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

Core Protocol Version 4 dated 5th November, 2024

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1. ABBREVIATIONS AND GLOSSARY

1.1. Abbreviations

ANZ	Australia and New Zealand
ARDS	Acute Respiratory Distress Syndrome
BHM	Bayesian Hierarchical Model
CAP	Community-Acquired Pneumonia
CRF	Case Report Form
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
eCRF	Electronic Case Report Form
ICH GCP	International Committee for Harmonization Good Clinical Practice
HDU	High Dependency Unit
HRQoL	Health Related Quality of Life
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
ITSC	International Trial Steering Committee
ITT	Intention-To-Treat
LOS	Length of Stay
OSFD	Organ Support Free Days
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
RMC	Regional Management Committee
RSA	Region-Specific Appendix
SAC	Statistical Analysis Committee
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SOPs	Standard Operating Procedures

VFD	Ventilator Free Days
WHODAS	World Health Organization Disability Assessment Schedule

1.2. Glossary

Bayesian inference is the process of fitting a probability model between a set of data and model parameters, where the inference is driven by the probability distribution on the parameters of the model and any unobserved quantities, such as predictions for new observations.

Bayesian Hierarchical Model characterizes a set of parameters from a common distribution where the parameters of the distribution are modeled in a hierarchical structure. The model allows for inferences on one parameter to depend on the empirical similarity to other parameters in the common distribution.

Borrowing is the process within the statistical model, whereby, the evidence of effectiveness for an intervention within a state/stratum or a pre-specified nest contributes to the posterior estimate of the same intervention in a different state/stratum or other intervention(s) within the pre-specified nest.

Core Protocol is a module of the protocol documents that contains all information that is generic to the Randomized, Embedded, Multifactorial, Adaptive Platform (REMAP) trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested.

Domain consists of a specific set of competing alternative interventions within a common clinical mode, which, for the purposes of the Platform, are mutually exclusive and exhaustive. Where there is only a single active intervention option within a domain the comparator is all other usual care in the absence of the intervention (i.e., a 'no intervention' control). Where multiple interventions exist within a domain, comparators are the range of interventions either with or without a 'no intervention' option, depending on whether an intervention within the domain is provided to all patients as part of standard care. Within the Platform every patient will be allocated to receive one, and only one, of the available interventions within each domain for which they are eligible.

Domain-Specific Appendix is an appendix to the Core Protocol. These appendices are modules of the protocol documents that contain all information about the interventions within a domain that will be a subject of this Platform. Each domain will have its own Domain-Specific Appendix (DSA). The information contained in each DSA includes criteria that determine eligibility of patients to that domain, the features of the interventions and how they are delivered, the relevant units-of-analysis, and any additional endpoints and data collection that are not covered in the Core Protocol.

Domain-Specific Working Group is a sub-committee involved in trial management, the members of which take responsibility for the development and management of a current or proposed new domain.

International Trial Steering Committee is the committee that takes overall responsibility for the governance and conduct of the Platform with oversight over all regions and all domains.

Intervention is a treatment option that is subject to variation in clinical practice (comparative effectiveness intervention) or has been proposed for introduction into clinical practice (experimental intervention) and also is being subjected to experimental manipulation within the design of a REMAP. For the purposes of the REMAP an intervention can include an option in which a specified treatment or treatments are not provided.

Monte-Carlo Simulations are computational algorithms that employ repeated random sampling to obtain a probability distribution. They are used in the design of the study to anticipate trial performance under a variety of potential states of 'truth' (e.g., to test the way in which a particular trial design feature will help or hinder the ability to determine whether a 'true' treatment effect will be discovered by the trial). Monte Carlo methods are also used to provide updated posterior probability distributions for the ongoing analyses of the trial.

Nesting describes sets of interventions within a domain where the intervention effects are modeled hierarchically so as to allow for borrowing among the intervention effect estimates for the interventions within that nest.

The ***Patient, Pathogen and Disease Appendix*** *(PANDA)* is an appendix to the Core Protocol which describes how specific patient, pathogen, disease, illness severity and additional clinical features are defined and categorized within the Platform.

Pandemic Appendix describes an appendix to previous versions of the Core Protocol that specified the modifications to the Core Protocol that occurred during the COVID-19 pandemic. This Appendix is no longer operational under this version of the Core Protocol.

Platform Conclusion describes a decision of the International Trial Steering Committee (ITSC) to conclude that superiority, efficacy, inferiority, equivalence, noninferiority, harm, or futility has been demonstrated following the occurrence of a Statistical Trigger that has been evaluated by the Data Safety and Monitoring Board (DSMB). Under almost all circumstances a Platform Conclusion leads to Public Disclosure of the result by presentation and publication.

Public Disclosure is the communication of a Platform Conclusion to the broad medical community, participants and the public by means of presentation, publication or both.

Randomization refers to the random allocation of a treatment regimen. Randomization within a given State can only occur once, however some participants may be randomized more than once in different States. In some cases, randomized allocations may not be immediately revealed at the time of randomization.

Regimen consists of the unique combination of interventions from one or more domains (including 'no intervention' options), that a patient is allocated within a Platform.

Region-Specific Appendix is an appendix to the Core Protocol. These appendices are modules of the protocol documents that contain all information about the trial specific to the conduct of the trial in that region. Each region will have its own Regional-Specific Appendix (RSA). A region is defined as a country or collection of countries with study sites for which a Regional Management Committee (RMC) is responsible.

Regional Management Committee is a sub-committee involved in trial management. The members of the RMC take responsibility for the management of trial activities in a specified region. The role, responsibilities, and composition of each RMC are specified in each region's RSA.

REMAP is a variant of a platform trial that targets questions that are relevant to routine care and relies heavily on embedding the trial in clinical practice. Like other platform trials, the focus is on a particular disease or condition, rather than a particular intervention, and it is capable of running perpetually, adding new questions sequentially.

Response Adaptive Randomization is a dynamic process in which the analysis of accrued trial data is used to determine the proportion of future patients who are randomized to each intervention within a domain.

Sponsor is an organization that takes overall responsibility for the conduct of the trial in a defined region

State is a set of mutually exclusive and exhaustive categories, defined by characteristics of a patient within the Platform, that are capable of changing over time for a single patient at different time-points during the patient's participation in the Platform (i.e., they can be dynamic). State can be used to define unit-of-analysis and as an additive covariate within the Bayesian statistical model.

Statistical Analysis Committee takes responsibility for the conduct of the preplanned adaptations in the trial. This task generally consists of running predetermined statistical models at each adaptive analysis and providing this output to the DSMB. From a trial governance perspective, the Statistical Analysis Committee is under the supervision of the DSMB.

Statistical Model is a computational algorithm that is used to estimate the posterior probability of the superiority, efficacy, inferiority, equivalence, noninferiority, harm, or futility of the regimens and interventions that are being evaluated within the REMAP.

Statistical Trigger within the REMAP two or more interventions within a domain are evaluated and statistical models are used to determine if one or more interventions are superior, effective, inferior, equivalent, noninferior, harmful, or futile. A Statistical Trigger occurs when the statistical models used to analyze the REMAP indicate that the threshold for declaring superiority, efficacy, inferiority, equivalence, noninferiority, harm, or futility for one or more interventions within a domain has been crossed. A Statistical Trigger applies to the smallest unit-of-analysis specified for a given domain, but may be reached in more than one unit-of-analysis for the same intervention at the same adaptive analysis.

Strata comprise a set of mutually exclusive and exhaustive categories (stratum) defined by baseline characteristics of a patient within the Platform, in which the relative effects of interventions may be differential. These possibly differential effects of interventions are reflected in the statistical model, the randomization probabilities, and the Platform Conclusions. The criteria that define a stratum must be present at or before the time of enrollment.

Treatment allocation refers to the randomized components of the regimen that are revealed. The intention-to-treat (ITT) population for a domain is defined by a participant who received a revealed treatment allocation from the domain (irrespective of whether the allocated treatment is received).

Unit-of-analysis is the group of patients who are analyzed together within the model for a particular domain. The unit-of-analysis can be all participants who have received a treatment allocation in that domain or a sub-group of participants who received a treatment allocation determined by their status with respect to one or more strata. Within a domain, RAR can be applied to the unit-of-analysis.

2. INTRODUCTION

2.1. Synopsis

Background: Respiratory tract infections that are of sufficient severity to require admission to hospital are associated with substantial mortality. All hospitalized patients with respiratory tract infections will receive therapy that consists of a combination of multiple different treatments. For many of these treatments, different options are available currently. For example, several antibiotics exist that are active against the microorganisms that commonly cause pneumonia but it is not known if one antibiotic strategy is best, or whether all suitable antibiotic strategies have similar levels of effectiveness. Of all the treatments that clinicians use for patients with respiratory tract infections, only a small minority have been tested in randomized controlled trials to determine their comparative effectiveness. As a consequence, the standard treatments that are administered vary between and within countries. Current conventional clinical trials methods to assess the efficacy of treatments for respiratory tract infections generally compare two treatment options (either two options for the same treatment modality, where both are in common use; or a new treatment against no treatment or placebo, where the effectiveness of the new treatment is not known). Using this approach, in a series of separate and sequential trials, it will take an inordinate length of time to study all the treatment options. Additionally, with conventional trial designs it is not possible to evaluate interactions between treatment options.

Aim: The primary objective of this platform trial is, for patients hospitalized with respiratory tract infection, to identify the effect of a range of interventions to improve patient outcomes.

Methods: The study will enroll hospitalized patients with respiratory tract infection using a trial design known as a REMAP, which is a type of platform trial. Within this platform trial, eligible participants will be randomized to receive one intervention in each of one or more domains. The primary outcome is a composite of 90-day all-cause mortality and, among survivors, a daily ordinal scale analyzed as a trajectory of illness and recovery to 28-days. There will also be both Platform and domain-specific secondary outcome measures.

In a conventional trial enrollment continues until a pre-specified sample size is obtained, at which time enrollment ceases and the trial data are analyzed to obtain a result. The possible results are that a difference is detected, or no that no difference is detected. However, when the conclusion of the statistical test is “no difference”, this could reflect that there truly is no meaningful difference or

that the result is indeterminate (i.e., it is possible that if more patients had been enrolled a clinically relevant difference may have been detected).

In comparison to a conventional trial this Platform uses an adaptive design that:

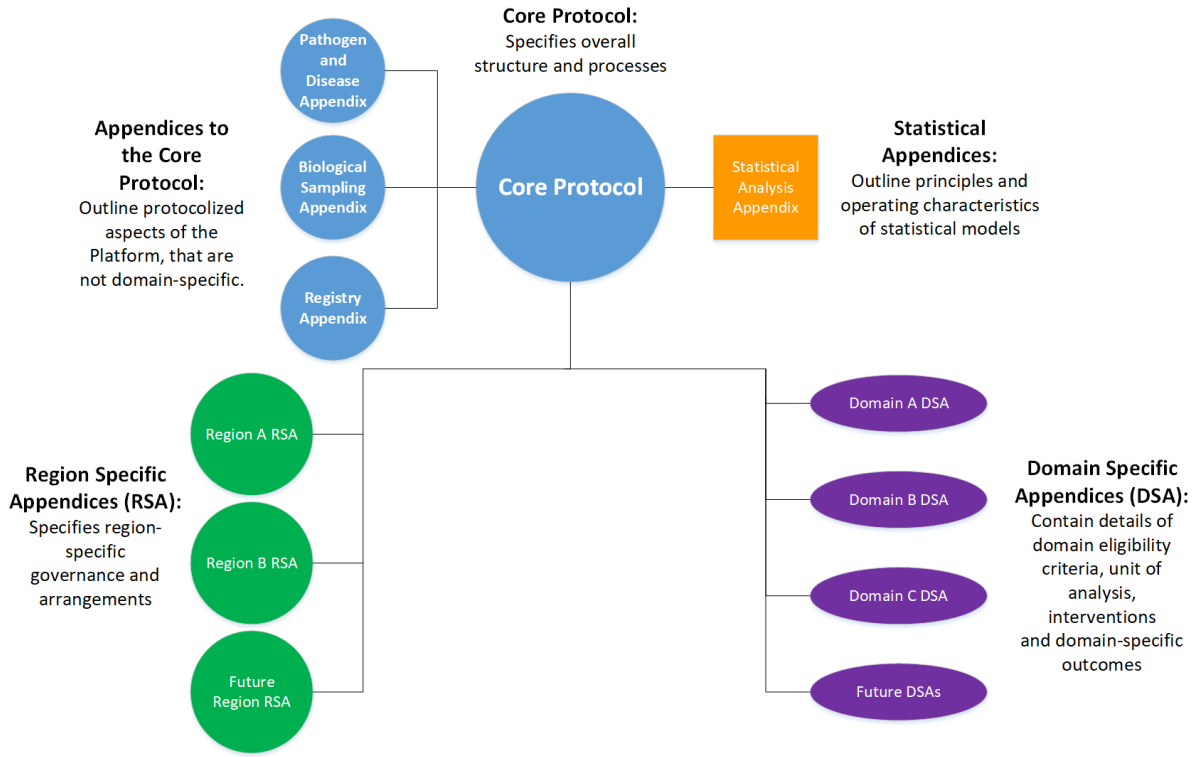
- avoids indeterminate results by concluding an answer to a question when sufficient data have accrued (not when a pre-specified sample is reached);
- utilizes already accrued data to increase the likelihood that patients within the trial are more likely to be randomized to treatments that are more likely to be beneficial;
- is intended to be perpetual (or at least open-ended), substituting new questions in series as initial questions are answered; and
- can evaluate the interaction between interventions in different domains, added at different timepoints into the Platform.

Bayesian statistical methods will be used to define Statistical Triggers that reflect thresholds for decision making within a domain. While a limited number of initial treatments and treatment domains were specified at initiation, other interventions and domains have been evaluated over time, and it is planned that this platform trial will continue to evaluate other treatments in the future. Furthermore, in the event of a future epidemic, this Platform is able to adapt to evaluate the most relevant treatment options. Each new treatment that is proposed to be evaluated within the Platform will be submitted for prospective ethical review.

2.2. Protocol Structure

The structure of this protocol is different to that used for a conventional trial 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, either within this document or corresponding DSAs, the structure of the protocol is designed to allow the trial to evolve over time. Examples of such modifications include the introduction of new domains or interventions or both (see glossary for definitions of these terms), the removal of domains or interventions in the event of Platform Conclusions, changing aspects of the trial during a pandemic, and commencement of the trial in new regions. The structure of the protocol is outlined in Figure 1.

Figure 1. Protocol Structure



The protocol has multiple modules, comprising a Core Protocol, a Patient, Pathogen and Disease Appendix (PANDA), Biological Sampling Appendix, Registry Appendix, multiple DSAs, and multiple RSAs. There are also operational documents that specify how aspects of the Core Protocol will be operationalized, including the Current State of the Statistical Model ("Current State"), Statistical Simulations Appendix, and a Statistical Analysis Appendix. These operational documents are updated periodically.

2.2.1. Core Protocol

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 has the following structure:

- The background and rationale for studying respiratory tract infections
- The background and rationale for the research approach
- The trial design including study setting, the criteria that define eligibility for the Platform, treatment allocation, strata, states, principles of application of trial interventions, trial

endpoints, methods to control bias, principles of statistical analysis, and criteria for termination of the trial

- The trial conduct including data collection, data management, and management of participant safety
- The overall / international trial governance structures and ethical considerations

2.2.2. Patient, Pathogen and Disease Appendix

The Patient, Pathogen and Disease Appendix (PANDA) specifies categories, within the larger population of respiratory tract infection, that may be applied by domains as eligibility criteria, or to define analysis populations. As such, the PANDA does not include information about the interventions that will be the subject of the platform trial, but rather describes the way that patients within those hospitalized with respiratory tract infection may be categorized within the Platform. It is intended that any amendments to the PANDA will be infrequent.

2.2.3. Domain-Specific Appendices

DSAs contain all information about the interventions that will be the subject of this platform trial, which are nested within domains. As such, the Core Protocol does not include information about the interventions that will be evaluated within the Platform, but rather provides the framework within which multiple different interventions, within domains, can be evaluated. Each new DSA or modification to an existing DSA will be submitted for ethical and regulatory approval (where applicable) prior to commencement. It is anticipated that the DSAs will change over time with removal and addition of interventions within an existing domain, as well as removal and addition of entire domains. Where an adaptation within a domain is pre-specified, such as removal of an intervention following a statistical trigger, it is not necessary to amend the DSA.

Each DSA specifies the following information:

- background on the interventions within that domain
- criteria that determine eligibility of patients to that domain
- features of the interventions and how they are delivered
- any endpoints and data collection that are specific to the domain and additional to those specified in the Core Protocol
- any ethical issues specific to the domain
- the organization of management of the domain
- Unit-of-analysis for the domain, including domain-specific strata

- Statistical Triggers applied to the domain, including any modifications to Statistical Triggers specified in the Core Protocol

2.2.4. Region-Specific Appendices

This REMAP is intended to be a global trial, conducted in multiple different geographical regions. Region Specific Appendices (RSAs) contain all information about the REMAP that is specific to the conduct of the trial in a particular region. This allows additional regions to be added or changes to each region to be made without needing to make major amendments to the Core Protocol in other regions. It is planned that, within each region, the documents submitted for ethical and regulatory review will comprise the Core Protocol, PANDA, relevant DSAs, Registry Appendix (where relevant), and the RSA for that region (but not other regions). Each RSA has the following structure:

- the definition of the region
- the organization of trial management and administration within the region
- region-specific data management and randomization procedures
- ethical issues that are specific to the region.

If there is information that applies to one or more sub-areas of a region (e.g., a country within Europe, or a state or territory within a country) and it is necessary to incorporate this information in the protocol, this information will be included within the RSA or a country-specific appendix to the RSA. Unless otherwise specified, the RSA will apply to all locations within that region.

2.2.5. Pandemic Appendix

The Pandemic Appendix (to the Core Protocol) contained information about how the core elements of the Platform were modified during the COVID-19 pandemic. There is no longer a Pandemic Appendix for this version of the Core Protocol, which now integrates the adaptations that occur in the context of a future pandemic.

2.2.6. Biological Sampling Appendix

The Biological Sampling Appendix describes the strategy for biological sampling at participating sites. The intention of these samples is to create a repository of biological samples that may be used to investigate a range of prespecified and post-hoc questions related to respiratory tract infections. Domain-specific sampling, if required, may also be specified in the relevant DSAs.

2.2.7. Registry Appendix

The Registry Appendix to the Core Protocol describes the linkage between patients meeting a minimum set of eligibility criteria for this Platform and existing healthcare registries, with the aim of providing an observational dataset of hospitalized patients with respiratory tract infection.

2.2.8. Operational Documents

A substantial number of operational documents are used to execute the Platform. These will be updated over time as necessary and will not require a protocol amendment. This includes the Current State document.

