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MEDICAL RESEARCH
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GLOBAL COALITION
FOR ADAPTIVE RESEARCH



Protocol Amendment to Pandemic Appendix to the Core Protocol Summary of changes

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

REMAP-CAP Pandemic Appendix to Core Protocol Amendment Summary Version 1 dated 24 May 2020

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1. CURRENT VERSIONS OF PROTOCOL DOCUMENTS

1.1. The current versions of pandemic specific protocol documents:

- REMAP-CAP Core Protocol Version 3, dated 10 July 2019
- Pandemic Appendix to Core Version 1.1, dated 12 February 2020
- Domain-Specific Appendices
 - COVID-19 Antiviral Therapy Domain-Specific Appendix Version 2, dated 01 April 2020
 - COVID-19 Immune Modulation Domain-Specific Appendix Version 1, dated 11 March 2020

2. AMENDMENT 1

The Pandemic Appendix to the Core Protocol document underwent an amendment in May 2020. There are two broad objectives associated with this amendment. Firstly, some aspects of the Appendix were updated to reflect accumulated knowledge and experience of how the Appendix applies to the COVID-19 pandemic. Secondly, in some regions of the world a separate and new Core Protocol had been developed, termed REMAP-COVID, which combines elements of the REMAP-CAP Core Protocol with the Pandemic Appendix to the Core Protocol, has been developed, approved and implemented. The REMAP-COVID Core Protocol is used in countries and locations that were not participating in REMAP-CAP prior to the COVID-19 pandemic and where the only objective of the platform was to evaluate treatments in patients with proven or suspected COVID-19 infection. Patients enrolled at locations in which REMAP-COVID Core Protocol is approved, as well as patients enrolled at locations in which the REMAP-CAP Core Protocol and Pandemic Appendix to the Core Protocol is approved, are all analyzed in the same pandemic statistical model. This version of the Pandemic Appendix achieves alignment between both sets of core documents.

2.1. Summary of changes

Section	Original text	New Text	Reason
Front page and whole document header	REMAP-CAP Pandemic Appendix to the Core Protocol Version 1.1 dated 12 February 2020	REMAP-CAP Pandemic Appendix to the Core Protocol (REMAP-COVID) Version 2 dated 18 May 2020	Administrative change
Summary Page 2	REMAP-CAP is an adaptive platform trial that evaluates multiple aspects of care of patients who are admitted to an Intensive Care Unit with severe Community Acquired Pneumonia. It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as severe Community Acquired Pneumonia with concomitant admission to an Intensive Care Unit. Previous pandemics and more localized outbreaks of respiratory emerging infections have resulted in severe Community Acquired Pneumonia and admission to an Intensive Care Unit.	REMAP-CAP is an adaptive platform trial that evaluates multiple aspects of care of patients who are admitted to an Intensive Care Unit (ICU) with severe Community Acquired Pneumonia. It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as severe Community Acquired Pneumonia with concomitant admission to an ICU. Previous pandemics and more localized outbreaks of respiratory emerging infections have resulted in severe Community Acquired Pneumonia (CAP) and admission to an Intensive Care Unit.	Administrative change
	Blank	Admission to an ICU may occur at the time of first presentation to a hospital or may be preceded by admission to a non-ICU ward or floor. For patients admitted to a non-ICU ward there is an opportunity to intervene to prevent the development of severe CAP.	Definition updated to align with the REMAP-COVID Core protocol that enrolls patients who are hospitalized but not in an ICU

	Blank	The Pandemic Appendix to the Core Protocol also achieves alignment with a separate document, REMAP-COVID Core Protocol, which comprises only those elements of the Core Protocol of REMAP-CAP and the Pandemic Appendix that applies to the COVID-19 pandemic. For the COVID-19 pandemic, a site can utilize either the REMAP-CAP Core Protocol combined with the Pandemic Appendix to the Core Protocol, or REMAP-COVID Core Protocol. Both sets of documents specify identical methods and data requirements. Data derived from sites using either set of documents is analyzed in the same pandemic statistical model. A single site must use either REMAP-COVID Core Protocol or REMAP-CAP Core Protocol with this associated pandemic appendix.	Explanation of the reason for amending this document
Summary Page 3	The objective of the Pandemic Appendix to the Core Protocol (PA t C) is to describe the adaptations to the Core Protocol that would apply during a pandemic, including how analyses of domains already operative during the interpandemic period as well as domains that are pandemic-specific, will be integrated during a pandemic.	The objective of the Pandemic Appendix to the Core Protocol (PA t C) is to describe the adaptations to the Core Protocol that would apply during a pandemic, including how analyses of domains already operative during the interpandemic period as well as domains that are pandemic-specific, will be integrated during a pandemic.	Administrative change
	The primary objective of the REMAP during a pandemic is to identify the effect of a range of interventions to improve outcome for patients with severe Community	The primary objective of the REMAP during a pandemic is to identify the effect of a range of interventions to improve outcome for patients admitted to a hospital	Definition updated to align with the REMAP-COVID Core protocol that

	Acquired Pneumonia, as defined by the pandemic primary end-point.	with acute illness due to suspected or proven pandemic infection, as defined by the pandemic primary end-point.	enrolls patients who are hospitalized but not in an ICU
	REMAP-CAP is a global trial examining the best treatments for community-acquired pneumonia. In the setting of a pandemic that causes pneumonia, some key aspects of the study will be changed to integrate new interventions into the trial, evaluate existing interventions within the trial specifically in patients with pandemic infection, alter trial governance, and provide time-critical data for public health.	REMAP-CAP is a global trial examining the best treatments for community-acquired pneumonia. In the setting of a pandemic that causes life-threatening respiratory infection, some key aspects of the study will be changed to integrate new interventions into the trial, evaluate existing interventions within the trial specifically in patients with pandemic infection, alter trial governance, and provide time-critical data for public health.	Updated to align with the REMAP-COVID Core protocol nomenclature. The disease of interest for both sets of core documents is acute illness due to suspected or proven COVID-19. A requirement for the presence of pneumonia no longer applies.
SECTION 3 PANDEMIC APPENDIX TO THE CORE PROTOCOL VERSION	Original text	New Text	Reason
3.1. Version History Page 9	Version 1.1: Approved by the Pandemic Working Group on 12 th February, 2020	Version 2.0: Approved by the Pandemic Working Group on 18 th May, 2020	Administrative change
SECTION 4 COVID-19 ANTIVIRAL DOMAIN GOVERNANCE	Original text	New Text	Reason
4.1. Members Page 9	Prof. Derek Angus	Prof. Derek Angus	Addition of investigator

