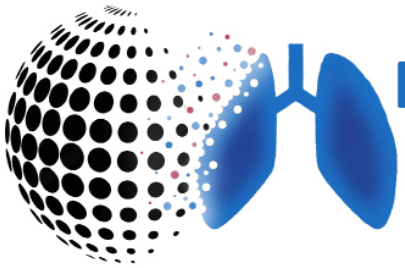

REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Domain-Specific Appendix: Cysteamine Domain

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

Cysteamine Domain-Specific Appendix Version 1 dated 21st June 2021

Summary

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

- No Cysteamine (no placebo)
- Cysteamine

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

☐ No Cysteamine (no placebo)

☐ Cysteamine

This DSA applies to the following states and stratum:

<table>
<tr><td>Stratum</td><td colspan="3">Pandemic infection suspected or proven (PISOP)</td><td>Pandemic infection neither suspected nor proven (PINSNP)</td></tr>
<tr><td>Core protocol documents</td><td colspan="3">REMAP-CAP Core Protocol + Pandemic Appendix</td><td>REMAP-CAP Core Protocol</td></tr>
<tr><td>Illness Severity State</td><td colspan="2">Moderate State</td><td>Severe State</td><td>Severe State</td></tr>
<tr><td>Interventions specified in this DSA</td><td colspan="2">Not available</td><td>No cysteamine
Cysteamine</td><td>No cysteamine
Cysteamine</td></tr>
<tr><td>Interventions submitted for approval in this jurisdiction</td><td colspan="2">Not available</td><td>• No cysteamine
• Cysteamine</td><td>• No cysteamine
• Cysteamine</td></tr>
<tr><td rowspan="2">Interventions offered at this site</td><td>Ward</td><td>ICU</td><td>ICU</td><td>ICU</td></tr>
<tr><td>Not available</td><td>Not available</td><td>• No cysteamine
• Cysteamine</td><td>• No cysteamine
• Cysteamine</td></tr>
</table>

REMAP-CAP: Cysteamine Domain Summary	
Interventions	• No cysteamine (no placebo) • Cysteamine
Unit of Analysis, Strata, and State	This domain is analyzed only in the inter-pandemic statistical model and includes both patients who are in the pandemic suspected or proven (PISOP) stratum and patients who are in the pandemic infection neither suspected nor proven (PINSNP) stratum. Unit-of-analysis may also be defined by influenza strata. Borrowing is permitted between strata. Response Adaptive Randomization may be applied.
Evaluable treatment-by-treatment Interactions	No interaction will be evaluated with any other domain.
Nesting	None
Timing of Reveal	Randomization with Immediate Reveal and Initiation of Randomization with Deferred Reveal if prospective agreement to participate is required.
Inclusions	Nil.

Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following:
	• More than 48 hours has elapsed since ICU admission, unless the patient has already been assigned a treatment in another domain in the Moderate State, in which case exclusion will occur if more 48 hours has elapsed since commencement of sustained organ failure support in an ICU.
	• Known severe liver disease or an alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) that is more than five times the upper limit of normal
	• There is intention to commence or continue:
	  ○ Cysteamine (by any route)
	  ○ Intravenous N-acetylcysteine
	  ○ Carbocisteine (by any route)
	• Patient has been randomized in a trial evaluating cysteamine (by any route), intravenous N-acetylcysteine, or carbocisteine (by any route), where the protocol of that trial requires ongoing administration of study drug or ongoing activity of study drug is anticipated.
	• The treating clinician believes that participation in the domain would not be in the best interests of the patient

Intervention-Specific Exclusions	Criteria that exclude a patient from one or more interventions are: • Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent. • Known hypersensitivity to N-acetylcysteine, penicillamine, or amifostine will exclude a patient from interventions that include cysteamine • Known or suspected pregnancy will result in exclusion from interventions that include cysteamine.

