respiratory infection is much more likely to be caused by a virus than a bacterium and, among viruses a distinction should be drawn between influenza, which is known to result in periodic but unpredictable pandemics, and other viruses, such as Coronaviruses, that may have pandemic potential, as the features of trial design may be different.

Previous pandemics and outbreaks of emerging infectious diseases have outlined the urgent need for evidence, preferably from Randomized Controlled Trials (RCTs), to guide best treatment. However, there are substantial challenges associated with being able to organize such trials when the time of onset of a pandemic and its exact nature are unpredictable[4-6]. As an adaptive platform trial that enrolls patients during the interpandemic period, REMAP-CAP is ideally positioned to adapt, in the event of a respiratory pandemic, to evaluate existing treatments as well as novel approaches.

One of the challenges associated with planning clinical trials during a pandemic is that the precise nature of the infecting organism, clinical consequences, and suitable interventions (particularly those that are pathogen-specific) cannot be reliably known in advance. Nevertheless, a range of scenarios can be anticipated and used to provide direction and guidance regarding the most appropriate research response.

The most likely organism responsible for a respiratory pandemic is a novel influenza virus that has undergone antigenic shift[7]; the most recent influenza pandemic occurred during 2009-2010. In recent years, there have been outbreaks of severe Community Acquired Pneumonia due to novel Coronaviruses which resulted in the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003

and the Middle-Eastern Respiratory Syndrome Coronavirus (MERS-CoV) outbreak that commenced in 2012. The pandemic potential of a novel Coronavirus that causes pneumonia is not known. The pre-specified adaptations to REMAP-CAP will need to be different for influenza in comparison to a non-influenza pandemic pathogen.

## 6.2. Pandemic research preparedness

### 6.2.1. Introduction

The conceptual approach to pandemic preparedness has been influenced substantially by the occurrence of the 2009 Influenza A H1N1(2009)pdm pandemic, outbreaks of SARS and MERS-CoV, the Zika pandemic, and Ebola virus disease outbreaks in West Africa[8]. A broad conclusion from these outbreaks is that it is likely that high quality research can change the incidence and consequences of the epidemic but that such research is extremely difficult because planning of research only commences after the discovery of the epidemic. As a consequence, researchers and organizations interested in developing improved processes for research have identified three key elements to facilitate time-critical research about an epidemic. These elements are that the research must be pre-planned, pre-approved, and practiced[9,10]. REMAP-CAP and, in particular, the PAtC, is an attempt to establish these pre-requisites and to guide treatment for patients who may be critically ill with pneumonia as a consequence of infection with a pandemic organism.

The World Health Organization (WHO) has recommended establishing and strengthening outbreak-ready, multi-center clinical research networks in geographically diverse regions to facilitate research during pandemics.[11] It has also recommended testing of protocols during interpandemic periods and stressed the value of such clinical research consortia in collecting and distributing information during a future pandemic.

### 6.2.2. Pre-planned

Pre-planned means that the trial protocol is written and that the trial processes related to project management, screening, recruitment, delivery of interventions, data collection, data management, analysis, and reporting are all in place. The PAtC, in conjunction with the existing REMAP-CAP protocol documents and trial processes, will mean that all aspects that can be pre-planned have been.

### 6.2.3. Pre-approved

The PAtC is a key component of the of the pre-approval strategy. The availability of this document allows ethics review boards, hospital research governance staff, existing and potential sites to

understand and approve the study processes that would be implemented during a pandemic. Where different options need to exist, depending on the nature of the pandemic, these are pre-specified, as much as possible. Any unanticipated substantive deviation from this Appendix would be subject to an amendment, hopefully expedited, in the event of a pandemic. The PAtC, like the Core Protocol, does not specify any interventions that are evaluated within the REMAP. It is highly likely that one or more research questions (in domains already approved during the interpandemic period) will be relevant specifically in patients with CAP caused by the pandemic infection. The PAtC allows these questions to continue to be answered specifically in patients with pandemic infection, where appropriate, using Bayesian prior probabilities derived from patients already enrolled during the interpandemic period. It is proposed to develop 'sleeping domains', which could be activated if appropriate during a pandemic, as well as retain the option of developing one or more completely new domains following the emergence of pandemic, which would require separate ethical approval and contracts with participating sites.

This strategy, as part of the study design, offers an ethically, clinically and legally acceptable mechanism for research in the context of a pandemic that can be initiated rapidly.