	<p>Prof. Yaseen Arabi Prof. Richard Beasley A/Prof. Scott Berry Prof. Frank Brunkhorst Dr. Lennie Derde Dr. Robert Fowler Prof. Anthony Gordon Mr. Cameron Green Dr. Ed Litton Prof. John Marshall Dr. Colin McArthur Dr. Srinivas Murthy Prof. Alistair Nichol Ms. Jane Parker Prof. Kathy Rowan Prof. Tim Uyeki Prof. Steve Webb</p>	<p>Prof. Yaseen Arabi Prof. Richard Beasley A/Prof. Scott Berry Prof. Frank Brunkhorst Dr. Lennie Derde Dr. Robert Fowler Prof. Anthony Gordon Mr. Cameron Green Dr. Ed Litton Prof. John Marshall Dr. Colin McArthur A/Prof Bryan McVerry Dr. Srinivas Murthy Prof. Alistair Nichol Ms. Jane Parker Prof. Kathy Rowan Prof. Tim Uyeki Prof. Steve Webb</p>	
SECTION 6 BACKGROUND AND RATIONALE	Original text	New Text	Reason
6.1 Introduction Page 11	It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as severe Community Acquired	It is reasonable to presume that any pandemic respiratory infection of major significance to public health will manifest as life-threatening respiratory infection including Severe Acute Respiratory illness and	Updated to align with the REMAP-COVID Core protocol nomenclature

	<p>Pneumonia (CAP) with concomitant admission to an Intensive Care Unit (ICU).</p>	<p>severe Community Acquired Pneumonia (CAP) with concomitant admission to hospital, and for some patients, admission to an Intensive Care Unit (ICU).</p>	
	<p>One of the challenges associated with planning clinical trials during a pandemic is that the precise nature of the infecting organism, clinical consequences, and suitable interventions (particularly those that are pathogen-specific) cannot be reliably known in advance. Nevertheless, a range of scenarios can be anticipated and used to provide direction and guidance regarding the most appropriate research response.</p>	<p>One of the challenges associated with planning clinical trials during a pandemic is that the precise nature of the infecting organism, clinical consequences, and suitable interventions (particularly those that are pathogen-specific) cannot be reliably known in advance. The speed of clinical progression, from initial infection to life-threatening severe respiratory infection is another feature that cannot be reliably known in advance. It is likely that a proportion of patients will present with severe CAP but other patients may present to medical attention with illness that is less severe, but remain at risk of progression to severe illness. Patients who require hospital admission, but have less severe illness are a particularly important group, because early intervention at this stage of illness may prevent progression to life-threatening illness. It is also possible that proposed treatment interventions may have differential treatment effect depending on the level of illness severity at the time that treatment is commenced, including treatment effects that are divergent. Nevertheless, a range of scenarios can be</p>	<p>Updated to align with the REMAP-COVID Core protocol that enrolls patients who are hospitalized but not in an ICU</p>

		anticipated and used to provide direction and guidance regarding the most appropriate research response.	
Page 12	The pandemic potential of a novel Coronavirus that causes pneumonia is not known.	SARS-CoV-2 is the cause of a pandemic of severe respiratory disease (COVID-19), including pneumonia, that commenced in 2019.	Updated to acknowledge that Coronaviruses can result in a pandemic.
6.2.3. Pre-approved Page 13	It is highly likely that one or more research questions (in domains already approved during the interpandemic period) will be relevant specifically in patients with CAP caused by the pandemic infection.	It is highly likely that one or more research questions (in domains already approved during the interpandemic period) will be relevant specifically in patients with severe respiratory disease including pneumonia caused by the pandemic infection.	Updated to align with the REMAP-COVID Core protocol nomenclature
6.2.5.1. Time-critical generation of evidence Page15	Furthermore, as the trial progresses during a pandemic the Data Safety Monitoring Board (DSMB) has access to information from adaptive analyses that may not achieve thresholds to allow reporting as a Platform Conclusion but may be relevant to public health which, under appropriate circumstances, can be shared with public health authorities without threatening the scientific validity of the ongoing trial.	Furthermore, as the trial progresses during a pandemic the Data Safety Monitoring Board (DSMB) has access to information from adaptive analyses that may not achieve thresholds to allow reporting as a Platform Conclusion but may be relevant to public health which, under appropriate circumstances, can be shared with public health authorities and the DSMBs of other trials evaluating the same or similar interventions without threatening the scientific validity of the ongoing trial.	Updated to acknowledge that communication between DSMBs of different trials that are evaluating the same or similar interventions may be an important component of timely generation of evidence during a pandemic.
SECTION 7 ADAPTATION OF REMAP-CAP DURING A PANDEMIC	Original text	New Text	Reason