The Statistical Analysis Appendix describes the principles of how the statistical analysis will be conducted for reporting treatment effects and reporting interaction between treatments, as well as Response Adaptive Randomization (RAR). Each domain will also have a corresponding Statistical Analysis Plan which will be published on the remapcap.org website before any data is unblinded to study investigators. The Current State of the Statistical Model ("Current State") is the operational document that provides specific instructions from the blinded statisticians to the unblinded SAC that are utilized to determine the structure of the statistical model(s) used for each adaptive analysis.

The Simulations Appendix is an operational document that contains the results of Monte Carlo simulations that are conducted to describe and understand the operating characteristics of the Platform across a range of plausible assumptions regarding outcomes, treatment effects, and interactions between interventions in different domains. The statistical power of the study (likelihood of type II error) and the likelihood of type I error are evaluated using these simulations. As the trial adapts, with, for example, the introduction of new interventions, the trial simulations are updated and the Simulations Appendix is correspondingly amended periodically. The Simulations Appendix is not part of the formal protocol but the conclusions from the Simulations Appendix will be reflected in protocol documents, which will be updated as required. The Simulations Appendix will be maintained as a publicly accessible document on the study website. Where appropriate, domain-specific simulations will be included in relevant DSAs.

2.2.9. Core Protocol Version History

Version 1: Approved by the ITSC on 20 November 2016

Version 1.1: Approved by the ITSC on 10 April 2017

Version 2: Approved by the ITSC on 12 December 2017

Version 2.1: Approved by the ITSC on 26 March 2019

Version 3: Approved by the ITSC on 10 July 2019

Version 3.1: Approved by the ITSC on 9 November 2022 (UK-specific)

Version 4: Approved by the ITSC on 5 November 2024

2.3. Lay Description

Patients hospitalized with respiratory tract infections routinely receive multiple treatments at the same time – medications to treat the infection (antibiotics or antiviral medications), medications that may modify the immune system (immunomodulators) and supportive treatments to support failing organs (such as mechanical ventilation) and prevent complications of acute illness or its treatment. For many categories of treatment there are many treatment options that are in widespread use and are believed or known to be safe and effective, but it is not known which option is best. This Platform aims to determine the best treatment in each category of treatment, for example, the best antibiotic, the best immunomodulation strategy, and the best method to support each failing organ system.

In a conventional clinical trial, selected patients are allocated to receive one treatment from a short list of alternative treatments, typically one or two. This trial differs from conventional clinical trials by being randomized, embedded, multifactorial, adaptive, and a platform (a "REMAP") (Angus, 2015). In this type of trial, we will test many alternative treatments ("multifactorial") by replacing *ad hoc* treatment decisions with "randomized" treatment allocation ("embedded"). Although treatments will be allocated randomly, patients may be more likely to be allocated to treatments that statistical models indicate are more likely to be the most effective treatments based on accumulating trial data. The trial will "adapt" in multiple ways, including answering questions as soon as sufficient data have accrued to answer the question of the effectiveness of each treatment, and by changing the treatments that are being tested over time so as to progressively determine the best set of treatments for pre-defined categories of patients with respiratory tract infection. The platform trial is also designed to adapt to test relevant interventions during a pandemic caused by respiratory tract infection.

2.4. Trial registration

This is a single platform trial conducted in multiple regions, but will, as a minimum, be registered with ClinicalTrials.gov. The trial registration number is: NCT02735707.

The Universal Trial Number is: U1111-1189-1653.

2.5. Funding of the trial

The Platform is funded by sources across regions and domains. All funders are displayed on the trial website. Additional funding will be sought throughout the lifespan of the platform trial.

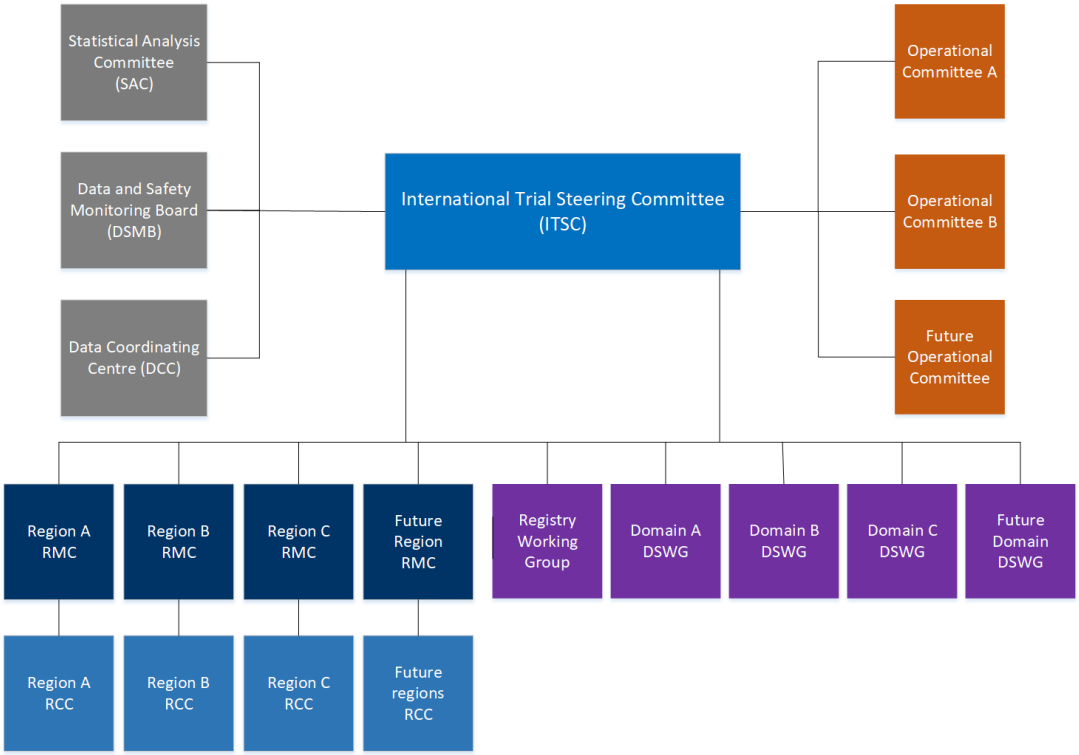
3. STUDY ADMINISTRATION STRUCTURE

The administration structure is designed to provide appropriate management of all aspects of the Platform, taking into account multiple factors including representation from regions that are participating in the trial, availability of skills and expertise related to trial conduct and statistical analysis, and content knowledge regarding respiratory infections and the interventions that are being evaluated. The administration model is designed to provide effective operational and strategic management of the Platform, which operates across multiple regions, is supported by multiple funding bodies and sponsors, and will evolve over time with addition of further regions and funding bodies as well as changes in the domains and interventions that are being evaluated.

The ITSC takes overall responsibility for the trial design and conduct. Each participating region has an RMC that takes primary responsibility for trial execution in that region. An internationally-based Domain-Specific Working Group (DSWG) exists for each domain (or for several domains that are closely related) and has responsibility for design and oversight of each domain. There are a variety of operational activities for a platform of this scope, with relevant operational committees governed by specific Terms of Reference agreed upon by the ITSC.

The organizational chart for this Platform is outlined in Figure 2.

Figure 2. Platform Organization Chart



3.1. International Trial Steering Committee

Membership and responsibilities of the ITSC are specified in the ITSC Terms of Reference document.

3.1.1. Responsibilities

The responsibilities of the ITSC include:

- development and amendment of the Core Protocol and its appendices
- approval of DSAs developed or amended by each DSWG
- recruitment and approval of new regions to the Platform
- liaison with the DSMB including, where appropriate, decisions regarding Platform Conclusions
- consideration of requests and approval of the addition of domains and their nested interventions to the Platform, including prioritization of new domains, new interventions within a domain, or both

- liaison with the academic community including the International Committee of Medical Journal Editors (ICMJE) regarding issues such as data sharing and reporting of platform trials including REMAPs
- in conjunction with DSWGs, the analysis and reporting of results from domains
- approval of manuscripts reporting results that are submitted by DSWGs
- coordination of the Platform during a pandemic
- obtaining funding for the Platform
- determine the strategic direction of the Platform

3.1.2. Members

Membership of the ITSC is specified in the ITSC Terms of Reference document, which will be modified over time, as required, by the ITSC. The ITSC may delegate activities to subcommittees, each of which will have a document specifying their roles and responsibilities. The current ITSC membership is listed on the trial website.

3.2. Regional Management Committees

The operation of the Platform in each region is undertaken by that region's RMC, the composition of which is be determined by investigators in each region with membership listed in each RSA. Cross-representation between RMCs is strongly encouraged.

3.2.1. Responsibilities

The responsibilities of each RMC include:

- development and amendment of the RSA for that region
- identification and selection of sites in that region
- obtaining funding for that region
- liaison with regional funding bodies
- consideration of the feasibility and suitability of interventions (and domains) for that region
- liaison with the Sponsor(s) for that region

3.3. Domain-Specific Working Groups

Each active and future planned domain (or closely related set of domains) will be administered by a DSWG.

3.3.1. Responsibilities

The responsibilities of each DSWG are:

- development and amendment of relevant DSAs
- proposal and development of new interventions within a domain
- in conjunction with the ITSC, analyzing and reporting results from the domain
- obtaining funding to support the domain, with a requirement that, if such funds are obtained, that an appropriate contribution to the conduct of the Platform is also made.

3.3.2. Members

Membership of each DSWG is set out in the corresponding DSA and will comprise individuals that provide broad international representation, content knowledge of the domain, and expertise of trial conduct and design.

3.4. Sponsors

The Platform has multiple Sponsor organizations. Certain responsibilities of the Sponsor may be assigned to a Regional Coordinating Center (RCC), as specified in relevant RSAs. Sponsor names and relevant signatures are included in the relevant RSA.

3.4.1. Role of Sponsor

The role of the Sponsor in each region is specified in each RSA.

3.4.2. Insurance

The provision of insurance in each region is specified in each RSA.

4. INTERNATIONAL TRIAL STEERING COMMITTEE AUTHORIZATION

The ITSC have read this document and authorize it as the official Core Protocol for this Platform.
Signed by the ITSC Chair, on behalf of the ITSC

ITSC Chair Date 5th November, 2024

Dr. Srinivas Murthy

5. BACKGROUND & RATIONALE

5.1. Respiratory Tract Infections

5.1.1. Introduction

This section provides some background on the epidemiology, causes, treatment categories, and evidence base for the management of patients with respiratory tract infection. Detailed information regarding the rationale for specific interventions to which patients will be randomized within the Platform can be found in a corresponding DSA. As the trial is intended to be perpetual, if background information changes appropriate amendments to the protocol documents will occur periodically, but it is anticipated that this will occur predominantly by amendment of DSAs.

5.1.2. Epidemiology

A wide range of micro-organisms are implicated in respiratory tract infections, but bacteria and viruses are responsible for the vast majority of cases where a cause is identified. Respiratory tract infections are an important health problem and a common cause of death from infection globally, with lower respiratory tract infection ranked as the fourth leading cause of disability-adjusted life years across all ages in 2019 (Diseases and Injuries, 2020). In developed countries, around half of patients with respiratory tract infections are treated successfully without admission to hospital (Almirall et al., 2000). Among patients who are admitted to hospital approximately 10 to 20% are admitted to an ICU (Alvarez-Lerma and Torres, 2004, Ewig et al., 2011). The population incidence of respiratory tract infections that involves admission to an ICU is about 0.4 cases per 1000 per year (Finfer et al., 2004b). Among patients admitted to an ICU with CAP, case-fatality is reported to be in the range from 20 to 50% (Alvarez-Lerma and Torres, 2004, Leroy et al., 1995, Sligl and Marrie, 2013). In low and middle-income countries, the overlapping syndromes of CAP, bronchiolitis, and bronchitis are a major public health problem and represent the world's most important cause of disability-adjusted life years lost and the third most important cause of death (World Health Organization, 2008). This is particularly the case for children, with lower respiratory tract infections persisting as the second leading cause of disability-adjusted life years (Diseases and Injuries, 2020).

5.1.3. Standard care for patients with respiratory tract infections

All patients, regardless of age, admitted to hospital with respiratory tract infections will receive multiple different component therapies and many of these therapies will be administered concurrently. These therapies can be grouped into the following categories: treatment of the

underlying infection (including antibacterial and antiviral agents); the optional use of agents, such as corticosteroids, that modulate the host immune response to infection; and multiple supportive therapies that are used to manage organ systems that have failed, or prevent complications of critical illness and its treatment (Table 1).

Table 1. Potential targets to improve outcomes in patients with respiratory tract infections

Target of intervention	Examples
Eradication of pathogens	Antibiotics (agents, route, dose) Antivirals (agents, route, dose) Microbiological diagnostic strategies
Modulation of the host immune response	Corticosteroid Macrolides
Methods to support failing organ systems and prevention of complications	Lung ventilation strategies and respiratory salvage modalities (e.g., extra-corporeal membrane oxygen, prone positioning) Renal replacement therapy Inotropic/vasopressor support Fluid resuscitation strategies Nutrition Mobilization Sedation Venous thromboembolism prophylaxis Stress ulcer prophylaxis

5.1.4. Treatment guidelines

A range of different guidelines have been published that are relevant to the care of hospitalized patients with respiratory tract infections, including COVID-19 (Eccles et al., 2014, Lim et al., 2009, Mandell et al., 2007, Wiersinga et al., 2012, Wilkinson and Woodhead, 2004, Woodhead et al., 2011, Metlay et al., 2019, World Health Organization, 2023). These guidelines, particularly those focusing

on patients without COVID-19, generally focus on recommendations related to assessment of severity, diagnostic evaluation, and empiric and guided antimicrobial therapy (Lamontagne et al., 2020). Guidelines from the Surviving Sepsis Campaign are relevant to many aspects of the supportive care of the critically ill patients with CAP (Evans et al., 2021).

There is a stark contrast between the substantial public health impact of respiratory infections and the low quality of evidence that guides therapy, with the exception of COVID-19. The number of treatment recommendations in guidelines that are supported by high quality randomized controlled trial (RCT) evidence is 4 of 44 for treatment recommendations in the European guidelines, 11 of 43 in the United States guidelines, and 7 of 93 in the Surviving Sepsis Campaign Guidelines. As a consequence of the limited evidence-base there are a number of inconsistencies and even complete contradictions among international guidelines for the treatment of respiratory tract infections.

5.1.5. Variation in care and compliance with guidelines

Several observational studies report substantial variation in compliance with guidelines, for example with administration of antibiotics recommended by guidelines occurring in between 40% and 75% of patients (Bodi et al., 2005, Frei et al., 2010, Lee et al., 2014, Shorr et al., 2006). These and other studies also report better clinical outcomes for patients who received antibiotics that were recommended by guidelines (McCabe et al., 2009, Mortensen et al., 2004, Mortensen et al., 2005). However, it remains unclear if adherence to guideline recommendations is due to a direct causal link, or whether it is a surrogate for better quality care generally. There is also widely reported variation in compliance with many supportive therapies for patients with severe respiratory tract infections, such as use of low tidal volume ventilation, type of resuscitation fluid, and thresholds for the administration of transfusion for anemia (Blood Observational Study Investigators of et al., 2010, Cecconi et al., 2015, Bellani et al., 2016, Finfer et al., 2010).

5.1.6. An unmet need for better evidence

Many factors contribute to the substantial unmet need for better evidence to determine the optimal treatment for patients hospitalized with respiratory tract infections. There is a strong rationale for the need for better quality evidence about the impact of the different treatment options that are in existing practice, the impact of different combinations of treatment options, and the timely and effective evaluation of new candidate interventions to improve outcomes. COVID-19 has demonstrated the value of high-quality evidence from randomized trials in improving the outcomes of patients with respiratory tract infections, and these lessons must be applied to all causes of respiratory tract infection.

5.2. Pandemics and emerging pathogens

A respiratory pandemic caused by a known (e.g., influenza) or previously unknown virus (e.g., SARS-CoV-2), can rapidly change the etiological spectrum of hospitalized patients with respiratory tract infection. This necessitates adaptation of empiric treatment protocols or diagnostic procedures or both. Naturally, there will be no evidence base for the medical management of such a disease at the time of its emergence, and medical decisions will be mostly based on expert opinion with extrapolation from evidence derived from the treatment of analogous clinical syndromes. There is substantial unmet need to generate evidence about the most effective treatment approaches early during a pandemic or regional outbreak, as was demonstrated with SARS-CoV-2. Such evidence must be capable of being generated, disseminated, and implemented rapidly.

5.3. Randomized Embedded Multifactorial Adaptive Platform Trials

This section provides higher level background for REMAP trials and is provided for those without foundational knowledge of the subject. Specific aspects of design and statistical analysis relevant to this platform trial are described in Section 7 of this Core Protocol.

5.3.1. Generating clinical evidence

Angus has noted several problems encountered when generating robust clinical evidence, including barriers to conducting clinical trials, the generalizability of data from populations that are too broad or too narrow, the issue of equipoise especially when comparing different types of existing care, and the delay in translating results into clinical practice (Angus, 2015). A REMAP provides a strategy to address many of these problems by gaining economies of scale from a common platform, which allows for broad enrollment but retaining the ability to examine for heterogeneity of treatment effects between defined subgroups. A REMAP focuses predominantly on the evaluation of treatment options for the disease of interest that are variations within the spectrum of standard care (although testing of novel or experimental therapies is not precluded) and does so by embedding the trial within routine healthcare delivery. In this regard the REMAP seeks to replace random variation in treatment with randomized variation in treatment allowing causal inference to be generated about the comparative effectiveness of different existing treatment options. The use of RAR, which allows the allocation ratios to change over time based on accruing outcomes data, maximizes the chance of good outcomes for trial participants. The embedding of such a platform within the day-to-day activities of healthcare services facilitates the translation of outcomes to clinical practice as a “self-learning” system. As such, it also functions as an embedded and automated continuous quality-

improvement program. A final advantage of a REMAP for acute respiratory tract infections is the ability to rapidly adapt to generate evidence if new respiratory pathogens emerge, avoiding the inevitable delays associated with conventional trials in an outbreak of a new infectious diseases (Burns et al., 2011), as seen with COVID-19 (Angus et al., 2021).

Adaptive platform trials (APTs), are able to study multiple interventions in a disease or condition in a perpetual manner, with interventions entering and leaving the platform on the basis of a predefined decision algorithm. APTs are one form of master protocols where an overarching protocol is designed to answer multiple questions. Usually, a single disease or related disease conditions are included, although there may be different disease sub-types and multiple therapeutic domains. Other master protocols include basket (single therapeutic for multiple diseases) and umbrella (single disease with multiple sub-types) designs. All master protocols aim to achieve better coordination and efficiencies than can be achieved in single trials. APTs and master protocols have been reviewed extensively and have become more commonplace across specialties. The rest of this section highlights elements of APTs specific to REMAP trials (Woodcock and LaVange, 2017, Adaptive Platform Trials, 2019, Collignon et al., 2021, Lu et al., 2021, Granholm et al., 2022, Meyer et al., 2020).