Outcome measures	Primary REMAP endpoint: refer to REMAP-CAP Core Protocol + Pandemic Appendix Secondary REMAP endpoints: refer to REMAP-CAP Core Protocol + Pandemic Appendix Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment): • Extended cardiovascular SOFA score • Change in baseline to peak available AST, ALT, and bilirubin during the treatment period • Serious Adverse Events (SAE) as defined in core protocol documents

TABLE OF CONTENTS

1. ABBREVIATIONS

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CF	Cystic Fibrosis
CRP	C-Reactive Protein
DSA	Domain-Specific Appendix
DSMB	Data Safety and Monitoring Board
DSWG	Domain-Specific Working Group
GLDC	Glycine Decarboxylase
ICU	Intensive Care Unit
IFN	Interferon
IL6	Interleukin-6
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
PAtC	Pandemic Appendix to the Core Protocol
PINSNP	Pandemic Infection is Neither Suspected nor Proven
PISOP	Pandemic Infection is Suspected Or Proven
PROM	Patient Reported Outcome Measures
RCT	Randomized controlled trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome

SOFA	Sequential Organ Failure Assessment
TEAE	Treatment Emergent Adverse Event

2. PROTOCOL APPENDIX STRUCTURE

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

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

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

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

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analytic model will also change over time in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase

over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

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

3. CYSTEAMINE DOMAIN-SPECIFIC APPENDIX VERSION

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

3.1. Version history

Version 1: Approved by the Cysteamine Domain-Specific Working Group (DSWG) on 21 June 2021

4. CYSTEAMINE DOMAIN GOVERNANCE

4.1. Domain members

Chair: Professor Manu Shankar-Hari

Deputy Chairs: Professor Anthony Gordon

Professor Alistair Nichol

Members:

Dr. Farah Al-Beidh

Prof. Derek Angus

Dr. Diptesh Aryal

Dr. Lennie Derde

Mr. Cameron Green

Dr. Ghady Haidar

Prof. David T Huang

Dr. Bharath Kumar

Prof. Francois Lamontagne

Dr. Patrick Lawler

Prof. John Marshall

Dr. Colin McArthur

Prof. Danny McAuley

Prof. Srinivas Murthy

Dr. Peter McGuigan

Prof. Rachael Parke

Prof. Sid Patanwala

Prof. Sandy Peake

Dr. Nicole Timmers

Prof. Steve Webb

Prof. Alexandra Weissman

4.2. Contact Details

Chair: Professor Manu Shankar-Hari

Department of Critical Care Medicine

St Thomas' Hospital, Westminster Bridge Road

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5. CYSTEAMINE DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

Chair

Manu Shankar-Hari

Date 21st June 2021

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP platform to test the effectiveness of Cysteamine for patients with severe CAP, including patients with suspected or proven influenza or COVID-19 infection, or both.

6.2. Domain-specific background

6.2.1. COVID-19 infection

6.2.1.1. Introduction

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

6.2.1.2. Clinical trials for COVID-19 infection

Observational data cannot determine treatment effects reliably due to the risk of systematic bias (Califf et al., 2020). Clinical trials to identify effective COVID-19 treatments are needed and a large number of trials are underway. Early in the pandemic, the WHO provided guidance regarding both trial design and prioritization of candidate therapies. With regards to trial design, the WHO noted that initially there were no treatments with proven efficacy in patients with COVID-19. Therefore, the recommended 'standard of care' comparator was a control group that did not receive an agent intended to be active against COVID-19 infection, its associated immune response, or other

complications (https://apps.who.int/iris/bitstream/handle/10665/330694/WHO-HEO-RDBlueprintnCoV-2020.4-eng.pdf?ua=1). As effective COVID-19 treatments are identified, it is anticipated that 'standard of care', both inside and outside of a clinical trial, will continue to change to incorporate the use of agents with proven efficacy. REMAP-CAP randomizes COVID-19 patients to a range of therapeutic interventions across different domains. Up to date information regarding active and inactive interventions and domains is available at www.remapcap.org.

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

6.2.2. Influenza and bacterial CAP

The background that is relevant to Influenza and bacterial CAP is located in the REMAP-CAP Core Protocol.