<p>7.1. Objectives Page 17</p>	<p>Blank</p>	<p>The primary objective of this REMAP during a pandemic is to identify the effect of a range of interventions to improve outcome for adult patients admitted to hospital with acute illness due to suspected or proven pandemic infection, as defined by the pandemic primary end-point.</p> <p>The secondary objective is to determine the effect of a range of interventions on additional endpoints, including endpoints developed by the World Health Organization and adopted core outcome sets.</p>	<p>Trial objectives updated to include an extended definition of the disease of interest and to incorporate collection of WHO recommended outcome measures as a secondary objective</p>
<p>7.2. Study setting: definition of an ICU and relationship of setting to severity of illness Page 18</p>	<p>Study setting: definition of an ICU</p> <p>During the interpandemic period, the REMAP recruits only participants who are admitted to an ICU. During a pandemic, there may be insufficient ICU beds available to care for all critically ill patients resulting in provision of advanced organ support occurring in locations other than an ICU.</p> <p>For sites at which the pandemic stratum (see below) has been activated, an area within the hospital that is able to deliver one or more of the qualifying organ failure supports specified in the Core Protocol (non-invasive ventilation, invasive ventilation, and vasopressor therapy) will meet the definition of an Intensive Care Unit. It is preferred in such circumstances that the</p>	<p>Study setting: definition of an ICU and relationship of setting to severity of illness</p> <p>During the interpandemic period, the REMAP recruits only participants who are admitted to an ICU, and a combination of admission to ICU as well as provision of treatments to support failed organs is used to define severity and eligibility. During a pandemic, there are several factors that may influence the relationship between admission to an ICU and severity of illness. Firstly, there may be insufficient ICU beds available to care for all critically ill patients. This may result in provision of advanced organ support occurring in locations that do not usually provide ICU-level care. During a pandemic, such a location is referred to as a re-</p>	<p>This section has been updated extensively as a consequence of practical experience with COVID-19. Definitions of both what constitutes an ICU and assumptions regarding a level of severity of illness that occurs in association with admission to an ICU are or have been important operational characteristics. These</p>

	<p>patient is under the care of a specialist who is trained in the provision of critical care, but this is not an essential requirement.</p>	<p>purposed ICU. However, a re-purposed ICU needs to be distinguished from a usual hospital ward that is capable of providing some forms of organ support, such as non-invasive ventilation. During a pandemic, there may be substantial delays in transferring a patient from an emergency department to either a ward or an ICU (or a re-purposed ICU). Patients in an emergency department who have been accepted for admission to an ICU are regarded as being admitted to an ICU. Patients in an emergency department who have been accepted for admission to a ward are regarded as being admitted to a ward. Secondly, patients who are not critically ill may be treated on an ICU for reasons that are not related to severity of illness, such as access to single rooms to achieve objectives related to infection control and prevention. This can influence both admission as well as discharge practices. Thirdly, the threshold at which support for failed organs is provided may be influenced by infection control practices. For example, some forms of respiratory support may be withheld because of concerns related to the risk that staff who are caring for patients may acquire the infection.</p> <p>To minimize these issues, during a pandemic, the primary determinant of severity is the provision of ICU-</p>	<p>updates are needed to ensure adequate matching between intention of protocol documents and need for operational definitions that take into account changes in practice and policy in healthcare systems in which REMAP-CAP is active.</p>
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		<p>level care, which can be interpreted in conjunction with the physical location in which care is being provided. Determination of severity may also take into account a decision to withhold some form of organ failure support that would otherwise have be provided. Where a definition of an ICU is needed, at sites at which the pandemic stratum (see below) has been activated, an area within the hospital that is repurposed so as to be able to deliver one or more of the qualifying organ failure supports specified in the Core Protocol (non-invasive ventilation, invasive ventilation, and vasopressor therapy) will meet the definition of an Intensive Care Unit. It is preferred in such circumstances that the patient is under the care of a specialist who is trained in the provision of critical care, but this is not an essential requirement. A respiratory or other ward that provides non-invasive ventilation (including oxygen therapy delivered by high flow nasal cannula) and continues to do so during a pandemic, will not, generally, meet the definition of an ICU, particularly if the patient is not under the care of a specialist who is trained in the provision of critical care.</p> <p>In some DSAs, an exclusion criteria is applied to only permit enrolment during a time-window that</p>	
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		<p>commences with ICU admission. For the reasons noted above, this may be operationalized using a time-window, of the same duration, that commences with the provision of sustained organ failure support.</p>	
<p>7.3. Eligibility criteria Page 19</p>	<p>Platform-level eligibility criteria may be modified if necessary to accommodate a published case definition, to align with criteria specified in guidelines, such as the ATS/IDSA guidelines on CAP16, or to accommodate necessary modifications to the online eligibility system used for enrolment. In previous epidemics of community-based infection, nosocomial acquisition has been well described. Relaxation of the requirement for community acquisition or organ failure criteria or both may be appropriate. All changes to eligibility criteria would apply only to patients in the pandemic stratum (see section 7.3).</p>	<p>Platform-level eligibility criteria may be modified if necessary to accommodate a published case definition, to align with criteria specified in guidelines, such as the ATS/IDSA guidelines on CAP16, or to accommodate necessary modifications to the online eligibility system used for enrolment. In previous epidemics of community-based infection, nosocomial acquisition has been well described. Relaxation of the requirement for community acquisition or organ failure criteria or both may be appropriate. In this regard, Version 2.0 of this Appendix modifies the organ failure support criteria so that these no longer apply as a platform-level inclusion criteria, permitting the enrolment of patients into the platform who are admitted to hospital or an ICU, either with or without organ failure support criteria. In association with the removal of the organ failure requirement, the requirement for a patient to meet criteria for pneumonia may be replaced with a requirement for acute illness due to suspected or proven pandemic infection. All changes to eligibility</p>	<p>Updated eligibility criteria to align with the REMAP-COVID Core protocol that enrolls patients who are hospitalized but not in an ICU and to align the nomenclature</p>

