



Domain-Specific Appendix: VITAMIN C

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

Vitamin C Domain-Specific Appendix Version 2.0 dated 08 June 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 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)

This DSA applies to the following states and stratum:

Stratum	Pandemic infection suspected or proven (PISOP)		Pandemic infection neither suspected nor proven (PINSNP)
Core protocol documents	REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol		REMAP-CAP Core Protocol
Illness Severity State	Moderate State	Severe State	Severe State
Interventions available in this Domain + State	No vitamin C Vitamin C	No vitamin C Vitamin C	No vitamin C Vitamin C
Interventions submitted for approval at this site	<input type="checkbox"/> No vitamin C <input type="checkbox"/> Vitamin C	<input type="checkbox"/> No vitamin C <input type="checkbox"/> Vitamin C	<input type="checkbox"/> No vitamin C <input type="checkbox"/> Vitamin C
Interventions offered at this site in these locations	Ward	ICU	ICU
	<input type="checkbox"/> No vitamin C <input type="checkbox"/> Vitamin C	<input type="checkbox"/> No vitamin C <input type="checkbox"/> Vitamin C	<input type="checkbox"/> No vitamin C <input type="checkbox"/> Vitamin C

REMAP-CAP: Vitamin C Domain Summary	
Interventions	<ul style="list-style-type: none"> No vitamin C (no placebo) Vitamin C (50 mg/kg IV every 6 hours for 16 doses)
Unit-of-analysis, Strata, and States	<p>This domain is analyzed in two different statistical models.</p> <p>In the interpandemic statistical model there is a single unit-of-analysis corresponding to the Pandemic Infection Neither Suspected nor Proven (PINSNP) stratum (which does not include patients in the Moderate State). Response Adaptive Randomization is not applied in the PINSNP stratum.</p> <p>The pandemic statistical model includes patients who are in the Pandemic Infection Suspected or Proven (PISOP) stratum. Within this stratum, the unit-of-analysis is defined by illness severity state at time of enrollment, defined as either Moderate State or Severe State. Unit-of-analysis may also be defined by SARS-CoV-2 infection strata. Borrowing is permitted between states and strata. If the SARS-CoV-2 infection strata is applied in analysis, Response Adaptive Randomization will be applied to all PISOP patients using probabilities derived from the SARS-CoV-2 confirmed stratum.</p>
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 those specified in the relevant core protocol documents. During the COVID-19 pandemic, the platform-level inclusion criteria are different for patients within the PISOP stratum and for patients within the PINSNP stratum. Patients in either stratum are eligible for this domain.
Domain-Specific Exclusions	<p>Patients will be excluded from this domain if they have any of the following:</p> <ul style="list-style-type: none"> More than 24 hours has elapsed since ICU admission (noting that this may be operationalized as more than 24 hours has elapsed since commencement of organ failure support) Received any intravenous vitamin C during this hospitalization (unless incorporated in parenteral nutrition) Any of the following 3 contraindications to vitamin C therapy: <ul style="list-style-type: none"> known glucose-6-phosphate dehydrogenase (G6PD) deficiency known allergy to vitamin C known history of symptomatic kidney stones within the past 1 year Patient has been randomized in a trial evaluating vitamin C, where the protocol of that trial requires ongoing administration of study drug 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	<p>Primary REMAP endpoint: refer to REMAP-CAP Core Protocol +/- PATC and REMAP-COVID Core Protocol</p> <p>Secondary REMAP endpoints: refer to REMAP-CAP Protocol +/- PATC and REMAP-COVID Core Protocol</p>

	<p>Secondary domain-specific endpoints (during hospitalization censored 90 days from the date of enrollment):</p> <ul style="list-style-type: none">• Serious Adverse Events (SAE) as defined in core protocol documents
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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
PA _t C	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 relevant Core Protocol (either REMAP-CAP Core Protocol +/- Pandemic Appendix or REMAP-COVID 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 1.0: Approved by the Vitamin C Domain-Specific Working Group (DSWG) on 25th April 2020

Version 2.0: Approved by the Vitamin C DSWG on 8th June 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
Dr. Angelique de Man
Dr. Lennie Derde

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Mr. Cameron Green
Dr. David Huang
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Dr. Shay McGuinness
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4.3. Interaction with LOVIT trial

LOVIT is a trial that also evaluates the treatment effect of vitamin C in patients with COVID or sepsis or both. There is overlap between the leadership of the LOVIT trial and the leadership of this domain. This domain and the LOVIT trial have been designed to be complementary with pre-specified plans to share data and methods of analysis. A single site should not participate in both the LOVIT trial and this domain, although a site choosing to participate in the LOVIT trial can participate in other domains of REMAP-CAP.