There are two further aspects relevant to ethical approval of the PAtC. The first is that existing or pandemic-specific domains of REMAP-CAP may include an intervention that specifies no treatment within that domain (noting that the Core Protocol specifies that all additional standard care is provided with treatment decisions being made by the treating clinician). This is clinically and ethically appropriate as the response of critically ill patients to a range of different treatments has proven to be unpredictable. There are many examples of treatments that have resulted in harm[12] and situations in which surrogate outcome measures were not reliable indicators of improvement in patient-centered outcomes. As such, there should not be any presumption that it is better for patients to receive active interventions.

The second is the capacity to apply Response Adaptive Randomization (RAR) within the REMAP. As outlined in the Core Protocol, RAR results in an increasing proportion of patients being allocated to any intervention within a domain that has a higher probability of being superior with that proportion increasing as statistical confidence accrues. Participants within REMAP-CAP during a pandemic may be able to benefit from information about the relative effectiveness of interventions that is not in the public domain and not available to patients who are not participants in REMAP-CAP. As outlined in the Core Protocol, any intervention confirmed to be superior within the REMAP is then implemented by application of a RAR proportion that is equal to 100%. RAR will be implemented for

pandemic patients as soon as sufficient data have accrued and operational implementation is feasible.

### 6.2.4. Practiced

REMAP-CAP will be recruiting during the interpandemic period in multiple countries in both Southern and Northern Hemispheres with the support of several Regional Coordinating Centers. This research activity, during the interpandemic period, ensures that sites, site training, project management, data management, analysis processes, and trial governance are functional and practiced. Furthermore, the eligibility process and delivery of trial interventions are optimized for embedding which allows study processes to occur within minimal disruption to the delivery of clinical care, which may well be under substantial strain during a pandemic. There is already extensive experience with the Case Report Form (CRF) that is used and will continue to be used during a pandemic.

### 6.2.5. Implications of REMAP design during a pandemic

#### 6.2.5.1. Time-critical generation of evidence

A pandemic will likely result in a large number of affected persons with cases occurring over a short period of time, perhaps as short as a few months. Conventional clinical trials that utilize frequentist statistical techniques require a fixed sample size with limited capacity to analyze the results of the trial until recruitment is completed. The setting of the sample size requires an estimate of the size of the treatment effect and it is known that the assumptions that are made in setting the size of the treatment effect are often incorrect[13,14]. A frequentist trial that over-estimates the size of the treatment effect may conclude without reaching a valid conclusion, whereas one that under-estimates the size of the treatment effect is delayed in providing time-critical information that the treatment is even more effective than estimated.

REMAP-CAP utilizes Bayesian statistical methods which allow frequent adaptive analyses to occur. This will ensure that time-critical information about the effectiveness of treatment interventions is not delayed unnecessarily. The REMAP design is particularly suited to pandemics because it requires no pre-trial assumptions about the size of the treatment effect and will allow dissemination of evidence as soon as possible. Furthermore, as the trial progresses during a pandemic the Data Safety Monitoring Board (DSMB) has access to information from adaptive analyses that may not achieve thresholds to allow reporting as a Platform Conclusion but may be relevant to public health which, under appropriate circumstances, can be shared with public health authorities without threatening the scientific validity of the ongoing trial.

### 6.2.5.2.    Multifactorial design and evaluation of interactions

If there are multiple interventions, each of which may have independent effects on outcome, the multi-factorial nature of a REMAP allows these to be evaluated simultaneously, rather than in series or in separate parallel trials (see *Figure 1*). This design feature contributes to efficiency and is also anticipated to result in more clinical evidence being generated more rapidly during a time-critical pandemic.
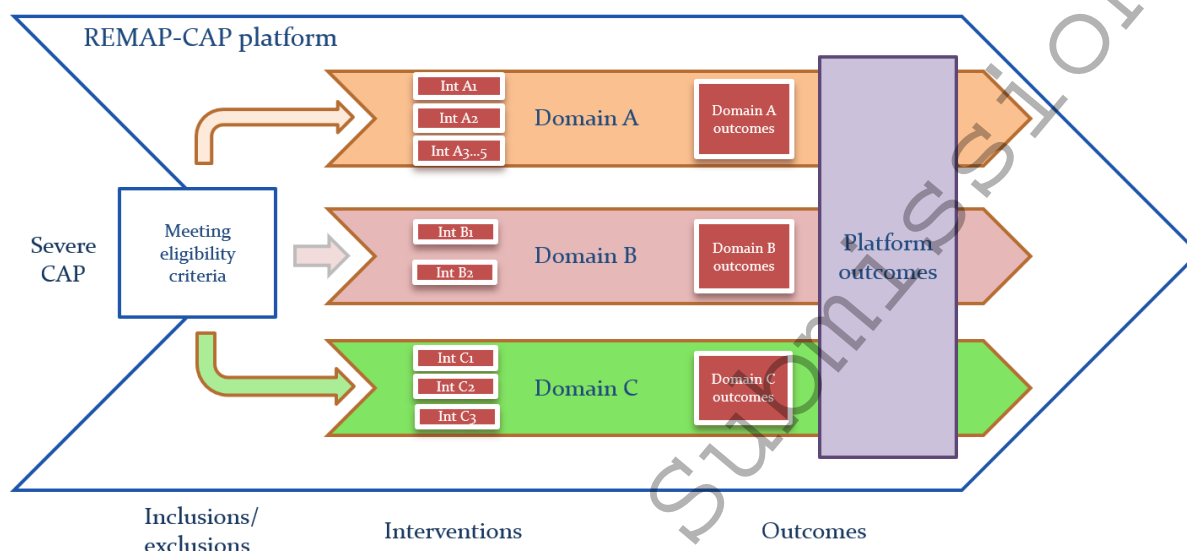


