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

Domain-Specific Appendix:

VITAMIN C

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

Vitamin C Domain-Specific Appendix Version 1 dated 25 April 2020

In collaboration with

Lessening Organ Dysfunction with VITamin C

Summary

In this domain of the REMAP-CAP trial, participants meeting the platform-entry criteria for REMAP-CAP admitted to participating intensive care units (ICU) will be randomized to receive one of two interventions:

- No vitamin C (no placebo)
- Vitamin C (50 mg/kg IV every 6 hours for 16 doses)

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

☐ No vitamin c (no placebo)

☐Vitamin C (50mg/kg IV every 6 hours for 16 doses)

REMAP-CAP: Vitamin C Domain Summary	
Interventions	• No vitamin C (no placebo) • Vitamin C (50 mg/kg IV every 6 hours for 16 doses)
Unit-of-analysis and Strata	There are two units-of-analysis for this domain specified by the presence or absence of suspected or proven pandemic infection. For patients in the PISOP stratum, the unit-of-analysis may be modified to allow analysis to be stratified by SARS-CoV-2 infection confirmed or not confirmed with borrowing permitted. If this occurs, Response Adaptive Randomization will be applied to patients in the PISOP stratum using probabilities derived from SARC-CoV-2 confirmed stratum. Response adaptive randomization is not applied in the PINSNP stratum.
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 or Randomization with Deferred Reveal if prospective agreement to participate is required.
Inclusions	Inclusion criteria are the same as the Platform see Core Protocol Section 7.4.1. 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.

Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following:
	• More than 24 hours has elapsed since ICU admission
	• Received any intravenous vitamin C during this hospitalization (unless incorporated in parenteral nutrition)
	• Any of the following 3 contraindications to vitamin C therapy:
	  ○ known glucose-6-phosphate dehydrogenase (G6PD) deficiency
	  ○ known allergy to vitamin C
	  ○ known history of symptomatic kidney stones within the past 1 year
	• The treating clinician believes that participation in the domain would not be in the best interests of the patient

Intervention-Specific Exclusions	• Nil, not applicable.
Outcome measures	Primary REMAP endpoints as defined in Core Protocol and PAtC Secondary REMAP endpoints refer to Core Protocol Section 7.6.2 Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrolment): • Serious Adverse Events (SAE) as defined in Core Protocol

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1. ABBREVIATIONS

CAP	Community Acquired Pneumonia
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
ICU	Intensive Care Unit
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
LOVIT	Lessening Organ Dysfunction with VITamin C trial
PAtC	Pandemic Appendix to Core Protocol
PISOP	Pandemic Infection Suspected or Proven
PINSNP	Pandemic Infection Neither Suspected Nor Proven
RAR	Response Adaptive Randomization
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RSA	Region-Specific Appendix
SAE	Serious Adverse Event
WHO	World Health Organization

2. PROTOCOL APPENDIX STRUCTURE

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

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

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

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

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

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

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

3. VITAMIN C DOMAIN-SPECIFIC APPENDIX VERSION

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

3.1. Version history

Version 1: Approved by the Vitamin C Domain-Specific Working Group (DSWG) on 25th April 2020

4. VITAMIN C DOMAIN GOVERNANCE

4.1. Domain members

Co-Chairs: Dr. Francois Lamontagne
Dr. Neill Adhikari

Members:

Dr. Derek Angus
Dr. Djillali Annane
Dr. Matthew Anstey
Dr. Yaseen Arabi
Dr. Scott Berry
Dr. Emily Brant
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5. VITAMIN C DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

Co-Chair
Francois Lamontagne

Date 25th April 2020

Co-Chair
Neill Adhikari

Date 25th April 2020

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP to test the effectiveness of vitamin C versus no vitamin C in patients with severe community-acquired pneumonia (CAP) who are admitted to an ICU.

6.2. Domain-specific background

In the context of increasing off-label use of vitamin C for sepsis and ongoing trials of vitamin C bundled with other pharmacological interventions, the Vitamin C Domain will constitute an assessment of the effect of vitamin C monotherapy on patient-important outcomes.