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 8th June 2020

Co-Chair
Neill Adhikari



Date 8th June 2020

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP platform to test the effectiveness of vitamin C versus no vitamin C in patients with severe community-acquired pneumonia (CAP) or patients with acute illness due to suspected or proven COVID-19 (or both).

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 pre-post single-center 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), and 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.

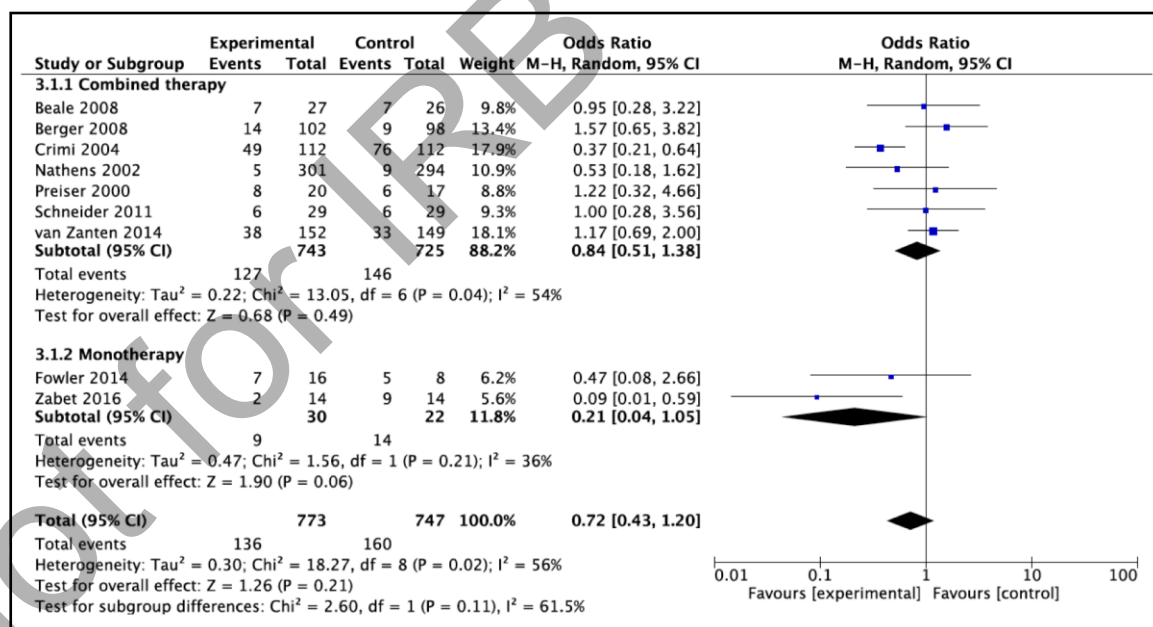


Figure 1. Forest plot: Randomized controlled trials of vitamin C as monotherapy vs. combined with other nutrients and medications

Since the publication of this systematic review, several trials evaluating vitamin C in sepsis are currently registered (<https://tinyurl.com/vitC-rct>) and published, 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.

6.2.3. 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 increase 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).

6.2.4. 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 hospital 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 clinical sites document the composite outcome 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 who are eligible for the platform.

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 vitamin C or 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, in patients with suspected or proven pandemic infection, the treatment effect of vitamin C is different depending on whether SARS-CoV-2 infection is confirmed to be present or absent.

We hypothesize that, in patients with suspected or proven pandemic infection, the treatment effect of vitamin C is different depending on illness severity state at time of enrollment.

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 admitted to ICU and patients with acute illness due to suspected or proven COVID-19 admitted to hospital, including patients admitted to ICU.

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 either the REMAP-CAP Core Protocol +/- Pandemic Appendix or the REMAP-COVID Core Protocol. 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.

This domain is available for patients who have acute illness due to suspected or proven pandemic infection in both the Moderate State and the Severe State.

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 (noting that this may be operationalized as more than 24 hours has elapsed since commencement of sustained organ failure support)
- 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
- Patient has been randomized in a trial evaluating vitamin C, where the protocol of that trial requires ongoing administration of study drug
- 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.