*Figure 1. The multifactorial structure of REMAP-CAP*

Furthermore, where pre-specified, the statistical model utilized in REMAP-CAP will allow estimation of treatment effect of interventions that may be contingent on other treatment assignments within the pandemic component of the REMAP. For example, it is plausible that the effectiveness of an intervention for immune modulation is dependent on co-delivery of an agent that is effective at inhibiting growth or replication of the pathogen. Conventional trials, in which only a single domain of treatment is evaluated, are not capable of detecting this type of treatment-by-treatment interaction, and thereby unable to identify the best overall treatment strategy for these patients.

## 6.2.6.   Setting of research priorities

In 2017, the WHO outlined the research priorities for a pandemic that was caused by a novel strain of influenza. These priorities were:

- Research on the effectiveness of empirical treatment with oseltamivir and other neuraminidase inhibitors (NAI) in critically ill patients, including placebo-controlled trials during seasonal as well as pandemic influenza.

- Investigating alternative strategies to NAI monotherapy to increase antiviral potency and improve clinical outcomes.

- Research on immune-modulatory strategies in severe influenza, including corticosteroids and macrolides.

- A need for high quality data on the effectiveness of most aspects of supportive care related to influenza.

- A need to assess the roles of virologic factors (e.g. replication sites, duration and viral load levels) in larger numbers of patients (including critically ill patients) in causing severe disease and associated complications, linking them to clinical outcomes.

REMAP-CAP is not able to meet all of these requirements but is well suited to evaluate the effectiveness of antiviral therapies active against influenza, immune modulatory strategies and different aspects of supportive care[15]. Identical or similar research questions would exist for any pandemic caused by an organism that was not influenza and REMAP-CAP has also similar capabilities in this scenario.

### 6.3.      WHO endorsement

REMAP-CAP has been designated by the WHO as a Pandemic Special Study. Under this designation, it has been tasked with helping answer crucial questions during a declared pandemic, as listed above. This designation ensures that knowledge translation of clinical trial results can occur directly with policymakers and public health officials for rapid implementation around the globe. It ensures that results generated from REMAP-CAP during a declared pandemic can be translated in an efficient and transparent manner to benefit affected patients.

## 7.  ADAPTATION OF REMAP-CAP DURING A PANDEMIC

This PAtC supplements the Core Protocol during a pandemic including deactivation at the conclusion of a pandemic. Decisions regarding the operationalization of the Pandemic Appendix to the Core Protocol are made by the ITSC with advice from the PWG (see Section 8.1). The Appendix sets out all potential adaptations of the Core Protocol and unless otherwise specified, all other aspects of the Core Protocol remain active. Activation of the PAtC will be advised to the DSMB with specification of the selected operational characteristics.

## 7.1.        Study setting: definition of an ICU

During the interpandemic period, the REMAP recruits only participants who are admitted to an ICU. During a pandemic, there may be insufficient ICU beds available to care for all critically ill patients resulting in provision of advanced organ support occurring in locations other than an ICU.

For sites at which the pandemic stratum (see below) has been activated, an area within the hospital that is able to deliver one or more of the qualifying organ failure supports specified in the Core Protocol (non-invasive ventilation, invasive ventilation, and vasopressor therapy) will meet the definition of an Intensive Care Unit. It is preferred in such circumstances that the patient is under the care of a specialist who is trained in the provision of critical care, but this is not an essential requirement.