6.2.1. Sepsis

The burden of sepsis is increasing worldwide and CAP is responsible for approximately half of all episodes of sepsis. Defined as a dysregulated immune response to infections that leads to organ failure and death (Andreis and Singer, 2016), sepsis is the cause of 11 million global deaths each year (Rudd et al., 2020). Currently, treatment options are limited to antimicrobials and supportive care such as intravenous fluids, vasopressors, mechanical ventilation, and renal replacement therapy. In the absence of effective therapies specifically targeting the dysregulated immune response, prolonged use of these life-sustaining therapies can be debilitating (Herridge et al., 2016, Garland et al., 2015). In resource-constrained settings, they are largely unavailable and the prognosis of septic

patients is poor (Dugani et al., 2017). This global burden led the World Health Organization (WHO) to adopt a resolution urging Member States and the WHO Director-General to take action to reduce the burden of sepsis through improved prevention, diagnosis, and management (Reinhart et al., 2017).

A growing body of evidence, summarized below, suggests that vitamin C, an inexpensive and readily available intervention, is potentially lifesaving in sepsis. Intravenous vitamin C may be the first therapy to mitigate the dysregulated cascade of events that leads to sepsis. If proven effective, vitamin C could be used worldwide and improve outcomes in high- and low-income settings alike.

6.2.2.Treatment of sepsis with vitamin C

Inflammation and oxidative stress are among the main mechanisms underlying sepsis-induced organ injury, and death that occurs in severe pneumonia (Angus and van der Poll, 2013). During sepsis, large quantities of reactive oxygen radicals are produced by leukocytes for phagocytosis of pathogens. Normally, endogenous antioxidants contain this response and protect body cells to collateral oxidative damage. Vitamin C, a key circulating antioxidant (Frei et al., 1990), cannot be synthesized by humans. Moreover, many critically ill patients are vitamin C deficient and, even when they are not, sepsis further exhausts vitamin C stores. Low levels of vitamin C are associated with sepsis-induced organ failure and death (de Grooth et al., 2014). Numerous preclinical studies have shown that, in addition to direct scavenging of oxygen radicals, vitamin C limits their production and restores endothelial function (May and Harrison, 2013, May et al., 2013, Oudemans-van Straaten et al., 2014, Wilson, 2013). In addition, vitamin C is a cofactor in the synthesis of noradrenaline, cortisol, and vasopressin, hormones that are crucial to maintain adequate vascular tone for organ perfusion (Carr et al., 2015).

The authors of a recent pre-post single-centre observational study (n=94) of intravenous vitamin C for septic shock reported a dramatic effect on vasopressor requirements, organ failure, and hospital mortality (mortality 8.5% [vitamin C] vs. 40.4% [control]; adjusted OR 0.13, 95% confidence interval [CI] 0.04-0.48) (Marik et al., 2017). While this study combined vitamin C with hydrocortisone and thiamine, results of two recent trials suggest that intravenous vitamin C alone may reduce organ injury (Fowler et al., 2014), the need for vasopressor therapy, and death (Zabet et al., 2016). A conclusion of these trials is that it is that there is credible evidence supporting the need for a large trial to investigate the efficacy of vitamin C alone.

A systematic review found nine clinical trials (1,322 patients) in mixed critically ill populations. While existing evidence does not support the claim that vitamin C improves clinical outcomes (pooled relative odds for death 0.72, 95% confidence interval 0.43-1.20, P=0.21, I^2=56%), most studies were small, methodologically flawed, and tested vitamin C administered enterally, in small doses, and combined with other nutrients (Langlois et al., 2019). The most compelling signal from this systematic review comes from a subgroup of two trials of high dose intravenous vitamin C administered as monotherapy over 72 or 96 hours (Figure 1). This systematic review underscores the need for large and rigorously designed trials that evaluate a sufficiently large dose of intravenous vitamin C.