6.2.3. Cysteamine

6.2.3.1. Pre-clinical rationale for Cysteamine in COVID-19, bacterial CAP, and severe influenza

Cysteamine (Cysteamine bitartrate) is an aminothiol derivative of co-enzyme A, with pleotropic antimicrobial (antibacterial and antiviral), immunomodulatory and antibiotic potentiating properties. Cysteamine is proposed as a novel adjunctive therapy, alongside standard of care treatments for the treatment of severe acute community acquired pneumonia including influenza and COVID-19 associated pneumonia.

Cysteamine binds susceptible cysteine residues to form mixed disulphides and depletes the bacterial intracellular thiol pools leaving them more susceptible to stress including that induced by a broad

range of antibiotics. Cysteamine can also dysregulate bacterial metabolism which potentiates antifolate antibiotics (Ferrari et al., 2017, Fraser-Pitt et al., 2018, Shrestha et al., 2017).

Cysteamine is an endogenous aminothiol produced in mammalian cells as a consequence of coenzyme A metabolism by the cleavage of pantetheine to form Cysteamine and pantothenate (vitamin B5) as a breakdown product of coenzyme A (Dupre et al., 1970). Mammalian cells can express aminothiol dioxygenase (ADO), which can oxidize CYS to hypotaurine and taurine. Bacterial, fungal, and many eukaryotic parasites (including *Plasmodium* spp.) do not possess the ADO gene, and this likely explains the selective effect on these classes of pathogen (Dominy et al., 2007). It should be noted that as cysteamine is a normal product of human metabolism, that the safety risks from short-term administration are predicted to be minimal.

Cysteamine concentrates within the lung. It is also known to improve the clearance of intracellular pathogens (Ferrari et al., 2017, Shrestha et al., 2017) and reduce scarring and cellular senescence in COPD models using Beas2b cells, C57BL/6 mice, and human (GOLD 0-IV) lung tissues (Vij et al., 2018). Cysteamine interferes with the glycine cleavage system common to bacterial pathogens and host mitochondria, temporarily interfering with DNA and RNA synthesis in bacteria and with virulence factor production (Fraser-Pitt et al., 2018).

Cysteamine may also offer benefit for viral infections, including those caused by a Coronavirus or influenza. Reversible inhibition of the glycine decarboxylase (GLDC) component of the glycine cleavage system has also been demonstrated to reduce viral load in influenza and MERS-CoV infection, using influenza-virus infected A549 cells and H1N1-infected BALB/c mice models (Zhou et al., 2019). This is achieved by a temporary restriction in pyrimidine synthesis, which can reduce viral replication through lower nucleic acid synthesis rates and increasing type I interferon (IFN) responses. With regards to Coronavirus infection, NovaBiotics have confirmed cysteamine is a potent inhibitor of GLDC in airway epithelial cells and that it stimulates IFN beta response to human coronavirus 229E infection, whilst reducing the IL-6 (pro-inflammatory) cytokine response (unpublished data). Single treatments with cysteamine, at therapeutically achievable levels, reduced viral load as detected by antibody and qPCR in human airway epithelial cells. NovaBiotics have also demonstrated dose-dependent protection of Vero cells from cytopathology following infection with SARS-CoV-2 and treatment with cysteamine and demonstrated concomitant reductions in viral load by qPCR.

6.2.3.2. Clinical evidence

There is existing evidence of benefit of cysteamine for patients experiencing infectious exacerbations of cystic fibrosis (CF). In the CARE CF 1 randomized clinical trial (EudraCT 2015-004986-99), adult patients were randomized 1:1:1:1:1:1 to the following total daily dose groups of oral cysteamine bitartrate or placebo: 450 mg as one dose (QD): 450 mg as 3 doses of 150 mg (TID): 900 mg as 2 doses of 450 mg (BID): 900 mg as 3 doses of 300 mg (TID): 1,350 mg as 3 doses of 450 mg (TID): placebo. The key findings of note include improved symptoms, significantly reduced blood leukocyte counts and CRP with cysteamine compared to placebo (Devereux et al 2020). With a cysteamine bitartrate dosing of 450mg twice daily orally, cysteamine C_{MAX} concentration achievable in sputum was ≥12 mg/L. Importantly, concentration of cysteamine required to elicit antimicrobial effects and to potentiate antibiotics activity against bacteria in sputum was ≤2 mg/L; to inhibit neutrophil elastase activity was ≤7.7mg/L; and to elicit anti-virulence effects was ≤4mg/L. Antiviral and immunomodulatory effects have been demonstrated with concentrations between 2-10 mg/L.