## 7.2.        Eligibility criteria

Platform-level eligibility criteria may be modified if necessary to accommodate a published case definition, to align with criteria specified in guidelines, such as the ATS/IDSA guidelines on CAP[16], or to accommodate necessary modifications to the online eligibility system used for enrolment. In previous epidemics of community-based infection, nosocomial acquisition has been well described. Relaxation of the requirement for community acquisition or organ failure criteria or both may be appropriate. All changes to eligibility criteria would apply only to patients in the pandemic stratum (see section 7.3).

## 7.3.        Pandemic stratum

### 7.3.1.  Introduction

As outlined in the Core Protocol, a pre-specified stratum of the REMAP is the presence or absence of suspected or proven pandemic infection. This is maintained as a 'passive stratum' during the interpandemic period that can become active during a pandemic. It consists of two exclusive strata categories: pandemic infection is neither suspected nor proven (PINSNP) and pandemic infection is either suspected or proven (PISOP) at baseline. At times when the PAtC is not activated, i.e. during the interpandemic period, all participants are categorized as PINSNP.

### 7.3.2.  Activation and deactivation of the PAtC and PISOP stratum

In response to a pandemic (see section 8.1), the PISOP stratum is activated using a two-step process. First there is a decision of the ITSC to open the PISOP stratum for the platform. The second step is site-by-site activation of the PISOP stratum, requiring agreement of both the site and the Regional

Coordinating Centre (RCC). This allows variation in activity of the pandemic infection to be accommodated with sites only open for PISOP recruitment when there is active pandemic infection locally. Switching-on of the stratum can occur at any time and expected to always be available with less than 24 hours lead time. The capacity to enroll patients into the PISOP stratum can be switched-off on a site-by-site basis, but the ITSC can switch off the PISOP stratum for all sites if it is believed that a pandemic is no longer ongoing. The REMAP applies a new and separate statistical model for participants in the PISOP stratum which can utilize, where appropriate, informative priors derived from pre-pandemic PINSNP participants.

It should be noted that for sites in which the pandemic stratum is open, that the REMAP allows for continued recruitment of patients into the REMAP who are in the PINSNP stratum. For example, during an influenza pandemic, PINSNP would include patients with infection that has been proven to be a non-pandemic strain of influenza. During a pandemic, patients who are in the PINSNP stratum continue to be analyzed using the interpandemic statistical model (see below). As such, there are two categories of PINSNP participants- those included during the interpandemic phase and those included during a pandemic. Both categories of patients contribute to the interpandemic model for all active domains.

The PAtC is activated and deactivated for a site at the same time as the PISOP stratum is opened and closed. If a pandemic commences prior to ethical and governance approval of the PAtC, the PISOP stratum can be activated using approvals for the Core Protocol, and the PAtC would be activated as soon as ethical approval is obtained.

## 7.4.    *The pandemic statistical model*

### 7.4.1.  Introduction

The model that is active during the pandemic and includes only PISOP patients (for some or all domains) is referred to as the ***pandemic model***. The model that is active before (and after) the pandemic, which includes PINSNP patients during the pandemic and may include some PISOP patients for some domains, is referred to as the ***interpandemic model*** (see *Figure 2*).
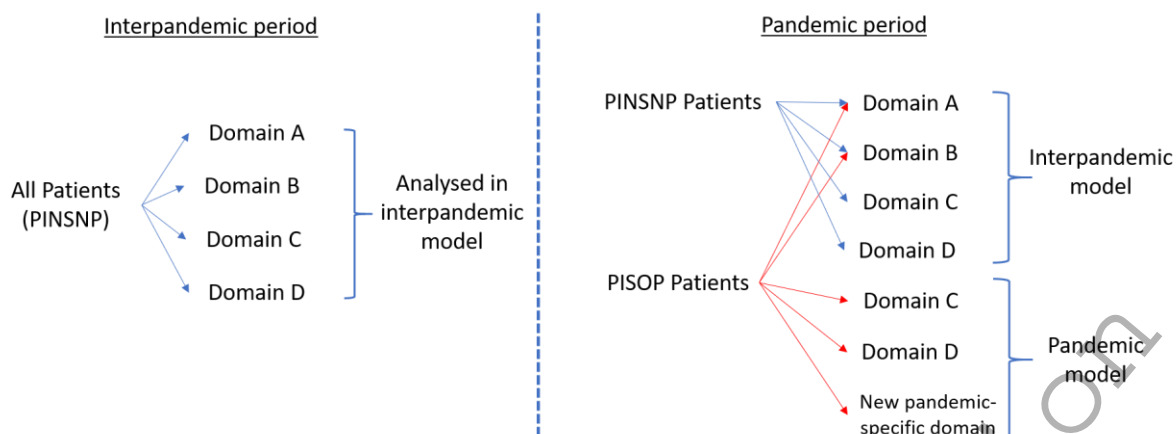
*Figure 2. Diagram of the interpandemic and pandemic models*

The pandemic model is only used for PISOP participants and only for those domains selected by the ITSC. A PISOP patient can contribute to both the pandemic and interpandemic model in different domains but each patient's contribution to a model is mutually exclusive with respect to each domain. The ITSC will select the domains to be included in the pandemic model where a differential treatment effect is postulated in the presence of pandemic infection or the need exists to learn about the outcome quickly, or both.