5.3.2. Underlying Principles of the Study Design

A REMAP applies novel and innovative trial adaptive design and statistical methods to evaluate a range of treatment options as efficiently as possible (Adaptive Platform Trials, 2019). The broad objective of a REMAP is, over time, to determine and continuously update the optimal set of treatments for the disease of interest. The set of treatments that may be tested within a REMAP comprise the set of all treatments that are used currently or may be developed in the future and used or considered for use in the disease of interest. The design maximizes the efficiency with which available sample size is applied to evaluate treatment options as rapidly as possible. A REMAP has the capacity to identify differential treatment effects in defined sub-groups (termed Strata), at different time-points or severity of disease course (termed States), address multiple questions simultaneously, and can evaluate interactions among selected treatment options. Throughout the platform, patients who are enrolled in the trial are treated as effectively as possible (Angus, 2015, Berry et al., 2015, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016).

Adaptive platform trials are able to address the limitations of some other trial designs, including 1) making assumptions about the plausible size of the treatment effect and the incidence of the

primary outcome, and thus the planned sample size; 2) assuming that treatment effects are not influenced by concomitant treatment options; and 3) participants not being able to benefit from knowledge accruing during a trial's conduct. In non-adaptive trials, these assumptions are typically held constant until the trial completes recruitment and is analyzed. Participants who are enrolled in a conventional RCT are not able to benefit from knowledge accrued by the trial because no results are made available until after the trial completes. A REMAP uses five approaches to minimize the impact of assumptions on trial efficiency and also maximizes the benefit of participation for individuals who are enrolled in the trial (Aikman et al., 2013, Angus, 2015, Berry et al., 2015, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016).

These design features are, but not limited to:

- frequent adaptive analyses using Bayesian statistical methods
- response adaptive randomization (RAR)
- evaluation of differential treatment effects in pre-specified sub-groups (Strata)
- evaluation of specified intervention-intervention interactions
- testing of multiple interventions in parallel and, subsequently, in series
- hierarchical borrowing

This creates a 'perpetual trial' with no pre-defined sample size, the objective of which is to define and continuously update best treatment over the life-time of the REMAP. The design aspects, including the risk of type I and type II error, are optimized prior to the commencement and during the trial by the conduct of extensive pre-trial Monte Carlo simulations, modification of the trial design, and re-simulation in an iterative manner.

5.3.3. Nomenclature

A specific set of nomenclature is used to categorize potential treatments evaluated and populations within a REMAP as well as other aspects of the trial design and statistical analysis. A detailed glossary can be found in Section 1.2.

5.3.4. Randomization and Response Adaptive Randomization

Within a REMAP, participants will be randomly allocated to one or more interventions, with each intervention described within a domain. In this regard, a platform trial is no different to other forms of RCT in that randomization provides the basis for causal inference. Within the study, RAR may be applied. The exact design of RAR (including instances where no RAR is applied) will depend on specific domain, Strata, and intervention characteristics. Where RAR is applied the proportion of

participants who are randomized to each available intervention within a domain does not have to be fixed. RAR typically uses random allocation with a weighted probability for each intervention, with the weighted probability being proportional to the extent to which similar participants recruited earlier in the trial benefited or not from each particular intervention (Aikman et al., 2013, Angus, 2015, Berry, 2012, Carey and Winer, 2016, Connor et al., 2013, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016). If properly designed, RAR will result in participants within each particular Stratum having a greater probability of being randomized to interventions that are performing better within that Stratum. At the initiation of a new domain, or when a new intervention is added to a domain, the randomization proportion of all new interventions is balanced and only changes with the application of RAR. Any application of RAR takes into account uncertainty about treatment effect so as to avoid excessive variability in proportions generated by RAR until sufficient sample size has accrued.

The major consequence of RAR is that better therapies move through the evaluation process faster, resulting in trial efficiency gains (Berry, 2012, Connor et al., 2013). It is beyond the scope of this document to review in depth the growing literature about RAR. There are many methodological advances occurring and improved understanding of how best to apply RAR (Angus, 2015, Berry, 2012, Carey and Winer, 2016, Connor et al., 2013, Harrington and Parmigiani, 2016, Meurer et al., 2012, Park et al., 2016, Rugo et al., 2016). As data accrues, newly randomized participants are more likely to receive interventions from which they are most likely to benefit. This is a highly ethical fusion of trial science with continuous quality improvement and a learning healthcare system (Institute of Medicine, 2013). Assuming at least some interventions are better than others, patient outcomes within the trial population will be better than would have occurred with a fixed randomization proportion. It is also particularly relevant to the ethical conduct of trials that enroll severely ill patients where unanticipated increases in mortality have been seen, and to the conduct of trials during a pandemic in which there is in-built implementation of the therapies that are more likely to be beneficial during the trial. The simulations underpinning this platform trial demonstrate that, in instances where particular interventions are indeed superior to others, the use of RAR will, on average, result in fewer participants exposed to the less efficacious therapies and, thus, fewer deaths.

There are potential disadvantages associated with RAR (Viele et al., 2020, Proschan and Evans, 2020). It is intended that participating sites and trial investigators will be blind to the RAR proportions. One disadvantage is that, for interventions that are provided without blinding, the treating clinicians may be able to draw inference about the RAR proportions and, as a consequence,

draw inference about the interim standing of interventions that are being evaluated in the REMAP. This could have adverse consequences, including that clinicians may be influenced to not enroll participants within a domain but rather directly prescribe the treatment that they believe to be doing better rather than subject the patient to randomization. However, a number of factors mitigate this potential concern. First, it can be difficult to distinguish between patterns of sequential allocation status that are derived from fixed randomization proportions versus RAR. Second, maximum allocation proportions will be pre-specified to avoid extreme unbalance in proportions. Finally, for many conditions, team-based management means that an individual clinician will directly observe only a small proportion of all participants enrolled within the trial at each participating site.

Another disadvantage of RAR is that, under certain allocation rules, statistical power can be reduced. This concern is mitigated via pre-trial simulation to test the effects of different allocation rules. Furthermore, a REMAP that comprises multiple domains with multiple interventions within each domain will generally have higher, rather than lower, power as a consequence of the use of RAR. Finally, by deploying RAR rules to minimize the probability of exposure to inferior interventions, the design is intended to motivate embedding in clinical practice and facilitate patient satisfaction, thereby resulting in more rapid recruitment.

One specific concern about use of RAR, particularly for infectious diseases and during a pandemic, is that of temporal trends. Over time, there may be changes in patient mix, vaccination rates, outcomes, and standards of usual care. There is a risk that type I error can be inflated and that estimates of treatment effects can become biased. The statistical models used in this Platform incorporate a time variable that adjusts for such temporal trends, which has been shown to have low levels of type I error through extensive simulation. There are also developments in methods to improve transparency of reporting of concurrently randomized cohorts (Roig et al., 2022, Marschner and Schou, 2022, Dodd et al., 2021, Proschan and Evans, 2020).

5.3.5. Embedding

It is recognized that embedded trial processes may not be straightforward with many hurdles to overcome. However, there are several strategies that can be used to very tightly embed trial processes in daily clinical care operations. The effectiveness of strategies to achieve embedding may be evaluated, updated and shared with sites, taking into account different clinical processes at different sites. Strategies that have been found to be beneficial include: 1) leadership engagement; 2) embedding trial activities into routine care processes including with pharmacy operations; and 3) embedding the trial into the electronic health record (e.g., a COVID-19 ‘Intake Form’ that solicits

basic clinical information at hospital admission and includes a question about whether the patient is interested in participating in research studies). Wherever possible, trial treatment allocations should be integrated with electronic customized order sets produced at the point of delivery of care, which also include each site's local care standards for concomitant therapies. Approaches such as this allow clinical staff to follow their typical workflow using protocolized order sheets to govern many aspects of patient care and serves to enhance compliance with the interventions allocated by the trial. The ultimate intention of embedding is that recruitment occurs 24/7 and is dependent on the usual medical staff who are responsible for patient care.

5.3.6. Multifactorial

If the REMAP randomizes in more than one domain of care, it is termed 'multifactorial'. The number of domains available within the Platform at any time is determined by a combination of the interventions that are appropriate and amenable for evaluation within the REMAP and the available statistical power, as determined by the conduct of simulations. Bayesian models can evaluate possible treatment effects (superiority, efficacy, inferiority, equivalence, noninferiority, futility, and harm) within each regimen and then estimate the independent effect of each intervention by isolating the effect of each intervention across all regimens in which that intervention is included. The capacity to evaluate interventions within multiple domains, in parallel, may substantially increase trial efficiency.

An additional advantage of the REMAP being multifactorial is the capacity to evaluate interactions between selected interventions in different domains. Where pre-specified, on the basis of clinical plausibility, statistical models can evaluate whether there is interaction between interventions in different domains. Where no interaction is suspected, interactions are not evaluated as part of the *a priori* statistical model.

Although participants within a REMAP will, typically, receive treatment allocations for multiple domains the decision-making regarding other concomitant therapies will be made by the treating clinician. These treatment decisions will be recorded and may be analyzed using observational methods.

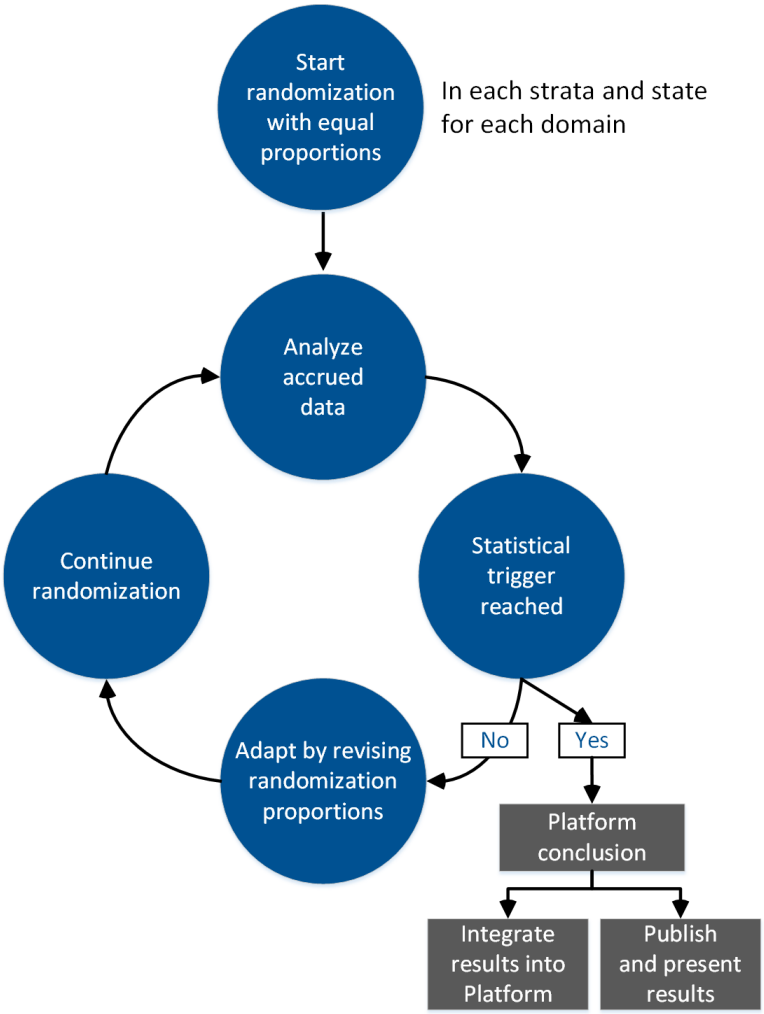
5.3.7. Adaptive

A feature of REMAPs is their ability to adapt over time on the basis of accumulating data. The nature of the adaptive analyses specific for this platform trial are described in Section 7 below.

5.3.7.1. *Analysis of data to reach conclusions*

The pathway for adaptation in response to each adaptive analysis is displayed in Figure 3.

Figure 3. Pathways for adaptation, and outcomes of adaptive analyses



5.3.7.2. *Analysis within and between strata and states*

Within REMAPs, frequent adaptive analyses are undertaken to evaluate the primary endpoint, *within one or more Stratum and within one or more States*. The statistical models for each Strata or State are able to 'borrow' information from adjacent Strata or States leading to the declaration of a Statistical Trigger in one, more than one, or all Strata or States. The extent to which borrowing occurs is dependent on the pre-specified structure of the model and the degree of statistical congruence of treatment effect between Stratum or States. Where treatment effects are divergent between Stratum or States there is less 'borrowing'. The capacity to evaluate strata or states is particularly important for interventions that might plausibly have differential, including opposite, treatment effects in different Strata or States (Evans et al., 2021, Finfer et al., 2004b, The Acute

Respiratory Distress Syndrome Network, 2000). In traditional trial designs, divergent treatment effects among sub-groups may cancel each other out and this is one plausible explanation for the trials that report no overall difference in outcome. It should be noted that Strata or States can be different for different domains and that Strata definitions can be changed over time.

5.3.7.3. *Frequency of adaptive analyses*

Adaptive analyses occur frequently throughout the lifespan of a REMAP, with the frequency being approximately proportional to the rate of recruitment.

5.3.7.4. *Advantages of adaptive analysis*

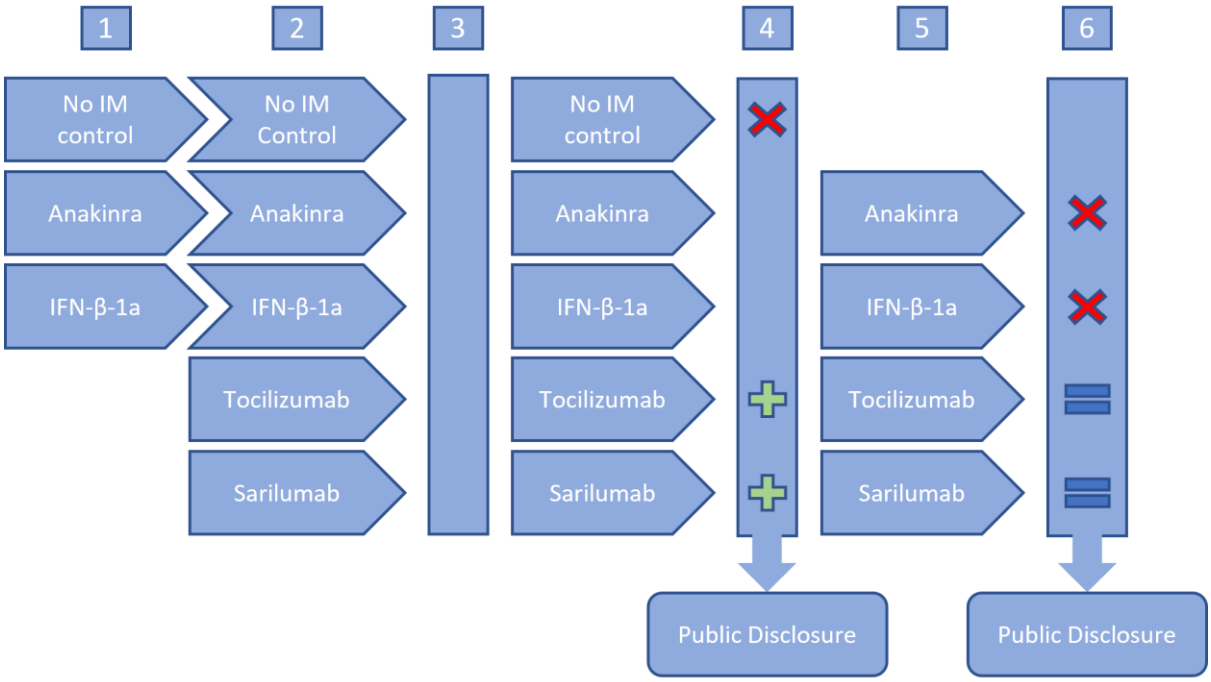
The major advantage of this type of analysis approach is that a conclusion is reached when there is sufficient information to support the conclusion, rather than when enrollment reaches a predetermined sample size. This approach allows a result to be obtained as quickly as possible with appropriate sample size. It also avoids indeterminate results by continuing randomization until a clear statistical threshold is achieved (Barker et al., 2009, Berry, 2012, Carey and Winer, 2016, Connor et al., 2013, Harrington and Parmigiani, 2016, Meurer et al., 2012, Park et al., 2016, Rugo et al., 2016).

5.3.7.5. *Substitution of new domains and interventions within the REMAP*

The REMAP design allows such trials to be 'perpetual'. In a REMAP, the sample size is not fixed; rather maximum use is made of the available sample and more questions may be asked for the same monetary investment (Aikman et al., 2013, Barker et al., 2009, Berry, 2012, Bhatt and Mehta, 2016, Connor et al., 2013, Meurer et al., 2012, Park et al., 2016). The only limit on the duration of a platform trial is the availability of ongoing funding, the availability of new interventions to evaluate, and that the disease continues to be a public health problem. The leadership responsible for the REMAP will develop appropriate processes for identifying and prioritizing the selection of new interventions and domains that are introduced progressively into the REMAP over time.

How the domains and interventions within a REMAP might evolve over time is depicted in Figure 4, using an example from the COVID-19 Immune Modulation Domain of REMAP-CAP.

Figure 4. An example of how the Platform may adapt over time, based on a domain of REMAP-CAP



1. Domain commenced with three interventions.
2. Two further active interventions added to domain.
3. Adaptive analyses performed on accumulating data and RAR proportions updated.
4. At an adaptive analysis, Tocilizumab and Sarilumab reached a Statistical Trigger for Efficacy compared to the 'no immune modulation' (IM) control. The control intervention was closed.
5. Recruitment continued to active interventions, utilising updated RAR proportions.
6. At an adaptive analysis, Anakinra reached a Statistical Trigger for inferiority, while Tocilizumab and Sarilumab reached a Statistical Trigger for equivalence. The IFN-β-1a intervention was closed for operational futility, due to low participation in this intervention.

5.3.8. Nesting of the REMAP within a Registry

The REMAP can also be nested within a registry, with the registry recording information for all participants who met eligibility criteria, or an expanded set of entry criteria, for the REMAP but who, for any reason, were not randomized. Information obtained from eligible but not randomized participants can be useful for evaluating the external validity of results and optimizing recruitment. Evaluation of non-randomized treatments received by all participants, both randomized and non-randomized, can be used to identify the consequences of natural variation in care so as to identify interventions that should be prioritized for evaluation by randomization within the REMAP (Byrne and Kastrati, 2013a). The design features of a REMAP and the conceptual advantages associated with each design feature are summarized in Table 2.

5.3.9. Platform

Platform trials simultaneously evaluate multiple potential therapies, where the focus is on finding the best treatment for the disease (Angus, 2015, Berry et al., 2015, Bhatt and Mehta, 2016, Carey and Winer, 2016, Harrington and Parmigiani, 2016, Park et al., 2016, Rugo et al., 2016). Thus, the goals of a platform trial are much more aligned with the goals of clinical care than a traditional, narrowly-focused phase III RCT of a single agent. All of the component design features of a REMAP have been used previously and have accepted validity. What is innovative and novel, for a REMAP, is the combination of all of these design features within a single platform combined with their use for phase III evaluations and by using embedding to integrate the trial within routine clinical care.