		<p>criteria would apply only to patients in the pandemic stratum (see section 7.4).</p> <p>As such, the modified platform-level inclusion and exclusion criteria are:</p> <p>In order to be eligible to participate in the pandemic aspects of REMAP-CAP, a patient must meet the following criteria:</p> <ol style="list-style-type: none">1. Adult patient admitted to hospital with acute illness due to suspected or proven pandemic infection <p>A potentially eligible patient who meets any of the following criteria will be excluded from participation in this trial:</p> <ol style="list-style-type: none">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 treatment2. Patient is expected to be discharged from hospital today or tomorrow3. More than 14 days have elapsed while admitted to hospital with symptoms of an acute illness due to suspected or proven pandemic infection4. Previous participation in this REMAP within the last 90 days	
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		<p>This extension of the platform-level inclusion criteria can apply to patients admitted to an ICU or a ward. In association with the involvement of different clinical teams, the domains and interventions that are available for patients admitted to a ward compared with those admitted to an ICU are permitted to be, but do not have to be, different.</p>	
<p>7.5.1. Introduction Page 21</p>	<p>A PISOP patient can contribute to both the pandemic and interpandemic model in different domains but each patient’s contribution to a model is mutually exclusive with respect to each domain. The ITSC will select the domains to be included in the pandemic model where a differential treatment effect is postulated in the presence of pandemic infection or the need exists to learn about the outcome quickly, or both.</p>	<p>A PISOP patient can contribute to both the pandemic and interpandemic model in different domains but each patient’s contribution to a model is mutually exclusive with respect to each domain. The ITSC will select the domains to be included in the pandemic model where a differential treatment effect is postulated in the presence of pandemic infection or the need exists to learn about the outcome quickly, or both. The extension of this platform-level entry criteria does not apply to domains that are analyzed exclusively within the interpandemic statistical model.</p>	<p>Updated to improve clarity of disposition of patients and domains with respect to the interpandemic and the pandemic statistical models.</p>
<p>Page 22</p>	<p>For example, PISOP patients may be analyzed within a pandemic version of the domain specific statistical model utilizing a modified primary end-point, with application of informative priors derived from the interpandemic time period.</p>	<p>For example, PISOP patients may be analyzed within a pandemic version of the domain specific statistical model utilizing a modified primary end-point, with application of informative priors derived from the interpandemic time period.</p>	<p>Correction of spelling errors. The protocols use US spelling.</p>

<p>7.5.2. Pre-specification of trial parameter options Page 22</p>	<p>The selected trial parameters would be placed in the public domain, on the study website, and provided as an update to participating sites and relevant ethical review bodies prior to the first adaptive analysis of the PISOP stratum.</p>	<p>The selected trial parameters would be placed in the public domain, on the study website, and provided as an update to participating sites and relevant ethical review bodies prior to the first adaptive analysis of the PISOP stratum. These parameters are set out in a document termed Operating Characteristics and this document applies to both REMAP-CAP core protocol documents as well as the REMAP-COVID Core Protocol, to the extent that is necessary. It is also acknowledged that specification in a new domain, may influence a pre-existing domain, such as specification of evaluation of an interaction between domains. In this situation, the DSA for the pre-existing domain will not necessarily be amended immediately with the most recently approved or amended DSA serving to specify the inter-relationship between the two domains.</p>	<p>Updated to improve clarity regarding the role of the Operating Characteristics document</p>
<p>7.5.3. Application of other strata specified in the Core Protocol in the pandemic model Page 23</p>	<p>For PINSNIP patients, the “influenza present” stratum would continue to apply and would be used to differentiate patients infected with a non-pandemic strain of influenza from patients in the “influenza not present” stratum.</p>	<p>For PINSNP patients, the “influenza present” stratum would continue to apply and would be used to differentiate patients infected with a non-pandemic strain of influenza from patients in the “influenza not present” stratum.</p>	<p>Correction of acronym spelling error. PINSNP - Pandemic infection is <u>neither suspected nor proven</u></p>
<p>Page 24</p>	<p>If eligibility criteria were modified to allow inclusion of a wider spectrum of illness severity, an additional strata</p>	<p>If eligibility criteria were modified to allow inclusion of a wider spectrum of illness severity, two or more states, related to severity of illness, may be applied within the</p>	<p>The possibility of enrolling patients with a wider spectrum of illness</p>

	<p>may be applied within the PISOP stratum to distinguish current versus extended severity of illness.</p>	<p>PISOP stratum to distinguish current versus extended severity of illness.</p>	<p>severity, i.e. patients with less severe illness, was acknowledged in the previous version but this should have identified the dynamic nature of severity of illness, i.e. a state not a strata.</p>
<p>7.5.5. States within the PISOP stratum Page 24</p>	<p>Blank</p>	<p>The Core Protocol defines ‘state’ as a set of mutually exclusive and exhaustive categories, defined by characteristics of a patient within the REMAP, that are capable of changing over time for a single patient at different time-points during the patient’s participation in the REMAP (i.e. they can be dynamic). During the pandemic, and only for patients in the PISOP stratum, two or more states may be defined, depending on illness severity. The default categorization of severity will be into two categories:</p> <ul style="list-style-type: none"> • Severe State, defined by receiving organ failure support in an ICU • Moderate State, defined by <ul style="list-style-type: none"> o Not being admitted to an ICU, or o Admitted to an ICU but not receiving organ failure support 	<p>New paragraph that recapitulates the definition of ‘state’ from the Core Protocol and defines two states that will apply to PISOP patients during this pandemic. Added to align with the REMAP-COVID Core protocol</p>