 A consequence of the application of two separate statistical models is that treatment-by-treatment interactions can only be evaluated for those domains that are in the same model. The principal advantages of the use of two models are:

- that this is necessary where the pandemic model requires a different primary end-point
- the platform is able to continue recruitment of patients with CAP who are neither suspected nor proven to have pandemic infection
- where appropriate informative priors can be included at commencement of the pandemic model
- where appropriate thresholds for a Statistical Trigger can be modified
- only those domains that are relevant to the pandemic are included within the pandemic model.

During the interpandemic period, it is intended that there may be some domains, for example the Ventilation Domain, that will utilize a separate domain-specific statistical model. It should be noted that during the interpandemic period, such a domain is not part of the interpandemic statistical model. During a pandemic any such domain would continue to be evaluated with its own domain-specific statistical model. During a pandemic, the operating characteristics of the domain-specific

statistical model may be modified in the same way that the pandemic model is modified from the interpandemic model. For example, PISOP patients may be analysed within a pandemic version of the domain specific statistical model utilising a modified primary end-point, with application of informative priors derived from the interpandemic time period.

### 7.4.2.  Pre-specification of trial parameter options

There are many clinical features of a respiratory pandemic that cannot be predicted in advance. For several parameters related to trial design and statistical analysis, this Appendix pre-specifies a range of options from which the actual modifications will be chosen at the commencement of a pandemic. The appendix provides guidance regarding the principles that would guide selection from within the available options and often provides the planned default option. The provision of flexibility regarding limited aspects of trial design provides the capacity to tailor aspects of the trial to the characteristics of the pandemic. For these decisions, the ITSC has decision-making responsibility, with advice from the PWG. These decisions would be regarded as operational and, unless otherwise specified (5.3.4), will be made prior to the conduct of the first adaptive analysis using the pandemic model and would be made only from within the range of options pre-specified in this Appendix. It is not intended that the selected parameters would be modified in any way during the pandemic unless advised to do so by the DSMB. The selected trial parameters would be placed in the public domain, on the study website, and provided as an update to participating sites and relevant ethical review bodies prior to the first adaptive analysis of the PISOP stratum.

### 7.4.3.  Application of other strata specified in the Core Protocol in the pandemic model

The shock strata may be applied to the PISOP stratum. The default position is that the shock strata will not be applied to the PISOP stratum.

If the pandemic is caused by a novel strain of influenza the pre-existing influenza strata is not applied in the pandemic model. For PINSNIP patients, the "influenza present" stratum would continue to apply and would be used to differentiate patients infected with a non-pandemic strain of influenza from patients in the "influenza not present" stratum. Membership of PISOP and influenza present stratum are mutually exclusive. It is anticipated that the influenza present stratum would apply only to patients with infection due to a proven non-pandemic strain of influenza at baseline. Patients in whom influenza was suspected, but the results of strain-specific diagnostic tests were not available at the time of assessment of eligibility, will be allocated to the PISOP stratum at sites where the stratum is active.

### 7.4.4.  Strata within the PISOP stratum

A strata applied within the PISOP stratum is the confirmation status of pandemic infection, defined in two categories, present or absent, based on the results of microbiological tests for the pandemic organism. Any patient with clinically suspected pandemic infection who is not tested or the result is not yet known will be deemed positive.

The availability and interpretation of microbiological tests are likely to change during the pandemic and an operational document will be used to specify how different tests are interpreted. It is noted that pandemic infection confirmed status is defined by the final results of testing for the pandemic organism which may include analysis of samples collected after enrollment where it is reasonable to presume that the sample reflected pandemic infection status at time of enrollment.

The sensitivity of microbiological testing for the pandemic organism may not be known at the beginning or even during the pandemic[17]. It is anticipated that initial analysis of the pandemic model will occur without application of this pandemic confirmation status strata but this would be applied when there was sufficient confidence about the operating characteristics of diagnostic tests in patients who are critically ill. If the pandemic confirmation status is applied, the probabilities derived from patients who have confirmed pandemic infection will be used to determine the RAR proportions for patients receiving treatment assignments in the pandemic specific domains within the PISOP stratum. Borrowing is permitted between the pandemic infection confirmed stratum and the pandemic infection not present stratum, using the methods outlined in the Core Protocol (with gamma = 0.15).