Table 2. Features of a REMAP that contribute to advantages of the design

	Efficient use of information	Safety of trial participants	Avoiding trial down-time	Fusing research with care	Determining optimal disease management	Self-learning healthcare system
Multifactorial	✓		✓	✓	✓	
Response Adaptive Randomization	✓	✓		✓		✓
Embedding				✓		✓
Frequent adaptive analyses	✓	✓			✓	✓
Analysis of strata	✓	✓			✓	
Evaluation of interaction		✓			✓	
Substitution of new interventions	✓		✓		✓	

6. OBJECTIVES

6.1. Primary objective

The primary objective of this Platform is, for hospitalized patients with acute respiratory tract infection, to evaluate the effect of a range of interventions on a composite of 90-day all-cause mortality and, among survivors, a daily ordinal scale of trajectory of illness and recovery to 28 days.

6.2. Secondary objectives

The secondary objectives of this Platform are to determine the effect of interventions on hospital length of stay (LOS) and 90-day mortality, as well as other domain-specific endpoints and, where feasible or specified in a DSA or RSA, survival, health related quality of life (HRQoL), and disability assessed after 180 days.

7. SUMMARY OF TRIAL DESIGN

7.1. Introduction

This is a REMAP that aims to evaluate many interventions across a number of domains. Frequent adaptive analyses will be performed. A Bayesian analysis method will be used to evaluate Statistical Triggers, as well as to inform the adaptive randomization strategy within each domain. Where it is anticipated that interactions between interventions in different domains may be likely, the statistical models will allow evaluation of such interactions. Where the statistical models evaluate such an interaction the models can incorporate the relative likelihood of such interactions, but with low prior probability in cases where it is biologically implausible for interactions to occur. Each intervention within each domain will be evaluated within prospectively defined and mutually exclusive Strata (sub-groups) of participants, but information from one Stratum may be used (via 'borrowing') to contribute to the analysis of the effect of that intervention in other Strata. An RAR algorithm will be used to increase the probability of participants being randomized to interventions that appear to be performing better at each adaptive analysis. Extensive simulation studies have been performed to define the type I error, power to detect specified differences, and demonstration of equivalence as well as a broad range of operating characteristics. It is planned that further simulation studies will be conducted in conjunction with consideration of the introduction of new interventions or domains or both into the REMAP. The intention-to-treat (ITT) principle will be used for all primary analyses.

7.2. Nomenclature

A specific set of nomenclature is used to categorize potential treatments evaluated and populations within a platform trial as well as other aspects of the trial design and statistical analysis. A detailed glossary can be found in Section 1.2. The following section can only be understood in the context of an understanding of the definition and meaning of these specific terms.

7.3. Study setting and participating regions

The Platform will recruit only participants who are admitted to hospital. It is intended that the trial will be conducted in multiple regions. A region is defined as a country or collection of countries with study sites for which an RMC is responsible.

Participating hospitals will be selected by an RMC on the basis of criteria including resources available to support research activities, and track record in conducting investigator-initiated multicenter trials.

There is no limit to the number of regions and number of participating sites. The current participating regions are listed on the trial website.

7.4. Eligibility criteria

The eligibility criteria for the Platform are applied at multiple levels. One level is that there are inclusion and exclusion criteria that determine eligibility for randomization within the Platform. Another level is that, once eligible for inclusion within the Platform, additional criteria (typically exclusion criteria) are applied that are specific to each domain. Finally, intervention-level eligibility criteria *may* be applied for interventions within a domain. A patient is eligible for inclusion within a domain when:

- All Platform inclusion criteria are met
- None of the Platform exclusion criteria are met
- Domain-specific eligibility criteria are met
- The patient is eligible for at least two interventions within a domain

As such, the key “inclusion criteria” for being eligible for a domain are that the patient is eligible for the Platform.

Criteria for inclusion in the Registry, in which patients do not receive any randomized intervention, may be broader than the entry criteria for randomization within the Platform and are specified in the Registry Appendix, where applicable (i.e., it is only a subset of ‘registry-eligible’ patients who are eligible for randomization within the Platform).

7.4.1. Platform Inclusion Criteria

In order to be eligible to participate in this trial, all patients must meet the following criteria:

1. Hospitalized patient
2. Acute respiratory tract infection
3. Aged 28 days or older

7.4.2. Platform Exclusion Criteria

A potentially eligible patient who meets any of the following criteria will be excluded from participation in this trial:

1. Death is deemed to be imminent and inevitable during the next 24 hours AND one or more of the patient, substitute decision maker or attending physician are not committed to full active treatment.
2. Patient is expected to be discharged from hospital within the next 24 hours
3. Previous enrollment in this Platform within the last 90 days

7.4.3. Domain- and Intervention-Specific Entry criteria

Each domain may specify domain-specific eligibility criteria. Patients who fulfill the overall Platform eligibility criteria will be assessed for enrollment into all domains that are active at a site. The additional eligibility criteria that are specific to a domain are provided in each DSA.

In addition, intervention-level eligibility criteria may be applied. Where a participant meets an exclusion criterion for one or more interventions within a domain, but there are at least two interventions within that domain for which the patient is eligible, the patient will be randomized between the remaining interventions that they are eligible for.

7.5. Interventions

7.5.1. Domain-Specific Information

All information related to the background, rationale, and specification of interventions that will be administered within the trial, and applicable states and strata, are located in the DSAs. The minimum number of interventions within a domain is two and the maximum number is limited only by statistical power. Each RMC will select the interventions that will be available within a domain that will be offered to participating sites in that region but the default position is that all interventions that are available and feasible in that region or country should be offered to sites. Individual

participating sites will select the interventions within a domain that will be available at their site with the default position being to participate in all available interventions. The randomization program will only provide treatment allocations that are permitted at each participating site. This allows interventions that are not necessarily available in all regions, for example because of licensing reasons, to be included within the Platform. Within the context of comparative effectiveness research, this also allows sites to determine the interventions that are within their usual or reasonable spectrum of care. However, the viability of a domain is dependent on at least one intervention being available at a substantial majority of participating sites. This level of 'connectedness' is necessary for the validity of the statistical models that are used to analyze trial results.

7.5.2. Treatment allocation and Response Adaptive Randomization

RAR may be used to vary the proportion of participants who are allocated randomly to each available intervention. Randomization occurs at the intervention level within a single domain. The proportion of participants who receive a specified intervention will be determined by a weighted probability, with that probability being determined by the probability of that intervention being the optimal intervention within the domain, taking into account all accrued data. RAR is intended to result in participants having a higher probability of being randomized to interventions that are performing better.

The proportions that are specified by RAR are determined by analysis of the available data informing the primary outcome measure in participants after at least 28-days of follow-up from the time of randomization. The same statistical model will be used to both analyze the results of the trial as well as specify the randomization proportions, acknowledging that 90-day follow-up is required for full primary outcome results reporting.

RAR weights reflect the probability that each particular intervention is the most effective in a given domain over all possible interventions within that domain in each stratum. The probability an intervention is optimal reflects not just the point estimate of difference in outcomes, but also the uncertainty around that estimate. At initiation of a new domain, the proportion of participants allocated to each intervention is balanced (i.e., all interventions have equal proportions), unless otherwise specified in a DSA. In domains where interventions are nested, initial randomization proportions may be adapted to account for the sharing of information between the interventions, resulting in non-equal randomization proportions. RAR proportions are then updated at the first adaptive analysis and at all subsequent adaptive analyses. When sample sizes are small, such as at

the initiation of a domain, credible (probability) intervals are wide and therefore randomization proportions remain close to being balanced among all regimens (i.e., randomization weights are weak and allocation remains close to balanced). Unless otherwise specified in a DSA, when a new intervention is added to an existing domain it will commence with balanced randomization (equal to 1/K where K is the number of interventions in the domain) and the randomization proportions will be updated with each subsequent adaptive analysis.

As data accrues and sample sizes increase, if the probability that an intervention is the optimal intervention within a domain becomes large, but not large enough to claim superiority, the randomization proportions will be capped. This is done because interventions are provided on an open-label basis and extreme allocation probabilities would be at risk of allowing clinicians who recruit participants to draw inference about the effectiveness of individual interventions or regimens. Additionally, in some scenarios extreme randomization probabilities may result in lower power in the domain and a less efficient trial design. For domains with a control arm, the control arm randomization probability is constrained to be between 25% and 75%. For domains without a control arm, no formal minimum or maximums are set unless specified in the DSA. For domains with only two available interventions, the default is that RAR will not be applied, unless specified in the DSA.

Some domains may have more than two interventions and it is possible that participant- or site-level characteristics may result in one or more interventions within a domain being inappropriate for an individual participant (for example, known intolerance to one of the interventions or a device that is necessary to deliver an intervention being unavailable). Where a participant is unable to receive one or more interventions, but there are still two or more available interventions, random allocation will still be performed using RAR. However, interventions that are not available will be ‘blocked’ and the remaining RAR proportions will be divided by one minus the sum of the unavailable proportions and applied to the available interventions.

7.5.3. Adaptation of Domains and Interventions

Over the lifetime of this platform trial, new interventions will be added to existing domains and new domains initiated, including domains that are planned for activation in the event of a pandemic. The addition of interventions within existing domains, and the creation of new domains, will be considered according to a set of priorities and contingencies developed by the ITSC and are dependent on existing or new clinical need and there being sufficient statistical power available

within the Platform. All new interventions and domains will be subject to ethics and regulatory approval prior to initiation.

Interventions that are identified as being inferior, harmful, or futile will be removed from a domain, with or without replacement, as appropriate. If all interventions are identified to have equivalence or to be noninferior to each other, the ITSC will consider options that include cessation of the domain or continuation of the domain with a smaller delta.

7.5.4. Principles for new domain stages

After completion of an initial stage of a domain in the Platform, new questions or hypotheses may arise from the analysis of the initial domain stage or externally from the Platform. To address these new questions, domains may be re-launched in the Platform with modified designs. Design modifications may be made to domain-specific endpoints, eligibility criteria, interventions, or statistical triggers.

When a domain is re-launched, the data from earlier stages of the domain may be incorporated into the analysis of the re-launched domain. There are multiple ways to incorporate the data from the initial stage:

- No borrowing of the data from previous stages.
- Full borrowing (pooling) of data from previous stages. With this approach, there may be a modification of the threshold applied to statistical triggers to decrease the probability of spurious conclusions.
- Dynamic borrowing of data from previous stages.
- Fixed borrowing (down-weighting) of data from previous stages.

When investigators are unblinded to the data from a previous stage of the domain and it is incorporated into later stages, there are statistical risks of potential bias and inflation of type I error rates. Simulations of the new domain stage are critical for quantifying the risk-benefit trade-off of incorporating the previous data. Simulations can be performed to address the following questions that may be relevant to the design of relaunched domains:

- Impact of a modified endpoint on power/type I error in a relaunched domain.
- Impact of borrowing strategy on power/type I error of a domain.
- Sample size required to reach statistical triggers within the re-launched domain.
- The need for a minimum sample size within the relaunched domain

- Impact of modified entry criteria on patient recruitment

7.6. Endpoints

The primary outcome for this Platform will apply to all domains, unless otherwise specified in a DSA. Secondary Platform outcomes are provided in this Core Protocol below. Secondary outcomes specific to individual domains are provided in the relevant DSAs. The primary endpoint (or the endpoint that is used for RAR) may be modified during a future pandemic.

7.6.1. Primary Endpoint

The primary endpoint, named Survival and Recovery Trajectory, will be a composite of 90-day all-cause mortality and, among survivors, a daily ordinal scale analyzed as a trajectory of illness and recovery to 28 days. This hierarchical ordinal scale is a composite of:

- Landmark mortality at Day 90 post-randomization,
- Among Day-90 survivors, their daily respiratory support level as defined by position on a five-category ordinal scale:
    - Hospitalized on extracorporeal life support (ECLS) or invasive mechanical ventilation (IMV)
    - Hospitalized on non-invasive ventilation or high-flow oxygen*
    - Hospitalized on low-intensity oxygen
    - Hospitalized, no oxygen
    - Discharged from index hospitalization

*High-flow oxygen defined as a fractional inspired oxygen concentration of 0.4 or higher and with flow rate of at least 30 liters per minute (or at least 2 liters per minute per kilogram of bodyweight in children less than 15 kilograms).

Mortality is defined as death from any cause before the end of study day 90. The trajectory of patients will be modelled through a Markov longitudinal proportional odds model, using daily ordinal scale categories. The estimand is the transition between categories and the relative time spent in each category, modelled to produce an odds ratio from an ordinal logistic model, incorporating covariate adjustment as described in Section 7.8.3.

This endpoint is designed to encompass all illness severity states, and builds on our experience with the distribution and power of the primary endpoints used in previous versions of this Core Protocol and the Pandemic Appendix to the Core Protocol. We acknowledge mortality is tied to a longer time

frame than the ordinal scale, however integrating 90-day mortality with a shorter-term outcome is patient-centered, allows continuity with previous versions of the Core protocol and the Pandemic Appendix to Core, and improves statistical power. 90-day mortality will be hierarchically integrated with the daily ordinal scale so that 90-day mortality will be deemed the worst possible category, regardless of prior trajectory.

7.6.2. Secondary Endpoints

A set of generic secondary endpoints will be evaluated in all domains. Additional secondary endpoints may be specified for a domain within the DSA. Some domain-specific secondary endpoints may be specified as Key Domain-Specific Endpoints and will be interpreted in conjunction with the primary endpoint in determining the overall effectiveness of interventions. DSAs dated before this Core Protocol amendment will additionally report the pre-specified endpoints as indicated in their respective documents and previous versions of the Core Protocol (available on the trial website).

The generic key secondary endpoints for the trial are:

- Hospital length-of-stay
- Mortality, censored at 90 days

The index hospital admission is defined as continuing while the participant is admitted to any healthcare facility or level of residence that provides an equivalent or higher level of care than that corresponding to where the participant was enrolled. Participants who have been, and still are, admitted to a healthcare facility 90 days after enrollment are coded as being alive. The secondary outcomes will have statistical testing performed.

There will be a list of tertiary outcomes where no formal hypothesis tests will be performed. These may include:

- Domain-specific efficacy outcomes, where applicable
- Domain-specific safety outcomes, where applicable
- Hospital survival
- 28-day survival
- Organ-support free days at day 28
- Vasopressor-free days at day 28
- Ventilator-free days at day 28
- Progression to IMV/ECLS/death

Additional outcomes that will be collected, where feasible, will comprise:

- Survival at 180 days after enrollment (where feasible, refer to relevant regional RSA)
- HRQoL at 180 days after enrollment using the EQ5D-5L or EQ-5D-Y and PedsQL-SF15 in participants aged less than 18 years (where feasible, refer to relevant regional RSA)
- Disability status measured at 180 days after enrollment using the WHODAS 2.0, 12-item instrument (where feasible, refer to relevant regional RSA) in those aged 18 or older

7.7. Bias Control

7.7.1. Randomization

Randomization will be conducted through a password-protected, secure website using a central, computer-based randomization program. Randomization will be at the patient level and occur after data have been entered into the secure randomization website. RAR will occur centrally as part of the computerized randomization process. Sites will receive the allocation status and will not be informed of the randomization proportions. RAR proportions will be determined by the SAC at relevant adaptive analyses and provided to the administrator of each study database that is used for randomization, who will update the RAR proportions.

7.7.2. Allocation concealment

Allocation concealment will be maintained by using centralized randomization that is remote from study sites.

7.7.3. Blinding of treatment allocation

The default position within the Platform is that treatments determined by randomization will be provided on an open-label basis. However, the blinding of treatment status is not precluded within the Platform. If required, details related to blinding of interventions will be specified in the DSAs.

7.7.4. Blinding of outcome adjudication

The primary outcome is not subject to ascertainment bias.

7.7.5. Follow up and missing data

Regional trial management personnel and Data Coordinating Centers (DCC) will perform timely validation of data, queries and corrections. Any common patterns of errors found during quality control checks will be fed back to sites. Missing data will be minimized through a clear and

comprehensive data dictionary with online data entry including logical consistency rules and validations. If values necessary for the Bayesian modelling of the primary endpoint and the RAR are missing they may be imputed using available data. Additional details are provided in the Statistical Analysis Appendix.

7.7.6. Utilization of Clinician-Assigned Treatment

Treatment guidelines may change due to new evidence (either internal or external) of effective (or ineffective) therapies in one of the Platform-defined Strata. This evolving standard of care can usually be captured with the time adjustment in the model when the new treatment is widely available (e.g., steroids in COVID-19). However, when treatment guidelines suggest a therapy that is sparsely available and therefore given to a select population of patients, an additional adjustment may be necessary to properly control for this change in baseline treatment.

One option is for the adjustment to be made through a covariate that captures the clinician-assigned treatment for patients at baseline. Specifically, the Platform would capture the clinician-assigned therapy within a specified timeframe (e.g., at baseline or within 48 hours of randomization). This data would be used to define a covariate for whether the patient received the therapy or not (definition may vary based on the details of the therapy). Because previous patients in the Platform will not have a value recorded for this covariate, an operational decision will need to be pre-specified about how to label patients previously enrolled in the Platform. The details for how the covariate will be modeled in the primary analytic model is detailed in the Current State Document.

The intention of this covariate adjustment is to capture any baseline differences between patients receiving the therapy versus those that do not. However, because the treatment allocation is not randomized but instead clinician-determined, the effect estimated in the model will not be reported as a causal effect due to potential confounding.

7.8. Principles of Statistical Analysis

7.8.1. Preface

The purpose of this section of the protocol is to introduce and summarize the statistical methods that will be used to analyze data within the platform. This section is intended to be accessible to individuals with an understanding of common clinical trial designs and classical frequentist analytical methods but without necessarily having advanced training in Bayesian statistics. Interpretation of this section also requires an understanding of the meaning of specific terms for which definitions are provided in the glossary (see Section 1.2).

A formal description of the adaptive Bayesian data analysis methods fundamental to the design of this Platform, which assumes substantial familiarity with Bayesian calculation of posterior distributions conditioned on observed data, is located in the Statistical Analysis Appendix. There is some limited overlap between these two documents so that each may serve an appropriate audience as a standalone description of the statistical methods.

The structure of the analytic model is reviewed and, if appropriate, updated prior to each adaptive analysis. The specifications for each adaptive analysis are contained within a separate document, entitled 'The Current State'. Modifications to the Current State are operational decisions that reflect the need for updates to the statistical model that occur as the Platform evolves. It is noted that during the COVID-19 pandemic, a Pandemic Appendix to the Core Protocol was applied to adapt the platform for COVID-19. The combination of the Core Protocol and the Pandemic Appendix to the Core Protocol led to the use of two statistical models: the Interpandemic Model and the Pandemic Model. This version of the Core Protocol specifies a merger of these two models. This model may also incorporate the Ventilation Domain which, in its DSA, had specified a separate model for the evaluation of that domain.