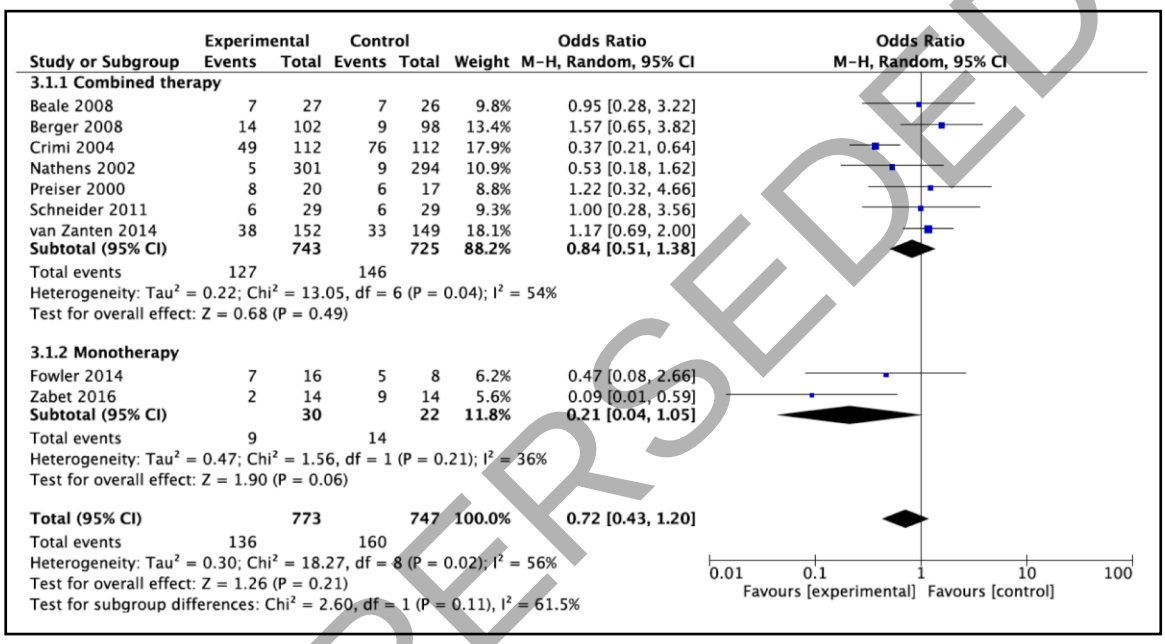

Figure 1. Forest plot: Randomized controlled trials of vitamin C as monotherapy vs. combined with other nutrients and medications

Several trials evaluating vitamin C in sepsis are currently registered (https://tinyurl.com/vitC-rct), but they lack statistical power to detect clinically important effects on mortality; the largest plans to enroll 500 patients. A phase 1 clinical trial suggested that 200 mg/kg/day yields higher plasma levels of vitamin C and more favorable SOFA scores (Vincent et al., 1996) compared to 50 mg/kg/day (Fowler et al., 2014). This preliminary signal of benefit is a compelling argument to use the same dosing strategy. A small trial (n=170) used this dose of vitamin C monotherapy for sepsis-related acute respiratory distress syndrome (Fowler et al., 2019). The trial was negative for the primary outcomes, but showed a reduction in 28-day mortality (one of 46 secondary outcomes): 30% [25/84] in the vitamin C group vs. 46% [38/82] in the placebo group, p=0.03, relative risk [RR] 0.642, 95% CI 0.415-0.984 (RR not provided in paper). Other secondary outcomes (e.g. evolution of ventilator

parameters, vasopressor use) did not favor vitamin C. Another trial randomized 216 patients to low-dose intravenous vitamin C, thiamine, and hydrocortisone and found no effect on the primary outcome of vasopressor-free time to 7 days or on 90-day mortality (HR 1.18 (95% CI 0.69-2.00)(Fujii et al., 2020). Given the uncertainty of the literature, additional clinical research is required.