		<p>Organ failure supports that qualify a patient as severe are aligned to those that previously determined eligibility to the platform (i.e. the Severe State corresponds to the previous platform eligibility criteria). These criteria are:</p> <ul style="list-style-type: none"> • Provision of invasive mechanical ventilation • Provision of non-invasive mechanical ventilation (including high flow nasal cannula with a flow rate of at least 30 litres per minutes and a fractional inspired oxygen concentration of 40% or higher) • Receiving infusion of vasopressor or inotropes or both <p>Where states are defined, eligibility for domains or selected interventions within a domain, may be specified according to state. As such, a domain may be available in one or more states. Where a domain is available in two or more states, the interventions available in that domain in each state are permitted to vary. States can also be utilized within the statistical model to define the unit-of-analysis, with declaration of Platform Conclusions, independently in one or more states, with borrowing permitted between states. A single patient can move between states, one or more times, during a period of time which the patient is potentially eligible within the REMAP. For the purposes</p>	
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		<p>of assessment of eligibility for one or more domains, state is ‘instantaneous’ as at the time of that assessment. A patient who has previously received non-invasive ventilation or an infusion of vasopressor or inotrope or both, but is not receiving either of those therapies at time of assessment is deemed to be in the Moderate State. A patient who has been in the Severe State, as a consequence of receiving invasive mechanical ventilation in an ICU, cannot re-enter the Moderate State for the purposes of assessment of eligibility. A patient who receives an assignment in the REMAP while in the Severe State cannot receive any subsequent assignments in the Moderate State. Where trial related processes, such as reveal of assignment or obtaining consent, create a time gap between initial assessment of eligibility and awareness of the patient’s assignment, the state in which the patient is analyzed is that which occurred at the time of assessment, not the time of reveal of the assignment.</p> <p>A patient enrolled while in the Moderate State, if reassessed for eligibility for additional domains having progressed to the Severe State, may have new microbiological information that has accumulated during this interval of time. This could result in a patient</p>	
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		with suspected pandemic infection having information that results in pandemic infection being excluded, at the time of reassessment. In this situation, the patient is analyzed in the pandemic model, as enrolled, in the Moderate State and is not eligible for enrolment in new domains in the Severe State (including domains evaluated in the interpandemic model). It is also noted that, for a patient who is enrolled in both states, that other time-varying baseline variables may have changed between each enrolment. For such patients, potential time-varying baseline variables will be collected in reference to enrolment in the Moderate State and again in reference to enrolment in the Severe State.	
7.5.6.1. Non-influenza organism Page 26	The Antiviral Domain (which includes only antiviral agents active against influenza) would not be applied in the pandemic model.	The Influenza Antiviral Domain (which includes only antiviral agents active against influenza) would not be applied in the pandemic model.	Addition of the word <i>influenza</i> to differentiate between the Antiviral Domain for pandemic (non-influenza) patients and the Antiviral Domain for non-pandemic (influenza) patients.
7.5.6.2. Influenza pandemic Page 27	The default plan is that during a pandemic, patients in the PISOP and PINSNIP stratum will be eligible to receive an assignment in these domains and will be analyzed in	The default plan is that during a pandemic, patients in the PISOP and PINSNP strata will be eligible to receive an assignment in these domains and will be analyzed in	Correction of acronym spelling error. PINSNP - Pandemic_infection is

	<p>the interpandemic model which will continue to be analyzed for statistical triggers and platform conclusions.</p>	<p>the interpandemic model which will continue to be analyzed for statistical triggers and platform conclusions.</p>	<p><u>neither suspected nor proven.</u> Correction of grammatical error <i>stratum</i> changed to <i>strata</i>.</p>
<p>7.6.1. Pandemic primary endpoint Page 27</p>	<p>The default pandemic primary endpoint will be a composite end-point that comprises the number of whole and part study days for which the patient is alive and not admitted to an ICU up until the end of study day 21. All patients who die before discharge from an acute hospital, irrespective of whether this occurs before or after D21, will be coded as zero days.</p> <p>If appropriate, based on an understanding of clinical and biological factors, as well as operational factors, an alternative pandemic primary end-point may be specified at the time of activation of the PATC. Other possible primary end-points include days alive and outside the ICU with alternative durations of follow up</p>	<p>The default pandemic primary endpoint will be an ordinal scale that is a composite end-point that comprises mortality during the acute hospital admission and the number of whole and part study days for which the patient is alive and not requiring organ failure support while admitted to an ICU up until the end of study day 21. All patients who die before discharge from an acute hospital, irrespective of whether this occurs before or after D21, will be coded as 1 day. All patients who never receive organ failure support while admitted to an ICU will be coded as 22.</p> <p>If appropriate, based on an understanding of clinical and biological factors, as well as operational factors, an alternative pandemic primary end-point may be specified at the time of activation of the PATC or at any time prior to the first interim analysis using the pandemic statistical model. Other possible primary end-</p>	<p>This represents a change to the primary end-point. The first interim analysis utilizing the pandemic statistical model has not yet occurred. The change in definition relates to the need for an end-point that is suitable for less severe patients as well as the observation that, in some locations, policies related to admission and discharge from the ICU are modified because of ICU-bed availability or infection control policies</p>

	<p>or the use of an alternative composite based on days alive without organ support. The pandemic primary endpoint will be used for the adaptive analyses that inform the RAR and for Statistical Triggers.</p>	<p>points include days alive and outside the ICU with alternative durations of follow up or the use of an alternative composite based on admission to ICU. The pandemic primary endpoint will be used for the adaptive analyses that inform the RAR and for Statistical Triggers.</p> <p>If the primary end-point includes a time-based outcome measure, assignment to one or more domains will occur at different time-points if the patient receives assignments in one or more domains while in the Moderate State and one or more domains in the Severe State. The commencement of the period of observation commences at the time of assignment, which can lead to the same patient having different values for different domains, as determined by the state in which enrolment occurred. This can be accommodated because there are separate statistical models for each state. Where a patient is eligible for two or more domains in a state, assignment can only occur at a single time-point, i.e. it is not possible to have more than one time of assignment different domains in the same state.</p>	<p>or both. As such, location of the patient no longer served as a valid surrogate for severity of illness. As a consequence, the primary end-point has been updated to capture actual provision of organ failure support while admitted to an ICU. Additionally, to improve the operating characteristics of the original ordinal scale, new categories have been created at either end of the scale to differentiate patients who die from those who have provision of organ failure support throughout 21 days of an ICU admission and to</p>
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			<p>differentiate patients ever admitted to an ICU from those who are never admitted.</p> <p>Operational clarity of how the end-point is applied to a patient who receives an assignment in the platform at different time points, while in different states, is provided.</p>
<p>7.7.2. Response adaptive randomization Page 29</p>	Blank	<p>Within the PISOP stratum, and only for domains with five or more interventions, the minimum RAR proportion may be decreased to less than 10% but will not be decreased to less than 5%.</p>	<p>An update to how RAR is applied in domains with a large number of interventions to maintain appropriate statistical properties with respect to participant assignment.</p>
<p>7.7.3. Unit-of-analysis Page 29</p>	Blank	<p>7.7.3. Unit-of-analysis</p> <p>7.7.3.1. Application of additional strata</p> <p>Patients within the PISOP stratum may be further stratified dependent on whether pandemic infection is</p>	<p>New sub-headings to distinguish application of additional strata and</p>