6.2.3.3. Safety of Cysteamine

Cysteamine in oral form has been licensed for clinical use for more than 25 years in cystinosis (with more than 30 years of accumulated safety data). There is additional safety data from early phase clinical trials of respiratory infections that drive pulmonary exacerbations of CF. The most common Treatment Emergent Adverse Events (TEAEs) include nausea, headache and vomiting. Less common TEAEs include mild and transient increases in liver function tests (ALT/AST and alkaline phosphatase). In summary, oral cysteamine in doses up to 450 mg TID were, in general, well-tolerated with no emergent safety concerns (Devereux et al., 2020).

This domain will evaluate cysteamine administered by the intravenous route and this formulation of cysteamine is not yet a registered medicine in any country. There is currently limited safety data for the intravenous formulation of cysteamine bitartrate. There is some experience with the use of intravenous cysteamine for the treatment of paracetamol toxicity with no significant adverse effects identified (Douglas et al., 1976, Hamlyn et al., 1981, Hughes et al., 1977, Prescott et al., 1974, Prescott et al., 1976). The doses used historically for paracetamol toxicity are substantially higher than those proposed in this domain. The similarity between cysteamine and N-acetylcysteine raises the possibility of mild hypotension occurring with intravenous administration. During long term use of cysteamine in preregistration studies, ALT elevations occurred in a small proportion of treated subjects (National Institute of Diabetes and Digestive and Kidney Diseases, 2012). The mechanism by which cysteamine might lead to serum enzyme elevations or liver injury is not known. Cysteamine is metabolized in most cells, and it does not seem to be a substrate for or affect the hepatic

cytochrome P450 system. In clinical trials of cysteamine, no evidence of drug-drug interactions was identified (National Institute of Diabetes and Digestive and Kidney Diseases, 2012). Amifostine is an aminothiol drug that has been associated with hypocalcemia. As cysteamine is an aminothiol compound, hypocalcemia may be a potential side effect.

The package insert lists abnormal liver function tests and neutropenia as potential adverse events for related oral preparation (cysteamine bitartrate), with long-term use in patients with cystic fibrosis (https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203389s010lbl.pdf). The domain-specific entry criteria, reportable SAEs, and safety secondary end-points have been chosen taking the known possible adverse events into account.

Studies in animals have shown reproductive toxicity, including teratogenesis and fetotoxicity at doses less than the recommended human maintenance dose (Assadi et al., 1998, Beckman et al., 1998). Observed teratogenic findings were cleft palate, kyphosis, heart ventricular septal defects, microcephaly, and exencephaly. There are no adequate and well controlled studies in pregnant women. Drug regulators in Australia, United Kingdom, and the United States broadly recommend avoidance of the drug during pregnancy. As such, women who are pregnant, or who are of child-bearing age with unknown pregnancy status, will not be eligible to participate in this domain.

6.2.4. Dosing of cysteamine

The dose of cysteamine that has been selected for this domain is 5mg per kg body weight, administered every 8 hours, with a maximum dose of 500 mg every 8 hours (i.e. maximum dose of 1,500 mg per day). The choice of dose is based on the following:

- Cysteamine is licensed for use in cystinosis patients at up to 2,000 mg per day for life (https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203389s010lbl.pdf).
- NovaBiotics have conducted two Phase 2 clinical trials in infectious pulmonary exacerbations of cystic fibrosis where enteral administration of up to 1,800 mg per day for up to 5 weeks was well tolerated. In the second of these studies, a twice daily dose of 450mg of oral cysteamine for 14 days (approximately 7.5mg/kg body weight) brought about therapeutic benefit as measured by patient reported outcome measures (PROM) and resulted in statistically significant benefit in the resolution of respiratory infection in patients with the reduction in white blood cell counts and CRP. The dose in the second study achieved a plasma C_{MAX} 2.86 mg/mL and cysteamine concentrated in lung secretions at a sputum:plasma ratio of 4.2:1 in these patients (Devereux et al., 2016, Devereux et al., 2020).