6.2.1.Treatment of COVID-19 with vitamin C

The potential benefit of vitamin C therapy may be even greater for sepsis associated with COVID-19 since vitamin C stimulates the proliferation and differentiation of T-lymphocytes and NK-lymphocytes and stimulates the production of interferons (Carr et al., 2017). These effects increases the likelihood that vitamin C may have specific effects in preventing and/or attenuating pulmonary sepsis caused by viruses and might explain shorter duration of symptoms from common colds observed in clinical trials of high-dose vitamin C therapy (Hemila, 2017). While the reported effect was small, a much greater absolute effect may be expected in the context of COVID-19 given the greater control event rate. Of note, high-dose vitamin C therapy is increasingly used in hospitals around the world, particularly in the United States (https://www.newsweek.com/new-york-hospitals-vitamin-c-coronavirus-patients-1494407; https://www.usatoday.com/story/news/factcheck/2020/03/24/coronavirus-fact-check-could-vitamin-c-cure-covid-19/2904303001/). This, in addition to a sound biological rationale, provides a strong argument to rigorously evaluate the clinical effects of what remains an experimental intervention. Accordingly, vitamin C was listed among the top research priorities for COVID-19 by the WHO (https://www.who.int/blueprint/priority-diseases/key-action/Coronavirus_Roadmap_V9.pdf).

6.2.2.The LOVIT Trial

The Vitamin C Domain of REMAP-CAP is coordinated with the ongoing LOVIT trial (Lessening Organ Dysfunction with VITamin C) protocol (ClinicalTrials.gov: NCT03680274). Briefly, LOVIT is a multicenter concealed-allocation parallel-group blinded randomized controlled trial that follows an umbrella design protocol. Patients admitted to ICU with proven or suspected infection as the main diagnosis are eligible for inclusion. Participants are randomly assigned to vitamin C (intravenous, 50 mg/kg every 6h) or placebo every 6 hours for 96 hours. Study personnel at the clinical sites will document the composite of death or persistent organ dysfunction at day 28. Daily assessments will occur for occurrence of stage 3 acute kidney injury and acute hemolysis, on days 1, 2, 3, 4, 7, 10, 14, and 28 for organ function, on days 1, 3, 7 for inflammation, infection, endothelial injury, and global tissue dysoxia biomarkers, during the experimental therapy and until 7 days after the last dose received for hypoglycemia, at baseline for vitamin C level, and at 6 months for mortality and health-

related quality of life. At least 800 patients will be included in LOVIT. The interventions in LOVIT and this domain are harmonized. Data collected from the LOVIT trial and the REMAP-CAP Vitamin C domain may be pooled as per the statistical analysis plans for each program of research.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of vitamin C for patients with severe CAP admitted to the ICU.

We hypothesize that the primary outcomes specified in the Core Protocol and the Pandemic Appendix to the Core Protocol (PAtC) will differ based on treatment with vitamin C versus no vitamin C. The following interventions will be available:

- No vitamin c (no placebo)
- Vitamin C (50 mg/kg IV every 6 hours for 16 doses)

We hypothesize that the treatment effect of vitamin C is different depending on the presence or absence of suspected or proven pandemic infection.

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

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial (see Core Protocol Section 7). Treatment allocation will be adaptive, as described in the Core Protocol Section 7.5.2.

8.1. Population

The REMAP enrolls patients with severe CAP admitted to ICU (see Core Protocol Section 7.3).

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 (see Core Protocol Section 7.4). 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

otherwise eligible for REMAP-CAP may have conditions that exclude them from the Vitamin C 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 24 hours has elapsed since ICU admission
- Received any intravenous vitamin C during this hospitalization (unless incorporated in parenteral nutrition)
- Any of the following 3 contraindications to vitamin C therapy:
    - known glucose-6-phosphate dehydrogenase (G6PD) deficiency
    - known allergy to vitamin C
    - known history of symptomatic kidney stones within the past 1 year
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

Known or suspected pregnancy is not an exclusion criterion unless required by the competent national authority in that jurisdiction.

8.3. Interventions

Patients will be randomly assigned to receive one of the following open-label study interventions.

8.3.1. No vitamin C intervention

Patients assigned to this intervention are not to receive high dose intravenous vitamin C during the index hospitalization. Administration of vitamin C as part of parenteral or enteral nutrition is permitted.

8.3.2. Dosing and duration of administration of vitamin C

The vitamin C will be administered intravenously, via a central or peripheral venous cannula, in bolus doses of 50 mg/kg of estimated or measured body weight, administered every 6 hours for 16 doses (i.e. 200 mg/kg/day, 96-hour course). Reconstitution and administration of Vitamin C will conform to the administration guide and local standards. In patients who are discharged from the ICU before completion of the course, continuation of administration to complete the course is at the discretion

of the treating clinicians. Omission of two or more consecutive doses or more than 4 total doses will be a protocol deviation.