		<p>confirmed or not confirmed by microbiological testing. Additional strata may be applied and this can be specified in a DSA. Any or all of these strata can be utilized to determine eligibility for a domain or an intervention within a domain. These strata can also be used to define a unit-of-analysis in the pandemic statistical model.</p> <p>7.7.3.2. Application of state</p> <p>The state, at time of first enrolment, can also be used to determine eligibility or be used to define a unit-of-analysis or both. Where specified in the statistical model, the treatment effect of an intervention is allowed to vary between different states. A Bayesian Hierarchical Model (BHM) is used for all treatment-by-state interactions. In the BHM a hyperprior is used for the differing treatment effects across states. The standard deviation of the hyperprior, gamma, is a modelling starting estimate for the variation in the magnitude of the difference in treatment effects between states. By default, the starting estimate of the difference is zero. The gamma parameter influences the extent to which the treatment effect of interventions is permitted to vary between states. At the</p>	<p>application of state are applied.</p> <p>Application of state is an entirely new section that deals with aspects of the statistical analysis that occur as a consequence of the specification and application of states.</p>
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		<p>commencement of a model, the gamma parameter must be set, for each domain-state pair.</p> <p>In this REMAP, only three options are permitted with respect to specifying the gamma parameter for each domain-state pair. Firstly, gamma may be set to zero. The effect of this is that treatment effect of an intervention is assumed proportional between specified states. The unit-of-analysis is not sub-divided according to state. If gamma is set to zero for all states for a domain, the unit of analysis is all patients randomized in that domain. Secondly, and at the opposite extreme, gamma can be set to infinity. In this situation treatment effect is evaluated separately and independently in each state (with no borrowing between states). Thirdly, gamma may be set to a defined number between zero and infinity. This parameter value cannot be varied for different domain-state pairs, a global REMAP value has been selected. This specified value for gamma places a constraint on the variance of the difference in treatment effect in different states but permits the model to estimate treatment effect for patients enrolled in one state by borrowing from patients enrolled in one or more adjacent states. Borrowing occurs to the extent that it is supported by the accumulated data, but the</p>	
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		<p>setting of gamma influences the amount of borrowing and how quickly borrowing is able to occur. The value of gamma 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 equivalence or superiority. Where a value for gamma is specified in the pandemic statistical model, in this REMAP the value of gamma will be 0.15.</p> <p>A patient who is enrolled in a defined state, may have a clinical course that evolves with the patient entering a new state. Progression from one state, to another, may trigger eligibility for one or more domains. Where this occurs and the change in state defines a new unit-of-analysis, the RAR proportions may be different in each state. In this situation the RAR proportions that are relevant to that patient's state will be applied. In this regard, randomization to one or more domains in an initial state will occur, using RAR proportions that apply to that state with a separate subsequent randomization to one or more domains occurring if the patient enters a new state, with RAR proportions that apply to that state. When a new state commences there may be insufficient patients to determine valid RAR proportions for that domain in the new state. In this situation either</p>	
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		<p>RAR proportions are balanced or RAR proportions from an adjacent state are applied (unless otherwise specified in a DSA).</p> <p>The RAR proportions that apply when state is used to define a unit-of-analysis are derived from all patients who receive an assignment in a domain in that state, irrespective of whether the patient was assigned an intervention in a different domain in a different state.</p> <p>7.7.3.3. Analyses for combinations of therapies</p> <p>Unless otherwise specified in a DSA, a Platform Conclusion can be reached for combinations of treatments that are being evaluated within the platform. This applies to interventions within a domain as well as interventions in different domains. As such, all of the following can be reported as Platform Conclusions: an interaction between interventions in different domains and that the treatment effect of more than one active intervention is different to a no treatment (standard of care) intervention. A domain that contains two or more treatments, each of which is assigned against a no treatment control in a factorial manner (i.e. the N x N table of yes / no for n treatments) will be analyzed as an N x N factorial. Structuring the</p>	
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		analysis in this way allows the model to learn more quickly about the effectiveness of each treatment, recognizing common treatment exposure across intervention assignments.	
7.7.4.2. Intervention Inferiority Statistical Trigger Page 31	At any adaptive analysis, if a single intervention has at least a 0.95 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population.	At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being a member of the optimal regimen, for that unit-of-analysis, then that intervention will be deemed as being superior to all other interventions in that domain in that target population.	Updated to a more stringent probability as a consequence of the conduct of simulations which demonstrated inadequate control of type I error with previous threshold probability.
7.7.4.3. Intervention Efficacy Statistical Trigger Page 32	Blank	7.7.4.3. Intervention Efficacy Statistical Trigger For any domain that has (or had) a non-active control intervention, statistical triggers for efficacy of other interventions can be determined. At any adaptive analysis, if a single intervention has at least a 0.99 posterior probability of being superior to the inactive control intervention, for that unit-of-analysis, then that intervention will be deemed as being effective in that domain in that target population. At any adaptive analysis, if a single intervention has a greater than 90% probability of being harmful, compared to an inactive control intervention, for that unit-of-analysis, then the	Addition of a new type of statistical trigger. The need for this has emerged as a consequence of several of the COVID-19 specific domains having a ‘no intervention control’ (i.e. standard of care control) rather than a comparative effectiveness structure.