- *In vitro* experiments carried out with cysteamine at the levels observed in plasma have achieved reductions in viral load with 229E (coronavirus) and significant reductions in IL-6 at concentrations below the anticipated C_{MAX} in plasma (NovaBiotics, unpublished data), noting that substantially higher levels should be achieved in lung tissue.

- In mouse models (evaluating effect of cysteamine on antimicrobial resistant *Pseudomonas aeruginosa* infection) doses that are more than double and as much as 20-fold higher than is proposed (1.25 mg/Kg - 12.5 mg/Kg) were well tolerated as well as effective in reversing antibiotic resistance against ciprofloxacin.

- Cysteamine has been administered by the IV route to one young male cystinosis patient at a dose of 10 mg/kg dose (Gahl et al., 1995). The plasma C_{MAX} of cysteamine was measured was 71 µM (5.478 mg/L) – which can be compared with the less bioavailable oral administration of 7.5mg/kg cysteamine given in the NovaBiotics clinical trial reaching 2.86 mg/L of cysteamine in the plasma (as detailed above).

- The decision to utilise IV administration in this domain is that, as a general principle of the management of critically ill patients, if a drug is available for parenteral administration this is preferred to the enteral route because of variable absorption and bioavailability. Cysteamine has a half-life of 3.7 hours which provides a pharmacokinetic and pharmacodynamic rationale for administration at 8 hourly intervals. NovaBiotics' previous research and research from literature suggests that with IV administration, compared with enteral administration, the C_{MAX} will be higher and the T_{MAX} will be earlier due to higher bioavailability and avoidance of first pass metabolism.

- Other aminothiols that are licensed for IV administration, such as n-acetylcysteine and amifostine, are administered at much higher doses (over 100mg/kg and 910mg/m^2 respectively) and as longer infusions than is proposed for cysteamine and it is reasonable to extrapolate safety for cysteamine.

6.2.5. Intervention strategy for this domain

This domain will test the potential benefits of cysteamine for patients with severe CAP, including patients with suspected or proven influenza or COVID-19.

If at any stage, external evidence of harm or definitive evidence of absence of effectiveness in critically ill patients emerges for an intervention specified in this domain, the ITSC, as advised by the DSWG, may remove the intervention(s) prior to declaration of a Platform Conclusion. If this occurs,

presentation and publication of results that relate to the intervention will occur, so as to contribute additional weight of evidence in the public domain.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of cysteamine in patients with severe CAP, including patients with suspected or proven influenza or COVID-19.

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

- No Cysteamine (no placebo)
- Cysteamine

We hypothesize that the treatment effect of cysteamine is different depending on the presence or absence of influenza or SARS-CoV-2 infection at the time of enrollment (strata-by-intervention interactions). Evaluation of the hypothesis related to SARS-CoV-2 infection is dependent on the addition of a SARS-CoV-2 strata to the model that will be used this domain, which is not currently a strata in the inter-pandemic model.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be adaptive, as described in the core protocol documents.

8.1. Population

The REMAP enrolls patients with severe CAP, including patients with suspected or proven influenza or COVID-19.

8.1.1. State

Among patients with suspected or proven pandemic infection, this domain is available only in patients in the Severe State. In patients who are pandemic infection neither suspected nor proven the platform entry criteria correspond to the Severe State.

8.1.2. Domain-specific strata

No domain-specific strata are applied to patients at the time of assessment for this domain.

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in the REMAP-CAP Core Protocol + Pandemic Appendix. It is noted that during the COVID-19 pandemic, that platform-level inclusion criteria are different for patients with pandemic infection suspected or proven (PISOP stratum) and for patients in whom pandemic infection is neither suspected nor proven (PINSNP). Patients in either stratum are eligible for this domain. Patients eligible for REMAP-CAP may have conditions that exclude them from this Domain.