7.8.1.1. *Transition between versions of the Core Protocol*

It is acknowledged that there will be a period of time over which participating sites and regions transition from the previous version of the Core Protocol to this version of the Core Protocol. This occurs because the date of approval of a protocol amendment will be different in different locations. During this time, the Primary Statistical Model used for analysis may switch from that described in the previous version of the Core Protocol to a model described in this version of the Core Protocol. The timing of implementation of a new statistical model will be determined by the ITSC in association with the SAC, but will not occur until approvals of this version of the Core Protocol commence. During the initial period between first approval of the updated version of the Core Protocol and the implementation of a new statistical model, statistical analyses will continue to occur using the preceding statistical model(s).

Following implementation of the new statistical model, it is possible that some participating sites will not yet have approval for this version of the Core Protocol. These sites will continue to recruit participants using the version of the Core Protocol approved at those sites (including eligibility criteria), but all data will be analyzed using the Primary Statistical Model that is operative at that time, as only one model can exist at any one time and the Primary Statistical Model utilizes all data in the Platform. The Current State document that describes the Primary Statistical Model and the

process for transitioning between protocols. This document will be updated as an operational decision.

7.8.2. Introduction

Within the Platform, two or more interventions within a domain are evaluated and sequential Bayesian statistical analyses are used over time to incorporate new trial outcome information to determine the probability distribution for an intervention in relation to the primary outcome that corresponds to a pre-specified statistical threshold, referred to as a Statistical Trigger.

Every participant will be allocated a set of interventions, comprising one intervention from each domain for which the participant is eligible. The combination of interventions to which a participant is allocated comprises the regimen. Participants will be classified by membership in different populations defined by one or more Strata. The unit-of-analysis for a domain is the most granular level, defined by one or more Stratum or a State, within which the treatment effect of interventions within that domain may vary in the statistical model. Participants are also classified by the criteria that determine eligibility for each domain (see PANDA).

Inference in this Platform is determined by analyses using pre-specified statistical models that incorporate variables such as region, country, time periods, and age to adjust for heterogeneity of enrolled participants that might influence the primary outcome. These models incorporate variables that represent each intervention allocated to participants and possible interactions between interventions in different domains. The efficacy of each intervention within a domain may be modeled as not varying in any of the Strata, or possibly varying in one or more of the different Strata in the Platform. Where the efficacy of each intervention within a domain is modeled as possibly varying, borrowing between Strata is permitted. The unit-of-analysis that will be modeled may comprise the entire population (i.e., no categorization by Strata is applied) or may be defined by one or more Stratum. The unit-of-analysis and whether borrowing can occur between Strata is pre-specified for each domain in the relevant DSA.

Whenever a model reaches a predefined threshold for an intervention with respect to the primary endpoint, this is termed a Statistical Trigger. At any given adaptive analysis, a Statistical Trigger may be reached for all participants, or for one or more Stratum or State. Statistical Triggers will be reviewed by the DSMB in the context of a thorough review of the data, including an evaluation of the proportion of patients for whom monitoring of variables that contribute to the model has been completed, and totality of evidence. Where no compelling reason exists not to reach a conclusion regarding that question, the result that has led to a Statistical Trigger will be specified to be a

Platform Conclusion. The declaration of a Platform Conclusion will lead to notification to the ITSC and the appropriate modification of the interventions available within that domain. A Statistical Trigger can be considered as a mathematical threshold, whereas a Platform Conclusion is a decision regarding one or more interventions within a domain. As there may be more patients recruited and further outcome data incorporated after the data is analyzed and available to the DSMB for confirming a Statistical Trigger, the data that is subsequently publicly reported may marginally differ.

7.8.3. Target populations (strata and states) and implications for evaluation of treatment-by-treatment and treatment-by-strata interactions

7.8.3.1. *Introduction*

In a clinical trial there are many different potential participant-level covariates. A covariate can be a demographic variable that remains unchanged throughout the trial (i.e., age at enrollment or sex) or a variable representing the severity or course of the disease that can vary over time (i.e., it can be assessed at the time of enrollment and at other times after enrollment during the course of the illness). In this platform there are two special roles for a subset of these potentially time-varying covariates.

First, covariates determined at the time of enrollment that are identified in the design as possibly having differential treatment effect (i.e., interventions may have differential efficacy for the different levels of the covariate) are referred to as Strata. Strata are used to define the unit-of-analysis for a domain within a model.

Second, within this REMAP there is interest in studying domains that are relevant for a target population or defined disease state that may be present at the time of enrollment for some participants, may only occur after enrollment for other participants, or may never occur for another set of participants. This disease state could be identified by the same covariate that might also have been used to define a Strata (but doesn't have to have been). In this regard, the concept of 'State' is used to define participants with characteristics that define a target population that will be evaluated by a domain, analyzed within the Platform, and for which the characteristics can be present at the time of enrollment or may develop after the time of enrollment. State can also be used to define the unit-of-analysis for a domain within the model.

The appropriate statistical handling of the analysis of patients who become eligible for a domain as a consequence of entering a State, after the time of enrollment, requires the use of models that take into account that the likelihood of entering the State after enrollment may have been influenced by

the allocation status for other domains that specified the initiation of interventions that commenced at the time prior to entry into the State.

7.8.3.2. *Stratum*

A covariate in the Platform that can be used as a unit-of-analysis within a Bayesian statistical model that allows for the possibility of differential treatment effects for different levels of the variable is referred to as a Strata. The covariate is classified into mutually exclusive and exhaustive sets for analysis of treatment effect, as well as for defining separate RAR. The criteria that define a Stratum are based on a characteristic that is present at or before the time of enrollment. The current Strata utilized in the Platform are described in the PANDA.

7.8.3.3. *Treatment-by-strata interactions: borrowing between strata*

Where specified in the statistical model, the treatment effect of an intervention is allowed to vary between different Strata. A Bayesian Hierarchical Model (BHM) is used for all treatment-by-Strata interactions. In the BHM a hyperprior is used for the differing treatment effects across Strata. The standard deviation of the hyperprior, gamma, is a modeling starting estimate for the variation in the magnitude of the difference in treatment effects between Strata. By default, the starting estimate of the difference is zero. The gamma parameter influences the extent to which the treatment effect of different interventions is permitted to vary between Strata. At the commencement of a model, the gamma parameter must be set, for each domain-Strata pair.

In this Platform, various options are permitted with respect to specifying the gamma parameter for each domain-strata pair. Gamma may be set to zero. The effect of this is that the treatment effect of an intervention is not permitted to differ between specified Strata, and the unit-of-analysis is not sub-divided according to the Stratum variable. If gamma is set to zero for all Strata for a domain, the unit of analysis is all patients randomized in that domain. At the opposite extreme, gamma can be set to infinity. In this situation, treatment effect is evaluated separately and independently in each Stratum (with no borrowing between Stratum). Gamma may also be set to a defined number between zero and infinity. This specified value for gamma places a constraint on the variance of the difference in treatment effect in different Stratum but permits the model to estimate treatment effect in one Stratum by borrowing from another Stratum. Borrowing occurs to the extent that it is supported by the accumulated data, but the setting of gamma influences the amount of borrowing and how quickly borrowing is able to occur. The value of gamma chosen is determined by simulations to achieve a compromise between type I and type II error in baseline scenarios that assume either equivalence or superiority, and may relate to the expected consistency (or lack

thereof) in treatment effect across Stratum. Where a value for gamma is not specified, the default value of gamma will be 0.15. Any alternative gamma that will be set, and hence the unit-of-analysis, for each domain-Strata pair will be specified in each DSA.

The specification of gamma determines the unit of analysis in the model and the extent of borrowing. For each domain-Strata pair, the unit of analysis can be all patients (gamma = zero), each Stratum with borrowing (gamma default = 0.15), or each Stratum separately (gamma = infinity).

7.8.3.4. *Timing of randomization and revealing of allocation status*

Several different scenarios are recognized that represent different combinations of randomization within a Stratum or a State and by the options for the time (at enrollment or later) at which administration of the allocated intervention is commenced.

At the time of enrollment, all participants are randomized to one intervention in each domain for which the participant is eligible for at enrollment. The patient may be randomized more than once, depending on progression of patients through different States (see PANDA).

For participants who, at the time of enrollment, are eligible for a domain and for which the intervention will be commenced immediately, the allocation status is revealed immediately and the participant then commences treatment according to their allocated intervention. This is referred to as **Randomization with Immediate Reveal and Initiation**.

In circumstances where the participant is eligible for inclusion in the Platform but is not eligible for a given domain at the time of enrollment but might become eligible pending further information or a change in their condition, the participant's allocation status is revealed only if and when the patient becomes eligible. This is referred to as **Randomization with Delayed Reveal**.

Another situation applies when eligibility is determined by information that relates to the condition of the patient at the time of initial assessment of eligibility and is relevant to determination of eligibility but is not known until later. In this circumstance, the participant's allocation status can be revealed when the additional information becomes available. Examples of this type of information include the results of microbiological tests and the outcome of a request for consent. Information related to the safety of an intervention in individuals that may change between the time of initial assessment of eligibility and initiation of an intervention may also be reassessed and be used to determine if an allocation status will be revealed. Where initiation of the intervention is deferred pending availability of this additional information, this is referred to as **Randomization with**

Deferred Reveal. It is noted that submission of this information regarding microbiological results, consent, or safety information occurs without knowledge of allocation status.

Variation in relation to the timing of revealing and initiation of an intervention has implications to the treatment-by-treatment interactions that are potentially evaluable. Analysis of participants who are enrolled in one or more domains on the basis of Randomization with Immediate Reveal can be conducted within a State, for which membership occurs for at least some participants at the time of enrollment. However, the analysis within this State will also include participants who are enrolled in the same domain on the basis of Randomization with Delayed Reveal with their eligibility for the act of revealing allocation status being defined by progression to the same State at some time-point after enrollment. Participants who are randomized within such a domain but never enter a State that corresponds to eligibility for a domain never have their allocation status revealed and do not contribute to the analysis of treatment effect for interventions in that domain. In this regard, the ITT principle is not violated as the allocation status of such participants is never revealed. The models that are used to provide statistical analysis of the effect of an intervention within a domain that is contained wholly within one State are not able to evaluate interactions with interventions in domains that are defined in different States.

The final scenario to consider involves participants who are enrolled in one or more domains on the basis of Randomization with Deferred Reveal within a Stratum. For such participants, their allocation status is revealed at, or close to, the time of deferred initiation of the intervention, when additional information necessary to establish eligibility has become available but relates to information that applies at baseline. Participants in this category are analyzed within stratum in an ITT fashion. As such, the model allows evaluation of interactions with treatments in other domains that share the same stratum. Within such a domain, it can be assumed that there will be some participants who are never eligible to commence receiving the intervention (for example, due to death, or never reaching the defined criteria for the intervention to be commenced) and do not receive the intervention. However, all participants who have an allocation status revealed, even if the intervention is never administered, are analyzed according to and in compliance with the ITT principle.

7.8.3.5. *Treatment-by-treatment interactions*

Where specified in the statistical model, the treatment effect of an intervention is allowed to vary depending on treatment allocation in another domain (i.e., allow evaluation of treatment-by-treatment interaction). A BHM is used for all treatment-by-treatment interactions. In the BHM, a hyperprior is used for the differing treatment-by-treatment interaction effects. The standard

deviation of the hyperprior, lambda, is a modeling starting estimate for the variation in the magnitude of the difference in treatment effect dependent on an intervention allocation in another domain. By default, the starting estimate of the difference is zero (i.e., no interaction). The lambda parameter influences the extent to which the treatment effect of different interventions is permitted to vary dependent on intervention allocation in other domains. At the commencement of a model, the lambda parameter must be set, for each domain-by-domain pair.

In this Platform, only three options are permitted with respect to specifying the lambda parameter for each domain-domain pair. Firstly, lambda may be set to zero. The effect of this is that there are no treatment-by-treatment interactions being evaluated between interventions in those two domains. Alternatively, lambda may be set to a defined number between zero and infinity. This specified value for lambda places a constraint on the variance of the difference in treatment-by-treatment interaction. Borrowing occurs to the extent that it is supported by the accumulated data, but the setting of lambda influences the initial amount of borrowing and the degree of borrowing as data accumulates. The value of lambda that has been chosen has been determined by simulations to achieve a compromise between type I and type II error in baseline scenarios that assume either no interactions or moderate interactions exist. Where a value for lambda is specified in the model, in this REMAP the value of lambda will be 0.075. The third choice is to allow no borrowing of the treatment-by-treatment interactions. This is equivalent to selecting a lambda of infinity. This choice would be the most aggressive choice in estimating treatment-by-treatment interactions. The lambda that will be set for each domain-domain pair is specified in each DSA.

The number of Strata (both across the platform and domain-specific strata) has important implications for statistical analyses, statistical power, and operational aspects of the platform, such as application of RAR. It is permitted that treatment-by-treatment interactions can be evaluated in the Primary Statistical Model, with statistical triggers available for combinations of interventions specified in different domains. However, when such interactions are specified, statistical triggers must be evaluated at the most granular level, i.e., all Strata that apply within a domain must also be applied in all other interacting domains. For example, if the unit-of-analysis for Domain A specifies two Strata (X1 and X2) and Domain B specifies two different Strata (Y1 and Y2) and an interaction was prespecified between Domain A and Domain B, treatment effect in domain A must also be evaluated for the Strata defined by the combination of Strata A and Strata B (e.g., X1Y1, X1Y2, X2Y1, and X2Y2), even if the Y Strata is not clinically relevant to Domain A. The need to specify the strata structure at the most granular level also reduces the number of patients in each ‘cell’ of the Strata matrix with an unfavorable effect on statistical power. As such, decisions to pre-specify

treatment-by-treatment interactions across domains, particularly if different Strata are applied in each domain, should only occur in association with simulations that evaluate the impact of such a decision on statistical power and operational conduct of the platform.

7.8.3.6. *Nested analysis of interventions within a domain*

Within domains in which there are three or more interventions, some interventions may be more likely to have a similar treatment effect. For example, the interventions within a domain may comprise a 'no intervention' option and two doses or strategy of administration of the same intervention, or two or more interventions within a domain may belong to the same class of drug which differs to the class of drug of one or more other interventions in that domain.

In situations in which interventions may be more similar than others, the model may nest the more similar interventions within a higher-level intervention category that comprises all the interventions deemed similar. In this situation, and to evaluate the occurrence of a Statistical Trigger, there are two approaches for analysis. Firstly, all patients receiving the nested interventions, treated as a single combined intervention, are compared with all other interventions in the domain. Secondly, all interventions are modeled individually. In this analysis, the interventions within a nest are modeled using a BHM incorporating the nesting structure. The BHM has a hyperprior specified for the shrinkage across interventions within the nest. This analysis will compare all interventions within a domain to all other interventions. This BHM analysis is used for the RAR assignments.

Whether nested analysis will be performed and, if so, the membership of category of more similar interventions will be specified in the DSA.

7.8.3.7. *Pre-specified subgroup analysis after achievement of a Platform Conclusion*

Following the achievement of a Platform Conclusion it is permissible for additional sub-group analyses to be conducted. The variables that specify such sub-groups are outlined *a priori* in each DSA. These variables are different to those that define Strata or States in the model and are not used in determination of a Statistical Trigger or RAR for that domain.

All such analyses will only be conducted following the determination of a Platform Conclusion and, although reported, such analyses are always regarded as preliminary. Following a Platform Conclusion, the results of a pre-specified subgroup analysis may be used to make changes to the model and, where appropriate and to an appropriate degree, data derived from the Platform can be used to set the prior distribution at the commencement of the new model.

7.8.4. Bayesian Statistical modeling

Inferences in this trial are based on a Bayesian statistical model that will calculate the probability of Statistical Triggers of the interventions (known as a posterior probability distribution) within a unit-of-analysis that is defined by one or more stratum, taking into account the evidence accumulated during the trial (based on data on the outcomes of participants) and on assumed prior knowledge (known as a prior distribution). For the evaluation of the main effects of interventions within a domain (and evaluation of regimens) the default design assumes that parameters in the model have uninformative prior distributions at the first adaptive analysis. This means that any subsequent Platform Conclusion is not capable of being influenced by any discretionary choice regarding the pre-trial choice of prior distribution (i.e., it is the most conservative approach, making no assumptions regarding the prior distribution). At each subsequent adaptive analysis, the prior distribution is determined by all accumulated data available at the time of the adaptive analysis. The Bayesian approach is seen as continually updating the distribution of the model parameters.

It is not precluded that, under certain circumstances, such as during a pandemic and where there was strong prior evidence along with an ethical imperative to evaluate a particular choice of therapy, that the design could allow an informative prior to be used for the analysis of results from the trial. It may also be permitted to use an informative prior when data that is incorporated in the informative prior is derived from patients already randomized within this Platform. If informative priors are used this will be specified in the relevant DSA.

The study design can use informed priors to guide some elements of the design, such as for the evaluation of interaction terms, and will be described in the Current State document. As outlined above, gamma will be set to allow and influence the evaluation of treatment-by-strata interactions and lambda will be set to allow and influence the evaluation of treatment-by-treatment interactions.

This method of statistical analysis differs from conventional (frequentist) trials. Frequentist statistics calculate the probability of seeing patterns in the data from a trial if a hypothesis is true (including patterns not observed). This approach relies on assumptions about frequency distributions of trial results that would arise if the same trial were repeated *ad infinitum*. Thus, it requires specific sample sizes, which in turn requires pre-experiment assumptions regarding plausible effect sizes and outcome rates. Although many clinicians are comfortable with this approach, the pre-trial assumptions are frequently incorrect, and the design lacks the flexibility either to easily address the complex questions more reflective of clinical practice or to make mid-trial corrections when the pre-trial assumptions are wrong without concern that the integrity of the final analysis is violated. To

allow increased flexibility and yet still generate robust statistical inferences, this platform relies on an overarching Bayesian, rather than frequentist, framework for statistical inference.

A Bayesian approach calculates the probability a hypothesis is true given the observed data and, optionally, prior information and beliefs. The advantage of this approach is that, as more data are accrued, the probability can be continually updated (the updated probability is called the posterior probability). In this trial, frequent adaptive analyses will be performed, creating a very complicated sample space, and hence the Bayesian approach is a very natural one for these adaptive designs. The characterization of the risk of false positive error, or power, are done through Monte Carlo trial simulation. In contrast to frequentist confidence intervals, Bayesian analyses return probability estimates that are directly interpretable as probabilities that statements are true (such as the probability that one intervention is superior to another).

A number of variables are incorporated into the statistical model so as to provide 'adjustment'. Some candidate variables for which such adjustment will be made include: the country in which a participant is treated; changes in outcome that occur over time (era); Stratum and State at enrollment; and age. Changes to these covariates may occur with accruing data, specifically as it relates to different domains of interventions, Strata or States, and will be pre-specified in operational documents. Given the analytic approach to the primary outcome, incorporating assessments of non-proportionality of treatment effects across the ordinal scale will be in the relevant statistical analysis plans.

The main effect in the model is the treatment effect of each intervention. Each pre-specified Stratum, combination of Strata or State (where eligibility is defined by a State) is analyzed separately, where relevant, but the model captures the commonalities across such sub-groups. Additionally, and where specified, the statistical model allows evidence relating to the effectiveness of an intervention in one Stratum to contribute (via 'borrowing') to the estimation of the posterior probability in other Strata, but this only occurs to the extent that treatment effect is similar in different Strata.