		<p>intervention will be deemed as being harmful in that domain in that target population.</p> <p>The declaration of a Platform Conclusion by the DSMB for efficacy may not result in any actions and may occur after the non-active intervention has been removed.</p> <p>This Platform Conclusion mathematically would occur simultaneously to Superiority in a 2-intervention domain. If a determination of efficacy for an intervention with a currently randomized non-active control then the non-active control should be dropped and the RAR set to 0. In contrast, declaration of a Platform Conclusion for harm will result in removal of that intervention from the platform for that unit-of-analysis, together with Public Disclosure.</p>	<p>As such, the inclusion of this type of statistical trigger permits conclusions to be drawn regarding effectiveness of an intervention against just the standard of care control, which corresponds to a highly clinically relevant question.</p>
<p>7.7.4.4. Intervention Inferiority Statistical Trigger Page 32</p>	<p>At any adaptive analysis, if a single intervention has less than a 0.05 posterior probability of being a member of the optimal regimen, for a unit-of-analysis, then that intervention will be deemed as being inferior to other interventions in the domain for that target population.</p> <p>An asymmetrical inferiority statistical trigger may be set, particularly if an active intervention was being evaluated against an intervention that specifies no active treatment in that domain.</p>	<p>At any adaptive analysis, if a single intervention has less than a 0.01 posterior probability of being a member of the optimal regimen, for a unit-of-analysis, then that intervention will be deemed as being inferior to other interventions in the domain for that target population.</p> <p>The 0.01 threshold is reduced as a function of how many units-of-analysis are available for the inferiority calculation (divided by the number of units minus 1). An asymmetrical inferiority statistical trigger may be set, particularly if an active intervention was being</p>	<p>Updated to a more stringent probability as a consequence of the conduct of simulations which demonstrated inadequate control of type I error with previous threshold probability. Operationally, this permits removal of</p>

		evaluated against an intervention that specifies no active treatment in that domain.	standard of care control when the aggregate effect of two or more active interventions is superior to the control, even if it is not yet known which active interventions are effective or their relative effectiveness. Similarly, it permits, with an asymmetric trigger, the removal of an intervention that is worse than a standard of care control.
7.7.4.5. Equivalence and futility Page 32	7.6.3.4. Equivalence The equivalence boundary (delta) for different endpoints selected for the PISOP stratum may be changed depending on the clinical impact of the delta for the chosen endpoint. The default delta for the Core Protocol will be used to select clinically similar effects on the chosen primary endpoint. If a 21-day ICU free	7.7.4.5. Equivalence and futility The equivalence boundary (delta) for different endpoints selected for the PISOP stratum may be changed depending on the clinical impact of the delta for the chosen endpoint. The default delta for the Core Protocol will be used to select clinically similar effects on the chosen primary endpoint. If a mortality or 21-day ICU or organ support free day endpoint is selected the	There is no change to the evaluation of equivalence but introduces a trigger for futility, which corresponds to a ‘one-sided’ evaluation of equivalence, which is

	<p>day endpoint is selected the 20% proportional odds equivalency delta will be the default.</p> <p>Alternatively, a DSA may specify a futility boundary (delta) with respect to the primary end-point. For the pandemic primary end-point, the default futility boundary for an intervention will be set as a posterior probability of less than 0.05 for at least a 20% odds-ratio improvement. This rule corresponds to the one-sided equivalency region.</p>	<p>20% proportional odds equivalency delta will be the default.</p> <p>Alternatively, a DSA may specify a futility boundary (delta) with respect to the primary end-point. For the pandemic primary end-point, the default futility boundary for an intervention will be set as a posterior probability of less than 0.05 for at least a 20% odds-ratio improvement. This rule corresponds to the one-sided equivalency region.</p>	<p>appropriate for a standard of care control.</p>
<p>7.7.4.6. Statistical thresholds for early phase interventions Page 33</p>	<p>Blank</p>	<p>7.7.4.6. Statistical thresholds for early phase interventions</p> <p>During the pandemic there may be need to test multiple candidate interventions that are at an early phase of development, identifying those interventions that are most promising to be retained within the platform. Such interventions may be evaluated after a fixed recruitment against a 'stop-go' criteria for retention, and expansion, within the platform. The default threshold for retention and expansion of an intervention will be a posterior probability of 0.5 or more that there is at least a 30% benefit in odds ratio.</p>	<p>This is an entirely new section that is designed for early phase (i.e. phase II type) interventions for which rapid learning is desirable.</p>
<p>SECTION 8 GOVERNANCE, ETHICAL, AND OPERATIONAL</p>	<p>Original text</p>	<p>New Text</p>	<p>Reason</p>

CONSIDERATIONS IN A PANDEMIC			
<p>8.2 Safety Monitoring and Reporting Page 34</p>	<p>Blank</p>	<p>8.2. Safety Monitoring and Reporting During the interpandemic period, the platform evaluates solely or predominantly interventions that are in widespread clinical use for severe CAP and for which the safety profile of the intervention is well described. During a pandemic, the platform may evaluate therapeutic agents that have been repurposed or are an Investigational Medical Product. Such therapeutic agents may not have an established safety profile or an established safety profile when used in critically ill patients. Where an intervention is not regarded as having an established safety profile, this will be specified in the DSA. For this type of interventions more specific or more detailed SAE reporting will be required that is specified in the Core Protocol, as follows. This may include Adverse Events of Special Interest (AESI). SAEs that might be attributable to specific interventions are included as secondary endpoints in each DSA but are recorded only for participants who are enrolled in that domain. If more detailed SAE or AE/AESI reporting is required for an intervention, then this additional safety reporting requirement will be specified in the relevant DSA and recorded only for participants</p>	<p>New section which substantially updates the approach to safety monitoring and reflects incorporation within the platform of some interventions that are re-purposed medications, as well as others which are unlicensed medicines. In both of these situations the prior safety knowledge of the intervention in this patient population is substantially less than when the platform was evaluating solely or predominantly comparative effectiveness interventions that were in widespread use.</p>