If eligibility criteria were modified to allow inclusion of a wider spectrum of illness severity, an additional strata may be applied within the PISOP stratum to distinguish current versus extended severity of illness.

### 7.4.5.  Domains incorporated in the pandemic model and use of informative priors derived from the interpandemic model

The domains that will be included within the pandemic model will be determined at the onset of a pandemic by the ITSC with advice from the PWG. Where appropriate and prior to the first adaptive analysis that is undertaken after activation of the PAtC, informative priors, derived from the interpandemic model (comprising patients enrolled in the REMAP prior to the pandemic), may be applied. If informative priors are applied, this is done by the Statistical Analysis Committee (SAC) who review the frequent adaptive analyses (and communicate these results to the DSMB on a regular basis). This will occur without knowledge of the values of the priors by the ITSC or any other

investigator. The amount of influence that priors apply and how quickly priors are applied in combination with accruing new data will be specified by the ITSC. Coding that specifies the weighting of priors will be done by statisticians who are separate to the SAC and blind to results from adaptive analyses. With regard to selection of domains and the use of informative priors, the following principles will be applied.

### 7.4.5.1.    Non-influenza pandemic organism

If the pandemic organism is not influenza, the following domains are intended to be included within the pandemic model:

- Corticosteroid Domain, without application of informative priors.
- Macrolide Duration Domain, without application of informative priors.
- New domains, as appropriate for the pandemic organism, without application of informative priors.

The Antiviral Domain (which includes only antiviral agents active against influenza) would not be applied in the pandemic model. It is noted that a patient at baseline could have suspected influenza and suspected pandemic infection which could lead to enrolment in the influenza domain (evaluated in the interpandemic model) and enrollment in other domains (evaluated in the pandemic model). It is not anticipated that the Antibiotic Domain is evaluated in the pandemic model, though this may be revised if the pandemic was caused by a bacterial pathogen. In this situation only those antibiotics that are known to be active against the pandemic organism would be available within the Antibiotic Domain for patients in the PISOP stratum.

### 7.4.5.2.    Influenza pandemic

If the pandemic organism is influenza, the following domains are intended to be included within the pandemic model:

- Corticosteroid Domain, using informative priors derived from the influenza present stratum.
- Antiviral domain, using informative priors derived from the influenza positive stratum but with exclusion of any antiviral interventions that are clinically inappropriate because of the resistance profile of the pandemic strain of influenza. If there were no antiviral agents to which the pandemic strain of influenza was susceptible the Antiviral domain would not be applied in the PISOP stratum. During the pandemic if the pandemic strain of influenza acquired resistance to antiviral

agents in the Antiviral Domain, these agents would be withdrawn from the domain at affected sites.

- Macrolide Duration Domain using informative priors derived from the unit-of-analysis of the Macrolide Duration Domain in the interpandemic model.
- New domains, as appropriate, without application of informative priors.

A number of other domains, related to organ failure support may be operative at the time of a pandemic. Domains such as oxygen saturation and hemodynamic targets would be expected to remain active during a pandemic. The default plan is that during a pandemic, patients in the PISOP and PINSNIP stratum will be eligible to receive an assignment in these domains and will be analyzed in the interpandemic model which will continue to be analyzed for statistical triggers and platform conclusions. Patients with pandemic infection will have their treatment assignments in such domains weighted according to RAR as specified by the interpandemic model which will continue to be updated during a pandemic.

The ventilation domain, which utilizes a statistical model that applies only to that domain, is expected to continue during a pandemic. If appropriate, the pandemic strata may be applied to this domain. If so, the PISOP stratum would apply informative priors.

Any new domain that is initiated during a pandemic will be submitted for ethical review and require ethical approval prior to commencement.

### 7.4.6. Use of informative priors derived from information available from outside the REMAP

The default position is that informative priors derived from information that is external to the REMAP will not be utilized. However, if appropriate, based on high quality evidence, informative priors may be applied. The decision to apply informative priors lies with the ITSC and must involve consultation with relevant external stakeholders, the DSMB, and appropriate statistical advice regarding the potential implications for the use of informative priors.