8.2.1. Domain inclusion criteria

Nil.

8.2.2. Domain exclusion criteria

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

- More than 48 hours has elapsed since ICU admission, unless the patient has already been assigned a treatment in another domain in the Moderate State in which case exclusion will occur if more 48 hours has elapsed since commencement of sustained organ failure support in an ICU.
- Known severe liver disease or an alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) that is more than five times the upper limit of normal
- There is intention to commence or continue:
    - Cysteamine (by any route)
    - Intravenous N-acetylcysteine
    - Carbocisteine (by any route)
- Patient has been randomized in a trial evaluating cysteamine (by any route), intravenous N-acetylcysteine, or carbocisteine (by any route), where the protocol of that trial requires ongoing administration of study drug or ongoing activity of study drug is anticipated.
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

8.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons. Patients who are eligible for only a single intervention at a site (i.e. all other interventions are contraindicated) are not eligible for this domain. Patients in whom all interventions are contraindicated will be treated according to the current standard of care at the clinician's discretion.

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

- Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
- Known hypersensitivity to N-acetylcysteine, penicillamine, or amifostine will exclude a patient from interventions that include cysteamine
- Known or suspected pregnancy will result in exclusion from interventions that include cysteamine (note that suspected pregnancy is operationalized as any female patient of childbearing age who has not had pregnancy excluded)

8.3. Interventions

8.3.1. Cysteamine Domain Interventions

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

☐ No Cysteamine (no placebo)

☐ Cysteamine

8.3.2. No Cysteamine intervention

Patients assigned to this intervention are not to receive cysteamine until the end of study day 10. There is no administration of placebo. Administration of cysteamine, by any route, to a patient assigned to the 'no cysteamine' intervention is a protocol deviation. After 10 days, decisions regarding cysteamine therapy are at the discretion of the treating clinician.

8.3.3. Cysteamine intervention

Cysteamine will be administered every 8 hours at a dose of 5 mg/kg of estimated or measured body weight, with the administered dose not to exceed 500 mg. The dose will be diluted in 50 to 100 ml of 0.9% saline and administered as an intravenous infusion over 10 minutes via a central or peripheral venous catheter.

The duration of cysteamine administration is 10 days, i.e. 30 doses. Cysteamine may be ceased at the time of ICU discharge in patients who are discharged from ICU before completion of the 10-day course. Omission of three or more consecutive doses is a protocol deviation. After 10 days, decisions regarding cysteamine therapy are at the discretion of the treating clinician. If clinically significant hypotension occurs during infusion, the infusion rate should be slowed and, if necessary, ceased.

8.3.4. Discontinuation of study intervention

The study interventions can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient. Discontinuation before study day 10, while still admitted to an ICU, will be considered a protocol deviation.

8.3.5. Strategy in patients negative for COVID-19 or influenza infection

In patients with suspected COVID-19 or influenza infection who receive an allocation status in this domain who subsequently test negative for SARS-CoV-2 or influenza infection should continue treatment according to their allocated intervention.

8.4. Concomitant care

The aminothiol agents, intravenous N-acetylcysteine and enteral carbocisteine are not to be administered. Administration of enteral or nebulized N-acetylcysteine outside of a clinical trial is permitted.

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

8.5. Endpoints

8.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome specified in the version of the REMAP-CAP Core Protocol that is operative at the time of each adaptive analysis.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the REMAP-CAP Core Protocol.

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

- Extended cardiovascular SOFA score, which is a secondary endpoint specified in the REMAP-CAP Core Protocol, will be reported as a safety end-point
- Change in baseline to peak available AST, ALT, and bilirubin during the treatment period
- SAE as defined in the core protocol documents and qualified in this DSA

9. TRIAL CONDUCT

9.1. Microbiology

Microbiological testing will be performed as per local practice, including bacterial and viral testing to guide clinical care. Results of these tests will be collected but no additional testing is specified in this protocol.

9.2. Domain-specific data collection

Additional domain-specific data will be collected.