When a Platform Conclusion is achieved, the results derived from the model, including any contribution from borrowing, will be reported. It is acknowledged that the estimate of treatment effect for a Stratum may be contributed to by borrowing from adjacent Strata; however, the results from the Strata that have contributed to borrowing may not be reported. The results of these analyses are used to achieve the primary objective of the trial which is to determine the effectiveness of interventions and, where specified, the extent to which that effectiveness varies

between Strata (intervention-stratum interaction). Additionally, but only where specified *a priori*, the model is able to estimate the effectiveness of an intervention in one domain contingent on the presence of an intervention in another domain (treatment-by-treatment interaction). Although the model can identify an optimal regimen this is not the primary objective of the trial.

Greater detail of the methods within the Bayesian model to be applied in this Platform are provided in the Statistical Analysis Appendix. The adaptive analyses will use data submitted from participating sites to their regional database. Each provider of regional data management will provide regular updates of data to the SAC for utilization in the adaptive analyses. The timely provision of outcome data from participating sites is critically important to the conduct of frequent adaptive analyses.

7.8.4.1. *Heterogeneity of Treatment Effect*

Individual DSAs will specify which *a priori* strategy will be used for evaluating heterogeneity of treatment effect based on relevant information such as clinical variables available and the results of simulations. These strategies may incorporate one or more of post-platform conclusion pre-specified subgroup analyses, risk-score analyses, and effect score analyses, where appropriate, and may use various statistical approaches, including Machine-Learning.

7.8.5. Statistical Handling of Ineligible Participants

The goal of this platform is to enroll as wide a participant population as possible. Because of this, and the desire to explore multifactorial regimens, it will not be uncommon that a participant will be ineligible for single interventions or entire domains, or that interventions may be temporarily unavailable for use. In this section we present the details for how this platform deals with these possible circumstances.

If an intervention is unavailable at the time of randomization due to site restrictions (for example, exhausted supply or unavailable device) then the participant will be randomized to all remaining interventions that are available at the site. This participant will be included in the primary analysis set as though they were randomized unrestricted to their allocated intervention.

If a participant is ineligible for a domain, then that participant will not be randomized to an intervention from that domain. The participant will be randomized to a regimen from all remaining domains that they are eligible for. As long as the participant receives an allocation within at least one domain they will be included in the primary analysis. For domains that they are ineligible for, the participant will be assigned a covariate for that domain reflecting their ineligibility for the domain. This allows the model to learn about the relative efficacy of the remaining interventions in the

domains in which the participant has been randomized. If there is a domain with only two interventions and participant is ineligible for one of the two interventions then the participant will be treated as though they are ineligible for the domain. If there is a domain with more than two interventions but a participant is ineligible for all but one intervention then the participant will be deemed ineligible for the domain.

If there is a domain with more than two interventions and the participant is ineligible for at least one due to a patient-level factor (for example known intolerance to an intervention), but remains eligible for at least two interventions, then the participant will be randomized among those interventions that the participant is eligible to receive. The participant will have their allocation included in the primary Bayesian model with an appropriate covariate identifying their ineligibility status that takes into account that a patient-level factor that determines ineligibility for one or more interventions could be associated independently with outcome.

To estimate a valid treatment effect for each intervention, the control population should ideally be as similar as possible and, specifically, should include participants that could have received the intervention of interest. In some cases, the Primary Statistical Model may be adjusted for intervention-specific exclusion criteria to correct any potential differences in outcome between control patients that were or were not eligible for the intervention. The decision as to whether to adjust for the intervention-specific exclusion criteria will consider the expected prevalence of the exclusion in participants and the expected impact of the exclusion criteria on the patient outcome. A statistical adjustment should be considered in situations where the exclusion criteria is expected to be highly prevalent or impactful on patient outcomes. Statistical adjustments will be pre-specified within each DSA as appropriate. Additionally, in some domains, multiple interventions may share common intervention-specific exclusion criteria and separate adjustments in the model may not be appropriate if this results in double counting the same exclusion criterion. In these cases, combined adjustments for ineligibility to a group of interventions may be included in the statistical model. In addition to adjustment in the primary model, sensitivity analyses that restrict the control population to intervention-eligible control patients may be appropriate and will be specified in the relevant Statistical Analysis Plan.

7.8.6. Statistical Triggers

Each Statistical Trigger combines a probability threshold with either an odds ratio threshold or an odds ratio range. Each DSA will specify the set of Statistical Triggers that will be applied, and if there will be any modification of these default thresholds, with an accompanying rationale for this

modification; these are typically informed by pre-trial simulations. Early phase interventions or seamless Phase 2/Phase 3 domains may have a separate set of triggers not specified in the Core Protocol, which will be specified in the relevant DSAs.

Interventions within a domain include multiple active interventions (with or without a specified control) or domains with one or more active interventions and a 'no intervention' control. Statistical Triggers are chosen depending on the nature of the interventions and the clinical questions being evaluated.

It is noted that the set of Statistical Triggers that are applied in a domain with a 'no intervention' control will typically differ from a comparative effectiveness domain in which all participants receive an active intervention. These default triggers are for decision-making for enrolment and are distinct from trial conclusions. Diagrams of default thresholds for Statistical Triggers are shown in Figure 5.

7.8.6.1. *Intervention Superiority Statistical Trigger*

At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being the optimal intervention within a domain, for that unit-of-analysis, then that intervention will have achieved a Statistical Trigger for superiority.

7.8.6.2. *Intervention Efficacy Statistical Trigger*

For domains that have a 'no intervention' control, at any adaptive analysis, if an intervention has at least a 0.99 posterior probability of being superior to the 'no intervention' control, for that unit-of-analysis, then that intervention will have achieved a statistical trigger for efficacy.

7.8.6.3. *Intervention Inferiority Statistical Trigger*

At any adaptive analysis, if a single intervention has less than a 0.01 posterior probability of being the optimal intervention for the domain, for a unit-of-analysis, then that intervention will have achieved a Statistical Trigger for inferiority relative to at least one other intervention within the domain for that target population. If superiority and inferiority were to be discovered simultaneously (for example when there are only two interventions in a domain), the result will be interpreted as demonstrating superiority. In a domain with three or more interventions, the threshold probability is adjusted according to the number of interventions in the domain, such that the threshold is lowered as the number of interventions increases.

7.8.6.4. *Intervention Equivalence Statistical Trigger*

The Core Protocol does not specify a default Statistical Trigger for equivalence, and when equivalence is applied, the threshold odds ratio margin and probability will be specified in individual DSAs.

A measure of relative treatment effect (odds ratio) is specified, rather than an absolute difference in treatment effect. This choice is made because it is reasonable to expect the primary outcome to vary between Strata and States, and the relative effect is a more robust analysis method across these differences.

In a domain with two interventions, equivalence is evaluated between the single pair of interventions. In a domain with more than two interventions, equivalence is evaluated for every possible pairwise comparison.

7.8.6.5. *Intervention Noninferiority Trigger*

The Core Protocol does not specify a default noninferiority margin (delta), and when noninferiority is applied, the threshold odds ratio margin and probability will be specified in individual DSAs. Noninferiority can be declared when there is a pre-specified probability that the odds ratio is not worse by more than the margin (1-delta). This trigger applies to a comparison of active interventions only.

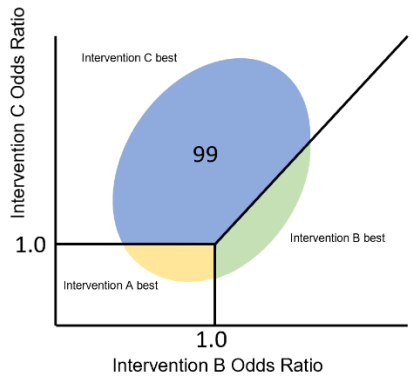
7.8.6.6. *Intervention Harm Statistical Trigger*

At any adaptive analysis, if an intervention has at least a 0.90 probability of the odds ratio being less than 1.0 in comparison to a defined control intervention (typically a ‘no intervention’ control), it will have achieved a Statistical Trigger for harm. It is likely that interventions will reach a Statistical Trigger for futility either concurrently or before a Statistical Trigger for harm, if both are pre-specified within a DSA.

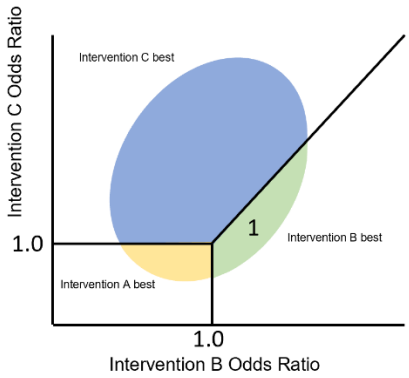
7.8.6.7. *Intervention Futility Trigger*

At any adaptive analysis, if an intervention has a probability of less than 0.05 for at least a 10% odds-ratio improvement (i.e., OR 1.1) compared to a ‘no intervention’ control or a defined active intervention, it will have achieved a Statistical Trigger for futility. This default rule corresponds to the one-sided equivalency region, meaning there is a low probability that the intervention is highly effective. This default threshold does not exclude a small beneficial treatment effect, and may be modified for each DSA.

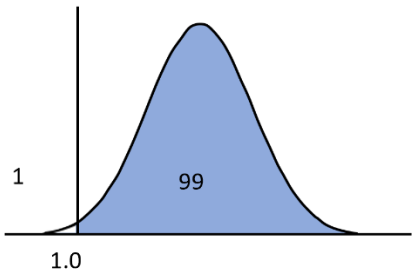
Figure 5. Diagrammatic examples of default Statistical Triggers



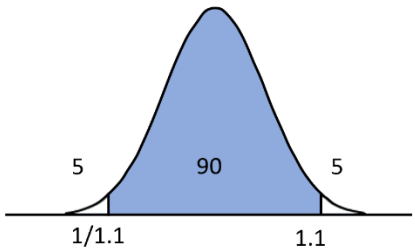
Superiority: Probability an intervention is in the optimal regimen **Pr(Optimal) ≥ 0.99**



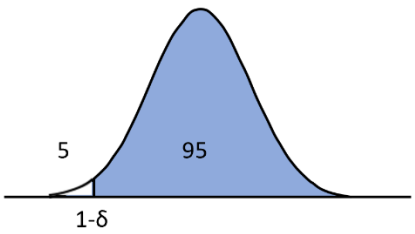
Inferiority: Probability an intervention is in the optimal regimen **Pr(Optimal) < 0.01**



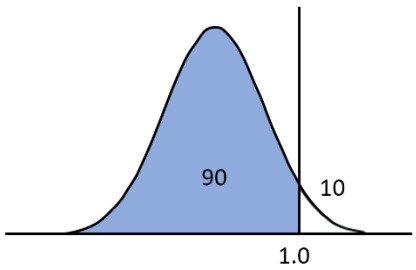
Efficacy: Probability that an intervention is better than a 'no intervention' control **Pr(OR > 1.0) ≥ 0.99**



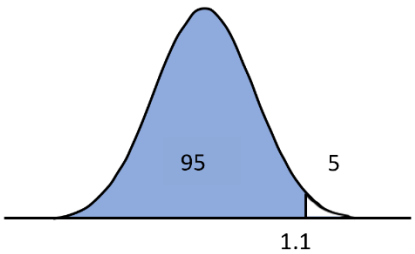
Equivalence: A pair of interventions differ by < 20% **Pr(1/1.1 < OR < 1.1) ≥ 0.90**



Non-inferiority: Intervention comparison not worse by more than a specified difference (δ) **Pr(OR > 1-δ) ≥ 0.95**



Harm: Intervention worse than a 'no intervention' control **Pr(OR < 1.0) ≥ 0.90**



Futility: High probability an intervention has minimal beneficial effect **Pr(OR < 1.1) ≥ 0.95**

7.8.7. Action when a Statistical Trigger is achieved

7.8.7.1. *Introduction*

If a Statistical Trigger is achieved this will be communicated by the SAC to the DSMB. The DSMB will oversee a range of actions as described in operational documents and the DSMB charter to confirm that the Statistical Trigger has been reached validly. The discontinuation of a domain, or interventions within a domain, in response to reaching a Statistical Trigger will not require a protocol amendment.

7.8.7.2. *Actions following Statistical Trigger for superiority, efficacy, inferiority, or harm*

If an intervention reaches one of the above thresholds and the DSMB declares this as a Platform Conclusion, the ITSC will be informed that the trigger has been met. At that point, randomization to all other remaining interventions in the domain and in that unit-of-analysis where superiority or efficacy has been declared will be halted at sites at which the relevant intervention is available. Randomization to the non-superior or non-efficacious interventions may continue at sites at which the superior or efficacious intervention is not available, pending its availability. The ITSC will take responsibility to undertake Public Disclosure as soon as practicable with the dissemination of the research result via presentation or publication or both.

It is possible that a superior or efficacious intervention will be retained but subjected to further evaluation to refine the optimal characteristics (for example duration of therapy or optimal dose). Such decisions will be specified in an amended DSA.

Where a Platform Conclusion is reached for superiority or efficacy, the DSMB may recommend that Public Disclosure should be delayed until additional results are available, so as to allow further recruitment to evaluate interactions between interventions in different domains or for other clinically or statistically valid reasons. However, declaration of a Platform Conclusion will always result in the removal of inferior or harmful interventions from a domain.

7.8.7.3. *Actions following Statistical Trigger for equivalence, or noninferiority*

If a Platform Conclusion arises because one or more pairs of interventions reach a Statistical Trigger for equivalence or noninferiority within a unit-of-analysis, this will be communicated to the ITSC by the DSMB. The ITSC in conjunction with the DSMB may undertake additional analyses, for example, of clinically relevant secondary endpoints.

The approach to a Statistical Trigger for equivalence or noninferiority is different depending on the number of interventions within a domain.

For domains with only two interventions a valid Statistical Trigger for equivalence or noninferiority will be reported as a Platform Conclusion. With respect to the adaptation of the domain, the following actions are possible:

- Removal of the domain from the Platform
- No change to the interventions within the domain with continuation of RAR. This could be to further evaluate secondary endpoints, a smaller delta, or interest in interactions with other interventions.
- Adapt the domain to better refine the optimal characteristics of interventions (i.e., duration or dose)

Factors that should be taken into account by the DSMB and the ITSC include the results of the primary analysis, analysis of clinically relevant secondary end-points, the possibility of treatment-by-treatment interactions, the relative burden and cost of the two interventions, the clinical interpretation of the adequacy of the delta, and the possibility that ongoing randomization with a smaller delta might also allow a Statistical Trigger for superiority (with a small effect size).

The options following a Statistical Trigger for a pair of interventions in a Domain with three or more Interventions are more complex. For a domain with three or more interventions, the information provided by the DSMB to the ITSC may include specification of the ordinal rank of the interventions within the domain. With respect to reporting of Platform Conclusions and adaptations of the domain the following actions are possible:

- A pair of equivalent interventions may be compressed into a single group for the purposes of ongoing analyses. Both interventions continue to be interventions that are available within the domain for allocation, but the primary analysis considers the effect of the two interventions as a single group, where a balanced randomization will be assigned to each of the intervention pair within this compressed group. Secondary analyses can continue to be conducted to determine if equivalence is maintained, with the possibility of the intervention being restored as individual interventions if results no longer support equivalence. It is acknowledged that re-analysis of the domain immediately following compression of one (or more) pairs of equivalent interventions may result in the occurrence of other Statistical Triggers (e.g., a compressed pair may be superior or inferior to all remaining interventions).

Any Statistical Trigger that results from compression of one or more pairs will be responded to as outlined in this section with reporting of the cascade of Statistical Triggers. Compression of a pair of interventions can occur with or without reporting of a Platform Conclusion.

- Removal of one of the pair of equivalent interventions from the domain, for example the more burdensome or more expensive intervention, which will result in a reporting of a Platform Conclusion.
- No change to the interventions within the domain with continuation of RAR. This could be to further evaluate secondary endpoints, a smaller delta of equivalence, or interest in interactions with other interventions. Such changes would require amendment to the DSA. This could occur with or without reporting a Platform Conclusion.

Factors that should be taken into account by the DSMB and the ITSC include the results of the primary analysis, analysis of clinically relevant secondary end-points, the possibility of treatment-by-treatment interactions, the relative burden and cost of the two interventions, the clinical interpretation of the adequacy of the delta, the possibility that ongoing randomization with a smaller delta might also allow a Statistical Trigger for superiority (with a small effect size) and the ordinal position of the equivalent pair within the domain.

In a domain that comprises three or more interventions, but in which two or more interventions are analyzed in a nested manner, the nested group may be combined for analyses of equivalence. Where compression converts a domain with three or more interventions into a domain with two interventions (and data continues to support equivalence of the compressed interventions) such a domain will be regarded as a two-intervention domain for the purposes of RAR and for evaluation of Statistical Triggers for superiority, inferiority, and equivalence. For RAR, allocation proportions will be capped at 60% for two-intervention domains, unless otherwise specified in a DSA.

Statistical Triggers for equivalence in domains with three or more interventions may occur with or without Platform Conclusions and public disclosure of results, as determined by the ITSC and DSMB. If a Platform Conclusion is reached, the ITSC will take responsibility to undertake Public Disclosure as soon as practicable with the dissemination of the research result via presentation or publication or both. There is no automated adaptation when equivalence is deemed to have occurred.

7.8.7.4. *Actions following Statistical Trigger for futility*

If an intervention reaches a Statistical Trigger for futility and the DSMB declares this as a Platform Conclusion, the ITSC will be informed that the trigger has been met. As with other triggers, the DSMB may recommend that Public Disclosure should be delayed until additional results are available, so as to allow further recruitment to evaluate interactions between interventions in different domains or for other clinically or statistically valid reasons.

7.8.8. Analysis set for reporting

The primary analysis set that will be used for determining a Statistical Trigger will comprise all participants who were included in the unit-of-analysis at the time of the adaptive analysis. As such, there will be some participants who have been randomized but are not fully included within this analysis, either because participants have not yet reached the censoring date for the 90-day component of their primary outcome or because data for a participant who has reached the censoring date for their primary outcome has not yet been submitted. At the time of public reporting, an analysis will be reported that comprises all participants who are evaluable and have appropriate consent through to the point at which there was cessation of randomization to the relevant comparator arms and a more complete outcome data set is incorporated into the analysis set. Posterior probabilities for the pre-specified outcomes will be reported from this full analysis set and, as a result, will usually differ from the posterior probability which reached the Statistical Trigger.

7.8.9. Simulations and statistical power

The design of the trial, at initiation, and in conjunction with the planning of the introduction of new interventions within a domain or of new domains, will be informed by the conduct of extensive simulations using standard Monte Carlo methods. Simulations may be updated whenever a new intervention is added within a domain or whenever a new domain is added to the Platform. However, simulations will not be updated when an intervention is removed from a domain because of the declaration of a Platform Conclusion that the intervention is inferior. These simulations will evaluate the impact of a range of plausible scenarios on the statistical properties of the trial.

The results of detailed simulations are located in the Simulations Appendix which is maintained as an operational document that is publicly accessible and updated as required.