## 7.5. Endpoints

### 7.5.1. Pandemic primary endpoint

Specified domains, for patients in the PISOP stratum, will be analyzed using a separate statistical model, for which the primary endpoint is called the "pandemic primary endpoint". The default pandemic primary endpoint will be a composite end-point that comprises the number of whole and part study days for which the patient is alive and not admitted to an ICU up until the end of study

day 21. All patients who die before discharge from an acute hospital, irrespective of whether this occurs before or after D21, will be coded as zero days. Patients who die between D21 and discharge from an acute hospital will be updated at the time of the next adaptive analysis. All whole and part days after discharge from an acute hospital and before D21 will be counted as being not admitted to an ICU. Hospital readmission that included a new admission to ICU between first discharge from an acute hospital and D21 will not contribute to the primary end-point.

If appropriate, based on an understanding of clinical and biological factors, as well as operational factors, an alternative pandemic primary end-point may be specified at the time of activation of the PAtC. Other possible primary end-points include days alive and outside the ICU with alternative durations of follow up or the use of an alternative composite based on days alive without organ support. The pandemic primary endpoint will be used for the adaptive analyses that inform the RAR and for Statistical Triggers.

### 7.5.2. Secondary endpoints

All secondary endpoints that are specified in the Core Protocol and active DSAs will continue to be active. The primary end-point specified in the Core Protocol (all-cause mortality at day 90) is a secondary end-point in the PISOP stratum.

## 7.6. Principles of the statistical analysis

### 7.6.1. Adaptive analyses

Adaptive analyses may be conducted more frequently and with varying cadence during a pandemic. For analyses conducted in the pandemic model and the PISOP stratum of the ventilation model, data from all available patients will be utilized using, where appropriate, modelling to impute missing data. Adaptive analyses may be conducted at different frequency for the PISOP and PINSNP stratum.

### 7.6.2. Response adaptive randomization

For PISOP patients, RAR proportions for domains that are analyzed using the pandemic model will be derived from the pandemic model and the RAR proportions for domains that are analyzed using the interpandemic model will be derived from the interpandemic model. For PINSNP patients, the RAR proportions for all qualifying domains will be derived from the interpandemic model.

If feasible, the option of allowing sites to start with imbalanced RAR proportions may be utilized. During a pandemic, issues related to equipoise for sites to participate may be facilitated by allowing sites to select from a range of starting RAR proportions that are imbalanced. Being able to

implement this would be dependent on logistic feasibility as well as evaluation to exclude any adverse impact on inference.

### 7.6.3. Thresholds for statistical triggers

#### 7.6.3.1. Introduction

The Core Protocol specifies thresholds for Statistical Triggers that apply to superiority, inferiority, and equivalence. For PISOP patients, different thresholds for Statistical Triggers may apply during a pandemic. The decision to modify a statistical threshold will be made by the ITSC prior to the first adaptive analysis of the pandemic model. Different thresholds may be applied to different domains. Thresholds can also be specified that are asymmetric for example less stringent for inferiority than superiority. Factors that the ITSC will take into account in considering whether to modify a threshold include whether the interventions being evaluated are comparative effectiveness options (i.e. interventions that are available as part of standard care and available outside the platform) or experimental interventions with uncertain safety and risk profile that may be available only within the platform.

All decisions regarding thresholds for Statistical Triggers will be communicated to participating sites and placed in the public domain on the study website. Once specified, thresholds cannot be modified unless recommended by the DSMB.

The default thresholds are outlined in the following sections.

#### 7.6.3.2. Intervention Superiority Statistical Trigger

At any adaptive analysis, if a single intervention has at least a 0.95 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population.

The declaration of a Platform Conclusion by the DSMB for superiority will result in application of 100% RAR (see section 7.6.4). Following implementation of 100% RAR, the posterior probability will continue to be updated and evaluated by the DSMB who are empowered to act if they have concerns regarding the validity of a Platform Conclusion.

#### 7.6.3.3. Intervention Inferiority Statistical Trigger

At any adaptive analysis, if a single intervention has less than a 0.05 posterior probability of being a member of the optimal regimen, for a unit-of-analysis, then that intervention will be deemed as being inferior to other interventions in the domain for that target population. An asymmetrical

inferiority statistical trigger may be set, particularly if an active intervention was being evaluated against an intervention that specifies no active treatment in that domain.

### 7.6.3.4.    Equivalence

The equivalence boundary (delta) for different endpoints selected for the PISOP stratum may be changed depending on the clinical impact of the delta for the chosen endpoint. The default delta for the Core Protocol will be used to select clinically similar effects on the chosen primary endpoint. If a 21-day ICU-free day endpoint is selected the 20% proportional odds equivalency delta will be the default.