- Administration of cysteamine (enteral and intravenous), N-acetylcysteine (enteral, nebulized, and intravenous), and carbocisteine (enteral)
- Baseline and peak AST, ALT, and bilirubin
- Baseline ferritin

9.3. Criteria for discontinuation

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

9.4. Blinding

9.4.1. Blinding

All medications will be administered on an open-label basis.

9.4.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The following Platform Conclusions are possible in this domain:

- Superiority (effectiveness) of cysteamine compared with no cysteamine
- Futility of cysteamine compared with no cysteamine

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

10.2. Unit-of-analysis and strata

This domain is analyzed only in the inter-pandemic statistical model and includes both patients who are in the pandemic infection suspected or proven (PISOP) stratum, as specified in the REMAP-CAP Pandemic Appendix, and patients who are in the pandemic infection neither suspected nor proven (PINSNP) stratum. The influenza strata and any future strata specified in core protocol documents, including a COVID-19 strata, may be applied to define the unit-of-analysis. Application of one or more of these strata will be an operational decision. Borrowing is permitted between strata. Response Adaptive Randomization may be applied. If RAR is applied, the cap on the maximum proportion of patients assigned to an intervention that is specified in core protocol documents may be reduced by the Statistical Analysis Committee (SAC) if needed to reduce the likelihood of sites being unblinded during a period of rapid recruitment. If a reduced maximum proportion for RAR assignment is applied this will be an operational decision of the SAC, who will inform the DSMB, but blinded trial personnel will not be informed.

The shock strata will not contribute to unit-of-analysis for this domain.

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation or Randomization with Deferred Reveal if prospective agreement to participate is required for this domain (see relevant core protocol documents).

10.4. Interactions with interventions in other domains

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

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

10.5. Nesting of interventions

Nesting is not applicable in this domain.

10.6. Threshold probability for superiority and inferiority

The threshold probability for statistical triggers for superiority and inferiority are those specified in the relevant core protocol documents.

10.7. Threshold odds ratio delta for equivalence and futility

The Platform Conclusion of equivalence will not be evaluated in this domain. The same odds ratio delta as specified in the relevant core protocol documents for equivalence will be used for futility. This will be applied in a one-sided analysis for futility for the active intervention specified in this domain.

10.8. Informative priors

This domain will launch with priors that are not informative for main effects.

10.9. Post-trial sub-groups

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

- Shock strata
- Microbiologically confirmed SARS CoV-2 infection (only if SARS-CoV-2 infection is not a strata within the primary efficacy model at the time of a platform conclusion)
- Receiving invasive mechanical ventilation at baseline
- Baseline CRP
- Baseline ferritin
- All remaining potentially evaluable treatment-by-treatment interactions with other domains

11.ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB should be aware that the superiority or futility of cysteamine with respect to the primary endpoints are possible.

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

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

11.2. Potential domain-specific adverse events

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

- Suspected or proven allergic or hypersensitivity reaction sufficient to require interruption of infusion or treatment or both. These may include one or more of the following clinical findings - urticaria, pruritus, facial flushing, wheezing, dyspnea, and hypotension
- Hypocalcemia that is symptomatic or requires treatment or both
- Total neutrophil count less than 1.0 x 10^9/L

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

11.3. Domain-specific consent issues

As noted in the background, and endorsed by the WHO (with respect to COVID), in the absence of evidence of effectiveness of any interventions specified in this DSA or alternative intervention that lies within this domain, the use of a usual care control is both appropriate and ethical.

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

For patients who are not competent to consent, and in accordance with local jurisdictional requirements, where permitted entry into this domain is preferred to be via waiver-of-consent or some form of delayed consent. In any jurisdiction in which prospective agreement is necessary, reveal of assignment status will only occur after prospective agreement has been obtained.

12.GOVERNANCE ISSUES

12.1. Funding of domain and intervention

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5.

Novabiotics, the company that have developed an intravenous formulation of cysteamine (as Nylexa®) will provide the drug and have contributed unrestricted research grants to support trial conduct. This domain has not received any other additional domain-specific funding but such funding, from any source, may be obtained during the life-time of the domain.

12.2. Domain-specific declarations of interest

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

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