		<p>who are enrolled in that domain. The following arrangements apply to such</p> <p>When submitting the SAE form the local site PI should determine if the SAE is attributable to one or more study interventions in this trial. The local PI will assess if it is possible, probable, or certain that there is a direct link between a trial intervention and the SAE (a Serious Adverse Drug Reaction, SADR).</p> <p>The regional / country project manager should review the SAE form for completeness and query any missing data with the site. Preliminary SAE report forms should be submitted as soon as the site becomes aware. It is recognized that follow-up information may be available later.</p> <p>The regional lead investigator, or medically qualified designee, should review the SAE to assess expectedness and causality. The regional lead investigator or delegate cannot downgrade the site's assessment of expectedness and causality. The following requirements are specified:</p> <ul style="list-style-type: none">• The regional Sponsor should be made aware of the SAE within 24 hours of the SAE being reported.• All SAEs must be followed-up until resolution, or end of trial if this is sooner.	
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		<ul style="list-style-type: none">• SAEs will be reported to the relevant ethics committee and competent authority according to local regulations and requirements. <p>All SAEs, pooled from all regions, will be reported to the DSMB at intervals agreed by the REMAP-CAP investigators and the DSMB. This may vary depending on the specific intervention being evaluated. The DSMB may request additional specialist review of safety data for certain interventions.</p> <p>If drugs have been supplied by a pharmaceutical company, then reporting of safety data to the company may be required. The details of this reporting will be included in individual Safety Data Exchange Agreements (SDEA).</p> <p>On an annual basis a Developmental Safety Update Report (DSUR) will be produced including all SAE data from all regions in REMAP-CAP and will be submitted to the relevant competent authorities as required. This may be shared with pharmaceutical companies as part of the SDEA.</p> <p>If an SAE is determined to be unexpected (not previously described in the Summary of Product Characteristics / Investigator Brochure / Protocol) and related to the study medication then it is considered a</p>	
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		<p>SUSAR. In these cases, the following steps should also be undertaken, in addition the performing the steps described above for handling SAEs:</p> <ul style="list-style-type: none"> • The relevant competent authorities and ethics committees should be notified of the SUSAR by the Sponsor or designee in each region. • A SUSAR that results in death or is life-threatening, should be reported to the aforementioned bodies within 7 days of the Sponsor (or designee) becoming aware of the event. Further relevant information should be sought and a follow-up report completed as soon as possible and submitted within 8 additional days. A SUSAR which does not result in death or is not life-threatening should be reported within 15 days of the Sponsor (or designee) becoming aware of the event or in accordance with the local regulatory requirements. Further relevant information should be given as soon as possible. The regional / country project managers should notify all investigators at all sites that a SUSAR has occurred. The REMAP-CAP DSMB should be notified that a SUSAR has occurred. <p>It may be necessary to take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety,</p>	
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		<p>without prior authorization from a regulatory body. If this occurs the regulatory bodies should be notified as soon as possible and in any event within three days, in the form of a substantial amendment, that such measures have been taken and the reasons why. SAEs reported will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA). Coding will be to lowest level terms. The preferred term, and the primary system organ class will be listed. Summaries of all SAEs by treatment group will include:</p> <ul style="list-style-type: none"> • The number and percentage of patients with at least 1 SAE by system organ class and preferred term • The number of SAEs by relationship to treatment (related, not related), presented by system organ class and preferred term 	
<p>8.4. Role of the DSMB Page 37</p>	<p>While the PISOP stratum is open the DSMB is also permitted to liaise with public health authorities, regarding the results and appropriate interpretation of adaptive analyses in keeping with prevailing international standards. If the DSMB communicates with public health authorities the ITSC must be informed that such communication has occurred but the content of that communication may remain confidential</p>	<p>While the PISOP stratum is open the DSMB is also permitted to liaise with public health authorities, regulatory authorities, or the DSMBs of trials evaluating the same or similar interventions regarding the results and appropriate interpretation of adaptive analyses in keeping with prevailing international standards. If the DSMB communicates with external groups the ITSC may be informed that such communication has occurred but</p>	<p>The description of external groups that the DSMB may liaise with has been expanded to be include the DSMB of overlapping trials. The word <i>must</i> has been changed to <i>may</i> to clarify</p>

	<p>between the DSMB and the relevant public health authorities. The DSMB may recommend to the ITSC that public reporting of posterior probabilities that have not attained a threshold for a Statistical Trigger should occur.</p>	<p>the content of that communication may remain confidential between the DSMB and the relevant group. The DSMB may recommend to the ITSC that public reporting of posterior probabilities that have not attained a threshold for a Statistical Trigger should occur.</p>	<p>that the DSMB is not obliged to inform the ITSC regarding communication with external groups.</p>
<p>8.6. Funding of the trial Page 37</p>	<p>Possible sources of additional resources include, but are not limited to, healthcare systems, public health authorities, and local and international research funding bodies.</p>	<p>Possible sources of additional resources include, but are not limited to, healthcare systems, pharmaceutical companies, public health authorities, and local and international research funding bodies.</p> <p>A section of the Core Protocol indicates that “the trial will not enter into a contract with a commercial organization unless the contract specifies that, among other clauses, “that all data are owned by the trial and the commercial organization has no authority to access data”. This clause should not be interpreted as indicating that access to data by a commercial organization is not permitted. Such as access can be agreed, for example, by licensing access to data, if agreed by both a commercial partner and trial sponsors.</p>	<p><i>Pharmaceutical companies</i> added to reflect that medicine interventions have been added that might be externally funded</p>