### 7.6.4.   Actions when a Statistical Trigger is achieved

The actions that occur when a statistical trigger is achieved are those which are specified in the Core Protocol. At the time of a Platform Conclusion that is relevant to public health or clinical management of patients with suspected or proven pandemic infection, the DSMB and ITSC are empowered to liaise directly with relevant public health authorities prior to public presentation or publication of results.

### 7.6.5.   Pre-specified subgroup analyses after achievement of a platform conclusion

Pre-specified subgroup analyses that will be conducted after a Platform Conclusion are outlined in each DSA. If a DSA does not specify a sub-group analysis related to the pandemic strata such analysis is permitted if the PISOP stratum has been open.

### 7.6.6.   Closure of the PISOP stratum and incorporation of data from pandemic statistical model into the interpandemic statistical model

The ITSC is permitted to close or suspend the PISOP stratum. At this time, evaluation of new patients within the pandemic model will cease. After the permanent closure of the PISOP stratum, the information related to domains that have been analyzed for PISOP patients within the pandemic model will be added to the interpandemic model retaining, if appropriate, a co-variate or stratum status, to reflect that the patient was enrolled in the PISOP stratum.

### 7.6.7.   Domains with their own statistical model

It is intended that domains with their own statistical model (e.g. as anticipated for the ventilation domain) will continue to be analyzed using the separate statistical model. If the PISOP stratum was applied to such a domain it is intended that a pandemic version of the separate model would be commenced and enroll only patients in the PISOP stratum. This model would utilize the pandemic

primary end-point and would use informative priors derived from the preceding model. An operational decision may be made to apply an end-point that is different to the pandemic primary end-point in a domain with its own model.

# 8. GOVERNANCE, ETHICAL, AND OPERATIONAL CONSIDERATIONS IN A PANDEMIC

## 8.1.    Decision to activate pandemic stratum

The decision to open the pandemic stratum lies with the ITSC. In deciding to activate the pandemic stratum the ITSC should take into account, but is not dependent on, declaration of a pandemic by the WHO and decisions about pandemic activation by regional pandemic preparedness consortia.

The decision to open will be communicated to RCCs and participating sites as an operational document. Each RCC will maintain a log of the dates for which sites were activated for the PISOP stratum.

## 8.2.    Data collection and management

A pandemic is likely to result in a substantial increase in clinical workload for sites participating in REMAP-CAP. This is acknowledged by the REMAP-CAP management, as is the primacy of patient care. The importance of contemporaneous data collection, particularly with respect to variables that are needed for adaptive analyses will be emphasized to sites. RCCs will seek to support sites as much as possible, including with requests to healthcare systems, public health authorities, and funding agencies to provide resources that allow sites to maintain data collection that is timely and complete.

## 8.3.    Role of the DSMB

In a pandemic the role of the DSMB is modified, taking into account the public health importance of clinical evidence during a pandemic. In meeting the requirements of their Charter during a pandemic the DSMB should consider issues of public health in addition to the well-being of participants and the scientific integrity of the platform. The in-principle views of the DSMB may be obtained by the ITSC with regard to the setting of modified thresholds for statistical triggers.

While the PISOP stratum is open the DSMB is also permitted to liaise with public health authorities regarding the results and appropriate interpretation of adaptive analyses in keeping with prevailing international standards. If the DSMB communicates with public health authorities the ITSC must be informed that such communication has occurred but the content of that communication may remain

confidential between the DSMB and the relevant public health authorities. The DSMB may recommend to the ITSC that public reporting of posterior probabilities that have not attained a threshold for a Statistical Trigger should occur.

The workload of the DSMB may be substantial during a pandemic and, if requested by the DSMB, the ITSC will appoint additional members.

## 8.4.      *Communication of trial results*

Any Platform Conclusion that is relevant to public health that occurs during a pandemic will be presented or published as soon as possible, noting that additional work to report baseline status and secondary end-points will need to occur prior to presentation and publication of results.

## 8.5.      *Funding of the trial*

The trial is currently funded as described in the Core Protocol.

During the interpandemic period and during a pandemic, additional funding will be sought to provide resources for activities that exceed those that will be occurring during the interpandemic period. Possible sources of additional resources include, but are not limited to, healthcare systems, public health authorities, and local and international research funding bodies.

## 8.6.      *Monitoring*

It is acknowledged that during a pandemic site monitoring may be delayed for logistical reasons. The operational monitoring plan may be updated to reflect issues that are specific to a pandemic. As outlined in Core Protocol, the DSMB will take into account intensity of monitoring and time of consideration of a Platform Conclusion. If appropriate, the contribution of data that has not been monitored as per the non-pandemic monitoring plan will be acknowledged in the public reporting of Platform Conclusions.

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