8.4. Concomitant care

All co-interventions will be left to the discretion of the treating physician. For patients in the 'no vitamin C' intervention, administration of any form of vitamin C, unless as part of parenteral or enteral nutrition, should not occur during the index hospitalization. For patients in the 'vitamin C' intervention administration of any form of vitamin C, unless as part of parenteral or enteral nutrition, should not occur after the course of intravenous vitamin C is completed.

8.4.1. Implications of allocation status for eligibility in other domains

None. Vitamin C allocation would not impact allocation to interventions in other domains.

8.5. Endpoints

8.5.1. Primary endpoint

The primary endpoint for this domain is the REMAP primary outcome as specified in Core Protocol Section 7.6.1. or PAtC, as appropriate.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the Core Protocol Section 7.6.2. or PAtC, as appropriate.

9. TRIAL CONDUCT

9.1. Domain-specific data collection

9.1.1. Clinical data collection

Additional domain-specific data will be collected.

- Administration of vitamin C
- Administration of thiamine
- Administration of corticosteroids

9.2. Criteria for discontinuation

Refer to Core Protocol Section 8.7 for criteria for discontinuation of participation in the REMAP-CAP trial

9.3. Blinding

Vitamin C will be administered on an open-label basis

10.STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

If a Platform Conclusion of equivalence in the primary endpoint is demonstrated the DSMB and the ITSC may consider continuation of randomization if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered plausible that clinically relevant differences in one or more secondary endpoints may be capable of being demonstrated. In all other respects the stopping rules for this domain are those outlined in the Core Protocol Sections 7.8.6 to 7.8.9.

10.2. Unit-of-analysis and strata

There are two units-of-analysis for this domain specified by the presence or absence of suspected or proven pandemic infection. As these strata are analyzed in different statistical models, no borrowing is permitted, until closure of the pandemic statistical model. For patients in the PISOP stratum, and as determined by the ITSC, and based on an understanding of the sensitivity and availability of testing for COVID-19 infection, the unit-of analysis may be modified to allow separate analysis of the COVID-19 infection confirmed and not confirmed stratum. This will be an operational decision. At the time of a Platform Conclusion, derived from the pandemic model, results will be reported for all randomized patients, patients in whom COVID-19 infection is confirmed by microbiological testing, microbiological tests do not detect or isolate COVID-19 infection, and testing is not performed. Response Adaptive Randomization (RAR) will be applied to patients enrolled in the PISOP stratum.

Assignment to the vitamin C domain for patients in the PINSNP stratum will be balanced and RAR will not be applied. Instead, REMAP-CAP data from patients enrolled in the vitamin C PINSNP stratum will be pooled with other data collected under the LOVIT umbrella model.(Masse et al., 2020)

10.3. Data sharing

Data collected from patients with suspected or proven COVID-19 that are enrolled in the LOVIT trial may be shared with the REMAP-CAP Statistical Advisory Committee and incorporated into the pandemic statistical model.

Data collected from patients who are enrolled in the PINSNP stratum of REMAP-CAP will be shared with the LOVIT investigators and used to contribute to the analysis of the LOVIT trial. In the event of a Platform Conclusion in this domain, from analysis of PINSNP patients in the interpandemic model, the REMAP-CAP DSMB will inform the LOVIT DSMB of this finding and implications to one or both studies will be determined by mutual agreement of both DSMBs.

A sensitivity analysis that includes and excludes shared data will be presented at the time of presentation and publication of results from both trials.

10.4. 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 Section 7.8.3.6 in Core Protocol).

10.5. Interactions with interventions in other domains

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

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

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

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

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

An *a priori* interaction with the COVID-19 Immune Modulation Domain is not considered likely and will not be incorporated into the statistical model used to analyze this domain.

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

10.6. Nesting of interventions

Nesting is not applicable to this domain.

10.7. Threshold odds ratio delta for equivalence

The threshold odds ratio for equivalence in this domain is that specified in the Core Protocol (Section 7.8.8) and the PAtC.