7.8.10. Updating model after monitoring

If any variable that contributes to the Primary Statistical Model is identified to be inaccurate at a monitoring visit, the data will be corrected and utilized for the next adaptive analysis. Any resulting change to a previous Statistical Trigger will be reviewed by the DSMB to determine the implications. The DSMB will advise the ITSC if there is any material change in a Platform Conclusion which, if published, will be reported to the journal as an erratum.

7.8.11. Discontinuation of domains or interventions in the absence of a Statistical Trigger

A domain, or interventions within a domain, can be discontinued by the ITSC for operational futility due to considerations including: emerging external data, altering equipoise; insufficient expected recruitment; or changing disease epidemiology. A decision to discontinue recruitment to a domain or intervention due to operational futility will be made by the ITSC and communicated to the DSMB. Any Public Disclosure of results arising from a domain or intervention closed due to operational futility will specify the rationale for deeming continued recruitment to the relevant domain or intervention to be operationally futile.

7.9. Interaction with other trials

7.9.1. Co-enrollment with other trials

Co-enrollment of participants in other research studies, including interventional trials, is strongly encouraged. The principle is that co-enrollment should always occur and is only not permitted when there is a clear threat to the validity of either study or it would materially influence the risk to participants. Decisions regarding co-enrollment with other trials will be made on a trial-by-trial basis. Where a potentially co-enrolling trial is being conducted in more than one region in which this trial is being conducted, the decision regarding co-enrollment will lie with the ITSC. Where a potentially co-enrolling trial is being conducted only in one region in which this trial is being conducted, the decision regarding co-enrollment will lie with the RMC. In all circumstances the ITSC and RMCs should liaise regarding decisions about co-enrollment. Decisions regarding co-enrollment with other trials will be distributed to participating sites as an operational document and will not require or involve amendment of this protocol.

7.9.2. Cooperation between the REMAP and other trials with overlapping populations or interventions, and federation of trials

7.9.2.1. *Co-enrollment and cooperation with other trials*

During the life-time of the Platform it is likely that there will be many other clinical trials that will enroll a cohort of patients who are similar, overlap, or are a subset of the patients who are eligible for this trial. This would include trials with a primary interest in patients with respiratory tract infection, but could also include patients with acute respiratory distress syndrome (ARDS), patients with COVID-19, and patients with severe sepsis or septic shock. Such trials will likely evaluate a range of interventions, some of which may also be the same as, or similar to, interventions evaluated within this Platform. This trial seeks to cooperate and coordinate maximally with other trials. Examples of such cooperation and coordination may include, but not be limited to, utilization of Platform infrastructure for screening and recruitment to other trials, sharing of data collected by the Platform, and sharing of allocation status so as to allow incorporation of allocation status within analysis models.

Where another trial is evaluating an intervention that is also included within this Platform each site (or region) would need to establish rules that determine circumstances in which each trial has preference for recruitment. Where another trial and this Platform are evaluating different interventions the extent to which cooperation is possible will also be determined by the extent to which the interventions are compatible and capable of having their effect evaluated independently within each trial.

7.9.2.2. *Federation with other Platform Trials*

It is the expectation that multiple platform trials for related and overlapping conditions, overlapping illness severity states, and different geographic locations will emerge over time. Such platform trials may be conducted in patients with similar severity of illness but different and potentially overlapping syndromes (e.g., critically ill patients with sepsis, ARDS, and pneumonia); similar syndromes but different severity-of-illness (e.g., outpatients or post-hospitalization patients with respiratory tract infection); or in similar populations, but with different funders or parent networks requiring separately governed platform trials. Allowing multiple Platforms to contribute to the same, or linked, statistical models will enhance statistical power and reduce the time before conclusions are able to be disseminated. The capacity for data to be evaluated in the same or linked statistical models requires a coordinated approach to terminology, data collection, and analysis. While a single, large, complex platform trial would accomplish this goal, such a Platform is likely untenable across regions

and governance models. This collaboration and coordination between Platforms is termed 'federation', and approaches may range from a 'loose' federation to a 'complete' federation (see Table 3).

Table 3. Overview of approaches to 'federation' between Platform Trials

	'Complete' Federation	'Tight' Federation	'Loose' Federation
Governance	Shared trial steering committee (with or without trial-specific steering committee).	Separate trial steering committees, with cross-representation and established processes for joint decision-making.	Separate trial steering committees, with established processes for joint decision-making.
Sponsorship	Single Sponsor, or single lead Sponsor with multiple Regional/Network Sponsors.	Multiple Sponsors.	Multiple Sponsors.
Protocol documents	Identical or fully-aligned protocol documents.	Aligned but separate protocol documents. May include shared over-arching Master protocol documents with trial-specific protocol documents.	Separate protocol documents.
DSMB	Single DSMB for the entire Federated Platform.	Shared/Meta-DSMB, or multiple DSMBs with cross-representation. Established rules and processes for joint decision-making.	Separate DSMBs in communication.
Data collection	Shared or highly-aligned Case Report Form (CRF).	Alignment of definition and collection of key variables.	CRFs sufficiently aligned to permit combined analyses and reporting.
Analyses	Combined analyses using a single primary statistical model.	Combined analyses using a single statistical model that may or may not be separate from each trial's primary statistical model.	Separate primary analyses. Prospectively-defined analyses for combined reporting.

For any platform trial(s) that aims to federate with this Platform, issues such as governance, DSMB oversight, funding, delegation of roles and responsibilities, and publication policies of the federated platform trials will be determined prior to the commencement of federation. This includes trial steering committee oversight, acknowledging that ITSC oversight may not be possible on separate platform trial processes. It is likely that an overarching 'federation steering committee' with representation from each of the individual platform trials will be required. Such a committee would

have responsibility for determining the extent of alignment of core protocol documents, development and modification of common minimum data specifications, delegating roles and responsibilities within the Federation, specifying data flow and processing, and development of statistical analysis plans. Each of the individual Platforms may retain their existing governance structures and be able to make independent decisions about their Platforms (e.g., to develop new domains, as well as choose which domains the platform will participate in) to the extent that these decisions do not affect the other trial(s) in the federation.

Different approaches to safety monitoring and oversight may be adopted. In completely- or tightly-federated Platform trials, it may be appropriate to have a single DSMB with oversight over the entire federated Platform; however, it is acknowledged that some situations may preclude this from occurring. In these circumstances, at a minimum, the multiple DSMBs must agree to collaborate and establish decision-making rules, assessing data from both trials and the common statistical model (where relevant) when making decisions. Alternative approaches may include formation of a meta-DSMB, or DSMB that is domain-specific (or specific to more than one closely-related domains) take responsibility for oversight of specified domains included in the Federated Platform. Ideally, domains with specified interactions should be managed by a single DSMB but, in the situation in which interacting domains have separate DSMBs, rules for decision-making must be established to specify the interaction between these DSMBs.

7.10. Investigational medical products

This Platform will evaluate a range of pharmaceutical interventions that may include fully licensed medications being used within its marketing authorization, licensed medications used in an indication or dosage outside of its existing marketing authorization, and unlicensed medications without a marketing authorization (in some or all regions). Therefore, details about drug labeling, distribution, storage, dispensing and administration will vary from use of normal clinical stock without trial specific labelling, through to research of investigational medicinal product (IMP) that will require more detailed drug accountability tracking and trial specific labelling. Details of these requirements will therefore be provided in the relevant DSA, and in operational documents including pharmacy manuals and administration guides, and RSAs. Similarly, the DSA will include any IMP-specific details about additional safety reporting and monitoring, including data sharing with relevant authorities or partners.

7.11. Registry of non-randomized patients

In some locations, the Platform may be nested within a registry. Where this occurs the operation of the registry, including eligibility criteria, ethical issues, and variables that will be collected, will be described in the separate Registry Appendix.

7.12. Criteria for termination of the trial

This trial is designed as a Platform, allowing for continued research in patients with respiratory tract infection admitted to hospital. The Platform allows for the study to be perpetual, with multiple different domains that can be evaluated at any one time, and over time. Frequent adaptive analyses are performed to determine whether the interventions under evaluation are still eligible for further testing or randomization should be stopped due to demonstrated inferiority, superiority or equivalence.

It is anticipated that the study will continue to include additional participants and test additional domains and interventions until one of the following occurs:

- Respiratory tract infection is no longer deemed to be a public health problem
- The effectiveness and/or cost-effectiveness of all interventions are known and there are no new plausible interventions to test
- Study funding is not available

Should the whole Platform be stopped, the end of trial is the date of the last scheduled follow up for any participant.

8. TRIAL CONDUCT

The trial will be conducted as per ICH GCP. Operational processes for site initiation and activation and participant enrolment will be specified in regional manuals of procedures. Individual processes for specific domains will be specified in the relevant DSA documents.

8.1. Site time-lines

8.1.1. Initiation of participation at a site

It is generally recommended that participating sites commence screening and recruitment to only a single domain and progress to open more domains as they become familiar with the trial. However,

sites may commence with multiple domains with the permission of their RCC, depending on considerations such as familiarity with clinical research, resources and staffing.

8.2. Recruitment of participants including embedding

8.2.1. Embedding

The trial is designed to substitute allocation of treatment status by randomization where a treatment decision would have otherwise been made by clinical staff (where it is clinically and ethically appropriate to do so), and for this to occur at the time that the treatment decision would have otherwise been made. It is not essential that embedding is used to achieve recruitment and randomization, but it is preferable and participating sites are encouraged to work in conjunction with the trial team to achieve embedding wherever possible and as soon as possible.

The success of embedding can be evaluated by the proportion of eligible participants who are recruited and randomized, that recruitment and randomization occur as soon as possible after the patient becomes eligible, and that there is compliance with the allocated intervention(s). Successful embedding will enhance the internal and external validity of the results generated by the trial.

Each site, taking into account its own clinical work practices, will be asked to develop internal processes that will be used to achieve successful embedding. Wherever possible the RCC will advise and assist sites to achieve successful embedding. In brief, each participating site will identify their admission procedures that occur with each new patient and then align these procedures to facilitate assessment of eligibility by clinical staff who provide routine care for each patient. This can be achieved through several methods, including checklists on electronic Clinical Information Systems (eCIS).

8.2.2. Participant recruitment procedures at participating units

Once a patient is screened and identified as eligible, the staff will randomize the participant. Standard Operating Procedures (SOPs) will be developed to guide staff who undertake randomization.

8.3. Treatment allocation

An eligible participant will receive a treatment allocation in each domain for which the participant is eligible. Information related to RAR is presented in the Interventions section of the Trial Design (Section 7.5.2) and in the Statistical Analysis Appendix. As noted elsewhere, all randomized

allocation will be determined at the time of initial randomization in a given State, but allocation status will not be made known for domains that operate using Randomization with Delayed Reveal or Randomization with Deferred Reveal (see Section 7.8.3.4).

8.4. Delivery of interventions

8.4.1. Treatment allocation and protocol adherence at participating units

In conjunction with participating sites, trial management staff will develop generic and site-specific documents that outline processes for implementation of and facilitate adherence with participants' allocated treatment status. Wherever possible these will seek to integrate trial processes with existing routine treatment processes to allow seamless adoption of the allocated treatments.

8.4.2. Transfer of participants between locations and protocol adherence

Participants may be transferred from one clinical location to another after randomization, including between departments (e.g., ICU and wards) within the same hospital, or from one acute hospital to another. The receiving location may or may not be participating in this trial, and if they are, may be participating in different domains and interventions from the randomizing location.

For participants transferred to a clinical location that is not participating in this trial, all treatment administered after their transfer is to be determined by the treating clinician. Continuation or discontinuation of any allocated treatments initiated at the randomizing location will be considered a clinical decision rather than an intervention administered under trial protocols, and study-specific drug accountability will cease.

Where participants are transferred to another clinical location that is also participating in this trial, any interventions that the participant has been allocated to should be continued as per protocol only where the receiving location is also participating in the allocated intervention. The continuation or discontinuation of any allocated interventions that the receiving site is not participating in will be considered a clinical decision, rather than an intervention administered under trial protocols.

8.5. Unblinding of allocation status

With respect to blinding, the default position within the Platform is that treatments determined by randomization will be provided on an open-label basis. Where interventions are conducted on an open-label basis, all members of the ITSC and all other staff associated with a RCC of the trial will remain blinded until a Platform Conclusion is reported by the DSMB. Although the default is the

provision of open-label treatments, the blinding of treatment status is not precluded within the Platform. Whether interventions are open-label or blinded will be specified in DSAs.

Unblinding of any blinded treatment by site research staff or the treating clinician should only occur only in when it is deemed that knowledge of the actual treatment is essential for further management of the participant. A system for emergency unblinding will be provided in the DSA of any domain that includes interventions that are administered in a blinded fashion. Any unblinding process will ensure that the investigator can directly and rapidly unblind in an emergency situation. Any unblinding and the reasons for unblinding will be documented as they occur. Unblinding should not necessarily be a reason for study drug discontinuation.

8.6. Criteria for discontinuation of an allocated intervention within the Platform

Trial participants may have their allocated intervention(s) from one or more domains discontinued according to predefined criteria for discontinuation. The criteria for discontinuation specific to each domain are specified in the relevant DSA.

Criteria for discontinuation of allocated interventions entirely include:

1. The treating clinician considers continued participation in the allocated intervention(s) are not deemed to be in the best interests of the patient
2. The participant or their authorized representative requests withdrawal from ongoing participation in the allocated intervention(s)

In the case of discontinuation, the reasons for withdrawal will be documented. Following discontinuation of an allocated intervention, participants will be treated according to the treating clinician. Participants who discontinue participation will not be replaced. All data will be analyzed using the ITT principle.

8.7. Concomitant care and co-interventions

All treatment decisions outside of those specified within the Platform will be at the discretion of the treating clinician. Prespecified co-interventions related to specific domains will be recorded in the CRF and are outlined in the relevant DSAs.

8.8. Data collection

8.8.1. Principles of data collection

Streamlined data collection instruments and procedures will be used to minimize the workload at participating sites. The CRF will be developed by the ITSC and made available to the participating sites as a paper CRF and electronic CRF (eCRF) for ease of data collection. All data will be collected by trained staff who will have access to comprehensive Data Completion Guidelines. Information recorded in the CRF and eCRF should accurately reflect the participant's medical notes and must be completed as soon as available from source data. The intent of this process is to improve the quality of the trial, including being able to provide prompt feedback to the site staff on the progress, accuracy, and completeness of the data submitted. The eCRF will be web-based and accessible by a site personnel using password protected login.

8.8.2. Variables to be collected

The generic variables to be collected for all domains in this Platform are as detailed below. Additional domain-specific variables are outlined in the relevant DSAs. Baseline variables are defined as at or before the time of randomization.

8.8.2.1. *Baseline and Eligibility data*

- Demographic data
- Screening information, including Platform, domain and intervention eligibility criteria
- Date and time of hospital admission
- Date and time of ICU admission(s) (where applicable)
- Status for all applicable states and strata
- Receipt of organ failure support
- Co-existing illnesses and risk factors for respiratory tract infection
- Source of hospital admission
- Physiologic and laboratory results indicative of severity of illness and organ dysfunction
- Results of microbiological testing

8.8.2.2. *Inpatient data*

Collected while participants are admitted to hospital between randomization and Day 28:

- Hypotension and administration of vasopressors/inotropes

- Administration of renal replacement therapy
- Administration of oxygen support including ECLS

8.8.2.3. *ICU Outcome data*

For participants admitted to ICU at the time of enrollment, or after enrollment:

- Date and time of ICU admission and discharge
- Dates of ICU readmission and discharge during the index hospitalization

8.8.2.4. *Hospital outcome data*

- Date and time of hospital admission and discharge
- Survival status at hospital discharge
- Hospital discharge destination

8.8.2.5. *Medication Administration*

- Administration of allocated medications
- Administration of relevant concomitant medications

8.8.2.6. *Post-discharge outcome data*

At the discretion of the site, unless specified otherwise in an RSA or DSA, and collected by phone:

- Survival status at 28 days
- Survival status at 90 days
- Survival status at 180 days
- Hospital readmission within 28 days
- HRQoL measured by EQ-5D or EQ-5D-Y and PedsQL-SF15 in participants aged less than 18 years at 180 days
- Disability status measured by WHODAS at 180 days and baseline information to interpret disability (adults)
- Opinions and beliefs regarding participation in research (reported at 180 days)

8.8.3. Data required to inform Response Adaptive Randomization

This Platform is designed to use frequent adaptive analyses and incorporate RAR. All variables used to inform RAR will be specified in the SAC Data Export Data Dictionary.

As data that is included in the regular adaptive analyses is used to inform RAR, it is important that data is entered into the eCRF contemporaneously. RCCs will be responsible for monitoring missing data for participating sites, in particular for data used to calculate the primary outcome.

8.8.4. Blinding of outcome assessment

Wherever feasible, outcome assessment will be undertaken by research staff who are blinded to allocation status. Such blinding will not be feasible in all regions or for many outcomes, particularly those that occur while the participant is still admitted to an ICU or the hospital. However, the primary endpoint and key secondary endpoints are not variables that are open to interpretation and so accuracy will not be affected by outcome assessors not being blinded to allocation status.

8.9. Data management

8.9.1. Source Data

Source data are contained in source documents (original records or certified copies). Source documents are original documents, data, and records from which participants' eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarized into the eCRF), clinical and office charts, laboratory and pharmacy records, radiographs, and correspondence. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary.

In some cases, where there are no existing source documents (i.e., no prior written or electronic record of data), data may be recorded directly into the eCRF and is considered to be source data. This may include, but is not limited to, data such as:

- Ethnicity
- Clinical Frailty Score at baseline
- Day 90 follow up
- Day 180 follow up

8.9.2. Confidentiality

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than signed consent forms and the subject identification log, the participant will be referred to using a unique trial-specific number or other anonymized identifier, not by name. Information linking the participant's medical data to database materials will be maintained in a secure location at the

participating site. This information will not be transmitted to the members of the ITSC, any DSWG, or RMC. The subject identification log, or key, to code and re-code participant identifiers will only be accessible to local site investigators (research nurse and principal investigator) but not to members of the central study team. Hospital and coded individual subject data and records will be held in strictest confidence by the site investigator and healthcare staff and by all central research staff, as permitted by law.

8.10. Quality assurance and monitoring

The trial will be conducted in accordance with the current approved protocol, principles of ICH GCP, relevant regulations and SOPs. In accordance with ICH GCP, the purpose of monitoring of clinical trials is to verify that:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable.
- Trial conduct is in compliance with the currently approved protocol documents, GCP, and relevant regulations.

The trial will use a risk-based monitoring approach, with monitoring activities determined by risk to participants and the scientific validity of the trial (Brosteanu et al., 2017). A combination of central, on-site, and remote monitoring may be used and will focus on study-, data-, and site-related risks (Brosteanu et al., 2009), with particular attention to variables that are of high importance to evaluating and monitoring the safety, well-being, and rights of participants as well as to the achievement of trial objectives (referred to as 'Key Variables').