10.8. Post-trial sub-groups

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

- Age (<65 vs. ≥65 years)
- Sex
- Frailty (Clinical Frailty Scale 1-4 vs. ≥5)
- Severity of illness (quartiles of predicted risk of death from baseline APACHE II score)
- Receiving vasopressor or inotrope infusion at baseline
- All other potentially evaluable strata
- All other 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, inferiority, or equivalence of different interventions with respect to the primary endpoint is possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints. The DSMB will be advised of the following safety profile for vitamin C (see next section).

11.2. Potential domain-specific adverse events

Two adverse events are prespecified. These are hypoglycemia and hemolysis. Other SAEs should be reported if, in the opinion of the site investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see Core protocol Section 8.13).

Briefly, the safety profile for vitamin C is remarkably favorable. A potential risk is the formation of calcium oxalate crystals in renal tubule. However, this occurs at much higher doses than are being tested in this protocol. Cancer patients, for example, sometimes receive vitamin C doses much larger than the dose we are planning to administer. Nonetheless acute kidney injury, sufficient to result in renal replacement therapy, will be monitored as a platform-level secondary outcome.

Another potential risk, albeit rare, is factitious hyperglycemia as recorded by capillary blood sugar point-of-care devices (Tang et al., 2000), which may lead to iatrogenic hypoglycemia if treated with insulin. Factitious hyperglycemia does not occur with core lab assays, with StatStrip glucometers (Nova Biomedical), or with point-of-care blood gas machines that are sometimes available in ICUs. We will provide education to participating sites and treating clinicians on mitigating the risk of iatrogenic hypoglycemia by measuring blood glucose using a safe device in patients receiving vitamin C and insulin or oral hypoglycemic agents.

We will report hypoglycemia as an adverse event, defined as a core lab-validated glucose level of less than 3.8 mmol/L, recorded at any time during the ICU stay. Of note, regular frequent glucose monitoring is standard of care in ICUs. For each episode of hypoglycemia, we will record whether the patient was receiving the vitamin C intervention (from the start of the first dose to 36 hours after the last dose) and was treated with insulin or oral hypoglycemic drugs during the same time interval. If hypoglycemia occurs, standard supportive care (dextrose and glucose monitoring) will be provided.

Lastly, vitamin C may be associated with hemolysis in patients with G6PD deficiency, who will therefore be excluded from participating in the trial. However, since the prevalence of G6PD deficiency is generally low and since the trial is designed to facilitate early administration to maximize benefit, the trial does not screen eligible patients for G6PD deficiency. Of note, existing trials of intravenous vitamin C for sepsis have not screened for G6PD deficiency; no related adverse event has been reported thus far.(Fowler et al., 2014)[23] The clinical diagnosis of hemolysis will be monitored and recorded as an adverse event. If hemolysis happens during the intervention period, study drug will be ceased and standard supportive care (e.g. monitoring of hemoglobin, red blood cell transfusion as needed) will be provided. Drug-induced hemolysis resolves when the causative drug is stopped.

Since no side effects have been reported in the previous studies on vitamin C used for the treatment of septic patients, we do not anticipate any drugs interactions.

11.3. Domain-specific consent issues

Vitamin C is used off-label for the management of pneumonia by some treating clinicians. This variation in practice occurs, predominantly, because of the absence of high-quality evidence. Sites will be able to opt out of this domain for all patients at that site if they believe that vitamin C is either not a reasonable option or should be provided as part of the routine care of patients with pneumonia. Where either treatment option is regarded as part of the acceptable spectrum of standard care and given the time imperative to commence potentially effective therapy, entry into the study is preferred to be via waiver-of-consent or some form of delayed consent. Where prospective agreement is required, a period of up to 12 hours from the time of establishing eligibility will be available to obtain agreement and commence the assigned therapy. In such situations allocation status will not be revealed until prospective agreement has been obtained.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the Core Protocol Section 2.5. This domain has not received any additional domain-specific funding although additional funding may be requested.

12.2. Funding of domain interventions and outcome measures

Vitamin C will be acquired by participating sites.

12.3. Domain-specific declarations of interest

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

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