The trial sets overall standards for quality assurance and monitoring across the Platform, with a minimum expected level of monitoring specified in the trial Monitoring Plan. RCCs will additionally comply with regional or institutional monitoring guidelines where applicable, and may choose to perform additional monitoring activities.

Operationalization of these principles are summarized in the sections below and detailed in an operational Monitoring Plan.

8.10.1. Protocol adherence and data quality

Common standards for protocol adherence and data quality are set for the Platform, however each region may set additional standards. Protocol training and adherence in each region will be coordinated by the relevant RCC.

8.10.1.1. *Protocol adherence*

Several procedures will be implemented to facilitate protocol standardization and to minimize bias. These include:

- Site selection based on availability and experience of key site personnel, estimated recruitment rate based on anticipated eligible patient volume, and acceptability of study interventions to clinicians at the site.
- Site initiation meetings for each site, to be held prior to study commencement to ensure consistency in protocol procedures, and with additional training as required with the opening of additional domains.
- Use of standardized training materials and study tools, for the platform and each domain
- Monitoring for protocol adherence, as described below.

8.10.1.2. *Data quality*

Several procedures will be implemented to ensure data rigor and to minimize bias. These will include:

- Site initiation meetings, ongoing education, and study tools/resources will include instructions and guidance to ensure consistency in data procedures
- Site users will have access to the 'live' study eCRF only after site initiation visits are completed and a RCC representative and site principal investigator is satisfied that the individual has received appropriate training
- Detailed Data Completion Guidelines will be provided to define each data point in the CRF, including text available for many data fields to help align data entry
- Automated validation checks are implemented in the eCRF to reduce risk of data entry error, and email reminders will be used to facilitate timely entry of data
- The DCC will perform data validation checks, generating queries where potential errors are identified, and evaluating data missingness
- Monitoring of study data, as described below

8.10.2. Monitoring of protocol adherence and data quality

Monitoring will be conducted by representatives of the RCC in each region in accordance with the trial Monitoring Plan. Each region may choose to perform monitoring that is more extensive than is recommended by the Monitoring Plan, according to feasibility and local regulations. Monitoring activities may be modified during a pandemic.

An initial monitoring visit may occur soon after a site has commenced recruitment, at which time an assessment of site risk level will be performed by the RCC. This site risk assessment will be based on factors such as recruitment rate, participant withdrawals, introduction of new domains, missingness of data, frequency of protocol deviations, and other relevant factors (Walker, et al. 2018). Subsequent monitoring activity and intensity will be determined by the site risk assessment, which will be documented and reassessed over time.

The DCC will assist with central monitoring by routinely generating reports to assist RCCs to identify sites, participants, and data points that may require review.

Details of the risk-based approach to monitoring for the trial can be found in the trial Monitoring Plan.

8.11. Data safety and monitoring board

The composition, roles and responsibilities of the single DSMB for the platform are specified in the DSMB Charter.

The DSMB will receive frequent updates of the trial's adaptive analyses from the SAC and monitor for safety. The role of the DSMB will be to ensure that the pre-specified trial algorithm is being implemented as designed, that the design remains appropriate from a scientific and ethical point of view, to confirm when a Statistical Trigger has been reached, and to recommend a Platform Conclusion with the ITSC, as outlined in Section 7.8.7.

A working group specified by the ITSC provides central oversight for all operational aspects of safety data, monitoring, and reporting for the platform, endorses a risk-based approach to trial monitoring and safety, and reports directly to the ITSC. This team is separate from the DSMB, is blinded to treatment assignments, and aims to support and facilitate DSMB work and requirements.

8.12. Safety monitoring and reporting

8.12.1. Principles

The principles used in the conduct of safety monitoring and reporting in this trial are those outlined by Cook *et al.* in the manuscript "Serious adverse events in academic critical care research" (Cook et al., 2008) and in guidance by the Good Clinical Trials Collaborative, which apply across the severity of illness for hospitalized patients with acute illness.

A core principle of safety reporting for the Platform is to focus on events (or event severity) that are not related to the course of the underlying illness or effect of a non-trial treatment that has been provided. The treating clinician is in the best position to adjudicate relatedness, in the context of all available clinical information regarding the patient's illness and provided treatment.

A high proportion of acutely ill patients who will be enrolled in this trial will experience mortality or substantial morbidity. The case-fatality proportion for critically ill patients with community-acquired pneumonia is likely to be in the order of 20 to 30%, with a smaller, but sizable proportion of mortality of between 5 to 15% in all hospitalized patients. Similarly, children will have high rates of complications and events occurring during their hospital course. There will be high proportions of patients who will have one or both of laboratory abnormalities or complications of acute illness and its treatment. Patients who are hospitalized and ill, irrespective of whether or not they are enrolled in a trial, will typically experience multiple events that would meet the conventional definition of a Serious Adverse Event (SAE). These conditions complicate SAE reporting.

Trials involving vulnerable populations, such as children, must have research oversight that protects patient safety and patient rights but also ensures that there can be public trust that the trial is conducted in a manner that safeguards the welfare of participants. The strategy outlined for the definition, attribution, and reporting of SAEs in this trial is designed to achieve these goals in a way that seeks to avoid the reporting of events that are considered to be part of the course of the patient's underlying illness or caused by non-trial treatments, or events that are recognized as important by their incorporation as trial endpoints. The goal is to aid DSMBs and oversight bodies by increasing the "signal to noise" ratio in safety reports.

The Platform may evaluate therapeutic agents being used for established indications, agents that have been re-purposed for a new indication or un-marketed investigational medical products (IMP). Established and re-purposed agents are typically in common clinical use and their safety profiles well described. Where an agent is not regarded as having an established safety profile, more specific and detailed safety reporting will be required beyond that specified in the Core Protocol. Whether or not an intervention is regarded as having an established safety profile, and any additional reporting requirements, will be specified in the relevant DSA.

As with overall data monitoring, the trial endorses a risk-based approach to safety monitoring, with monitoring activities and safety reporting that are based on risks to participants and to the scientific validity of the trial.

It is noted that, within the Platform, sites may choose which domains and interventions they participate in, depending on acceptability to the clinicians at the site and region. The perceived safety of interventions is an important consideration.

The application of these principles is summarized in the below sections and detailed in an operational Safety Reporting SOP.

8.12.2. Definitions

An Adverse Event (AE) is any untoward medical occurrence in a patient receiving a trial intervention but which does not necessarily have a causal relationship with this treatment.

An Adverse [Drug] Reaction (AR, ADR) is a response to a drug or other therapeutic intervention which is noxious and unintended and which occurs at doses or intensity normally used in humans for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

A Serious Adverse Event (SAE) is any untoward medical occurrence that: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

A Serious Adverse [Drug] Reaction (SAR, SADR) refers to any such adverse event for which there is a possibility that the trial intervention caused the adverse event.

Suspected Unexpected Serious Adverse Reactions (SUSAR) are SAEs determined to be unexpected (i.e., not previously described in the Summary of Product Characteristics / Investigator Brochure / Investigational Medicinal Product Dossier / Protocol).

Domain-specific SAEs can be pre-specified in DSAs, depending on the specific interventions in the domain.

Adverse Events of Special Interest (AESI) are SAEs that might be attributable to specific interventions and may be required as an additional safety reporting requirement for interventions without established safety profiles. In those cases, AESIs will be specified as secondary endpoints for participants enrolled in those domains.

8.12.3. Reporting Procedures for Safety and Serious Adverse Events

The trial endpoints, as outlined in the Core Protocol and as specified in DSAs, are designed to capture the majority of events that might otherwise constitute an SAE. In particular, SAEs that might

be attributable to specific interventions are included as secondary endpoints in each DSA given the need for unbiased reporting, but are recorded only for participants enrolled in that domain. If required, additional clarification of issues related to the identification of SAEs that are relevant to a specific domain will be described in the DSA.

Thus, safety reports provided to oversight bodies such as the DSMB will include serious AR, AESIs, or serious ADRs and trial endpoints that might otherwise constitute SAEs.

Any SAE considered by the site investigator to be possibly, probably or certainly related to a trial intervention or trial participation (i.e., a serious AR/ADR), should be reported (Section 8.13.4). For example, while development of an organ failure is recorded as a secondary outcome, if the site investigator believes the organ failure might reasonably have occurred as a consequence of a trial intervention or trial participation, the organ failure should also be reported as a SAE. However, AE and SAEs which are fully consistent with the patient's illness and non-trial treatments and are not considered by the site investigator to be attributable to a trial intervention should not be reported.

Qualifying SAEs, including AESIs and SUSARs, and that occur between trial enrollment but before hospital discharge, will be reported to the relevant RCC as per local reporting requirements as specified in the relevant RSA. SAE reports will include at minimum, the event date, a description of the event, and any treatment or intervention provided in response to the event. The RCC will review SAE reports for completeness and will liaise with the site to obtain any further required information. All SAEs, pooled from all regions, will be reported at agreed upon intervals to the DSMB. Each RCC has the responsibility to report SUSARs in their region to the applicable regulatory bodies and ethic committees, and to inform participating sites and the other RCCs.

It is acknowledged that some regions may be subject to additional ethical or legal requirements that differ from those requirements described above. In such cases, events that do not meet the Platform definition of a reportable SAE will be documented and reported as required to local authorities, but will not be reported to the trial DSMB. Regional reporting requirements and timelines are described in an operational Safety Reporting document.

8.12.4. Attribution of serious events to study interventions

It is likely that many trial participants will experience events that could be related to one or more trial interventions. However, it will often be difficult to distinguish in real-time between events that occur as a consequence of the participant's illness and non-trial treatments, and those that may be related to trial interventions. Site investigators will exercise judgment in assessing whether events

are related to trial interventions. In this Platform, the standard that should be applied to determine whether SAEs are related to trial interventions is that it is possible, probable, or certain that there is a direct link between a trial intervention and the SAE, or the SAE is not considered to be a normal feature of the evolution of the patient's illness and its treatment.

8.12.5. Attribution of a death to study interventions or study participation

Hospitalized patients who will be enrolled in this trial are at high risk of morbidity or death. The primary endpoint of the trial incorporates mortality and organ failure support, and the objective of the trial is to identify differences in the primary endpoint that can be attributed to treatment allocation which will often include treatments that are believed to be or known to be safe and effective but for which it is not known whether some treatments are more effective than others. Where the trial evaluates interventions that are novel and not part of usual standard care, the threshold for considering relatedness to the novel experimental intervention should be lower than if an intervention is already in widespread use and its safety profile has already been established.

9. GOVERNANCE AND ETHICAL CONSIDERATIONS

9.1. Management of participating sites and trial coordination

Each region will have a Sponsor and an RCC. Each RCC, at the direction of the Sponsor, will take primary responsibility for the management of participating sites. The processes by which each RCC will provide trial management and coordination is set out in each RSA.

9.2. Ethics and regulatory issues

9.2.1. Guiding principles

The study will be conducted according to the principles of the latest version of the Declaration of Helsinki (version Fortaleza 2013) and ICH GCP, and in accordance with all relevant local ethical, regulatory, and legal requirements as specified in each RSA.

9.2.2. Ethical issues relevant to this study

Patients who will be eligible for this study are hospitalized, and many eligible patients will be critically ill and receiving sedative medications for comfort, safety and to facilitate standard life saving procedures. In patients who are not necessarily receiving sedative medications, the presence of critical illness itself leads commonly to an altered mental state that will affect the patient's mental

capacity. The presence of these factors will mean that many patients who are eligible for the study will not be able to provide prospective consent for participation. Additionally, many interventions within this trial must be initiated urgently, either because there is an immediate time critical imperative to initiate the intervention, or because the most valid evaluation of the intervention occurs if the trial intervention is initiated at the same time-point as would occur in clinical practice.

The broad approach regarding consent that will be used in this study are as follows:

- In some regions or countries, consent from the patient, their authorized representative may be required prior to entering any data into the trial database to assess patients' eligibility for enrollment. In some regions or countries, an independent physician may confirm the emergency situation, capacity situation and potential benefit of study inclusion
- Patients who, in the opinion of the treating clinician, are competent to consent will be provided with information about the trial and invited to participate
- Many patients who are eligible for the Platform will not be competent to consent. For such patients, and as permitted by local laws and requirements for ethical approval:
    - For domains in which all interventions available at the participating site are regarded as being part of the spectrum of acceptable standard care by the clinicians at that site, entry to the study is preferred to be via waiver-of-consent or some form of delayed consent. If required by local laws or ethical requirements an alternative to this pathway will be participation in conjunction with the agreement of an authorized representative of the participant.
    - For domains in which at least one intervention available at the participating site is regarded as experimental or not part of the spectrum of acceptable standard care, then prospective agreement by an authorized representative will be required. An exception to this principle is recognized when there is a time-imperative to commence the intervention which would routinely preclude obtaining the prospective agreement by an authorized representative.
    - For domains in which eligibility may develop after initial enrollment in the trial, it is permissible to obtain contingent consent from the participant or contingent agreement from an authorized representative. This provides approval to randomize the participant for a domain subsequently contingent on meeting certain eligibility criteria.
    - Where any participant is enrolled without having provided their own consent the participant's authorized representative will be informed as soon as appropriate and

informed of processes to cease trial participation. If required by local laws or processes for ethical approval, the authorized representative will be asked to provide agreement to on-going participation. In undertaking these trial processes research staff will be cognizant of the need to avoid unnecessary distress or create unnecessary confusion for authorized representatives and all other persons who have an interest in the participant's welfare.

- Where any participant is enrolled without having provided their own consent, the participant should be informed of their enrollment after regaining competency and asked for their consent to continue participation, in accordance with local practice and jurisdictional requirements. Where any participant is enrolled and does not regain competency (due to their death or neurological impairment) the default position, subject to local laws and ethical review processes, will be that the enrolled person will continue to be a participant in the trial.

9.2.2.1. *Inclusion of participant data in analyses*

The multifactorial nature of the Platform, and the use of a common eCRF across all domains, creates issues related to withdrawal of consent by participants (or another person with authority to act on behalf of a participant in this context) after randomization. Participants or their authorized representatives may withdraw consent for participation at any time, which may constitute withdrawal of consent for continued receipt of interventions in one or more, or all, domains in which they have received an allocation (i.e., consent for participation), with or without withdrawal of consent for further collection of data. In some jurisdictions, participants or their authorized representatives may also be given the option to withdraw permission for the use of all data, including data that have already been collected. As the same CRF is used across multiple domains, it is not possible to withdraw consent for collection and use of data from one or more domains while permitting the collection and use of data for other domains.

All participants who withdraw consent for use of data will be reported in a CONSORT patient flow diagram, as per CONSORT requirements. A participant who withdraws consent for participation in an intervention allocated by the trial, but does not withdraw permission for data use, will be reported in CONSORT patient flow diagrams as having been randomized in that domain and, to abide by the ITT principle, will be analyzed in that domain, irrespective of their receipt of the allocated intervention.

Participants will be excluded from analyses if, at the time of the creation of the analysis dataset, it is known that consent has been withdrawn for participation in all domains in which they have received an allocation, and for the use of their data. In addition, participants will be excluded if they have been enrolled under a delayed consent model but consent cannot be obtained and ethical approvals do not permit the use of participant data without consent.

It is not possible to remove a participant's data retrospectively after an analysis that is being used for Public Disclosure. It is therefore important that the Consent CRF is completed as accurately and contemporaneously as possible, to ensure that consent information is available to the Data Coordination Centre and participant data is appropriately included or excluded from analyses.

9.2.3. Approvals

The protocol documents, consent form(s) and participant and/or authorized representative information sheet(s) will be submitted to an appropriate ethical review body at each participating country and institution and, as required, to any additional regulatory authorities. Written approval is required from all relevant ethical and regulatory bodies prior to commencement.

9.3. Protocol modifications

9.3.1. Amendments

A "substantial amendment" is defined as an amendment to one or more of the Core Protocol, Appendices to the Core Protocol, PANDA, DSA, or RSA that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial;
- the quality or safety of any intervention used in the trial;
- cessation of any intervention or domain for any reason;
- the addition of any new intervention within a domain; or
- the addition of new interventions within a new domain

All substantial amendments to the original approved documents, including all modifications of interventions available within a domain and the addition new domains, will be submitted for approval to all relevant ethical and regulatory review bodies that were required for original approvals. Non-substantial amendments will not be notified to such review bodies, but will be recorded and filed by the trial Sponsors.

Where the cessation of any intervention or any domain occurs for any reason, this is an operational issue and randomization to that intervention or domain will be ceased in the study database(s). Cessation of enrollment to an intervention or domain, either entirely, or within a prespecified subgroup, will be reported as required to all relevant regulatory bodies.

9.4. Confidentiality

The principles of confidentiality that will apply to this trial are that all trial staff will ensure that the confidentiality of all participants information will be maintained and preserved at all times. The participants will be identified only by a unique trial-specific number on all documents and electronic databases that contain any information specific to the participating individual. Each site will maintain a separate file that links each participant's unique trial-specific number to the participant's name and other identifying information. No other information will be maintained in the file that links the participant unique trial-specific number to participant identifying information.

9.5. Declarations of interest

All trial staff will be required to declare and update all interests that might or might be seen to influence one or both of the conduct of the trial or the interpretation of results. All members of the ITSC maintain a registry of interests. These are updated periodically and publicly accessible on the study website.

9.6. Post-trial care

The trial has no responsibility for the ongoing management or care of participants following the cessation of all trial specified interventions. See Section 8.4.2 for information relating to continuation of allocated interventions for participants transferred to other locations.

9.7. Communication

9.7.1. Reporting

Each participating site will comply with all local reporting requirements, as specified by that site's institution.

Should the entire trial be terminated, all relevant local ethical and regulatory bodies will be informed within 90 days after the end of the study. The end of the study is defined as the last participant's last follow-up.

9.7.2. Communication of trial results

Trial results will be communicated by presentation and publication, and made available on the trial website.

9.8. Publication policy

Manuscript(s) and abstract(s) resulting from the data collected during this study will be prepared by the corresponding DSWG in collaboration with the Reporting and Analysis sub-committee of the ITSC. Further details are provided in the trial Publication Policy. Where results are influenced by interaction between domains, the DSWG for both domains will take responsibility for preparation of manuscripts and abstracts. All manuscripts and abstracts reporting trial results that are prepared by one or more DSWGs must be submitted to and approved by the ITSC before submission.

Site investigators will not publish or present interim or definite results, including but not restricted to oral presentations without the prior permission of the ITSC. Authorship will be determined as outlined in the trial Publication Policy.

9.9. Data access and ownership

9.9.1. Data ownership

All data are owned by the responsible Sponsor under the custodianship of the ITSC. As the trial is intended to be perpetual, all data will be retained indefinitely.

9.9.2. Access to Data

Direct access will be granted to authorized representatives from ITSC, sponsors, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. The trial will comply with all relevant jurisdictional and academic requirements relating to access to data. Ownership and access to data where a commercial organization is involved in the trial (for example by provision of goods or services that are tested within a domain) will be set out in a contract between trial sponsors and that commercial organization.

9.10. Consent form

Template information and consent forms will be provided by RCCs to participating sites as an operational document.

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