8.2.3. Intervention exclusion criteria

Nil.

8.3. Interventions

8.3.1. Vitamin C interventions

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

- ☐ No vitamin C (no placebo)
- ☐ Vitamin C

8.3.2. 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.

8.3.3. 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) or until hospital discharge. Reconstitution and administration of Vitamin C will conform to the administration guide and local standards.

In patients who are discharged from an ICU before completion of the course, continuation of administration to complete the course is at the discretion of the treating clinicians. For patients enrolled on the ward who are transferred to an ICU, it will be considered a protocol deviation if the

treatment course is discontinued. Omission of two or more consecutive doses or more than 4 total doses will be a protocol deviation.

8.3.4. Discontinuation of study drug

Vitamin C should be discontinued if there is development of an SAE. Study drug can be discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

8.4. Vitamin C strategy in patients negative for COVID-19 infection

In patients with suspected COVID-19 infection who receive an allocation status to receive vitamin C but who subsequently test negative for COVID-19 infection after allocation may have treatment ceased unless the treating clinician believes that doing so is not clinically appropriate. This decision should take into account the known or suspected sensitivity of testing for COVID-19 infection.

8.5. 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.

8.6. Endpoints

8.6.1. Primary endpoint

The primary endpoint for this domain is the REMAP primary outcome as specified in the REMAP-CAP Core Protocol +/- Pandemic Appendix or REMAP-COVID Core Protocol.

8.6.2. Secondary endpoints

All secondary endpoints as specified in the REMAP-CAP Core Protocol +/- Pandemic Appendix or REMAP-COVID Core Protocol.

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

- SAE as defined in the relevant core protocol documents and qualified in this DSA

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

9.3. Blinding

9.3.1. Blinding

Vitamin C will be administered on an open-label basis

9.3.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The following Platform Conclusions are possible in this domain, in both the interpandemic and the pandemic statistical model:

- Superiority of vitamin C compared with no vitamin C
- Inferiority of vitamin C compared with no vitamin C
- Equivalence of vitamin C compared with no vitamin C

10.2. Unit-of-analysis and strata

With respect to 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 with suspected or proven pandemic infection, units-of-analysis will also be applied according to illness severity state and, also, 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 at sites using the REMAP-CAP Core Protocol 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 relevant core protocol documents).

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)
- For patients enrolled in an ICU, 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, efficacy, inferiority, futility, or equivalence of different interventions with respect to the primary endpoints are 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).

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 are required.

11.2. Potential domain-specific adverse events

Two adverse events are prespecified. These are hypoglycemia and hemolysis. Other SAEs should be reported 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).

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 acute care areas of hospitals. 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. In keeping with recently published trials evaluating the same vitamin C regimen (Fowler et al., 2019), for all participants receiving insulin or oral hypoglycemic agents, for the first 36 hours after commencement of vitamin C, blood glucose must be measured with one of the following three systems: core laboratory, arterial blood gas machine that has been validated in the setting of high plasma levels of vitamin C, or Nova Biomedical StatStrip glucometer (Nova Biomedical) that has been validated to be accurate in the presence of high concentrations of ascorbic acid.

Between 36 hours after commencement of vitamin C and 7 days after the last dose of vitamin C is administered, blood glucose levels can be monitored as outlined in the paragraph above. Alternatively, standard glucometers may be used, provided that the difference between the level reported using any one of the three methods outline above and the standard glucometer is not more than 2 mMol/L on two separate occasions, measured at least 4 hours apart.

If a participant is discharged home within 7 days of the last dose of vitamin C, the same protocol must be followed, using either the participant's glucometer (or, if not available, a standard hospital glucometer). This procedure is to ensure that a standard glucometer yields glucose values concordant with one of the 3 validated methods.

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 hospital stay. 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 trial-related adverse event has been reported thus far (Yanase et al., 2020). 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.

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

As noted in the Background, and endorsed by the World Health Organization, in the absence of evidence of effectiveness of specific treatments for COVID-19, the use of a no treatment control is both appropriate and ethical.

For patients who are not competent to consent, either prospective agreement or entry via waiver of consent or some form of deferred consent can be applied, as required by an appropriate ethical review body.

During a pandemic, visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods of confirming agreement to participate in this (and other) domains of the platform.

Clinicians are directed not to enroll an individual patient if the treating clinician believes that participation in this domain is not in the best interests of the patient. 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.

11.4. Data Sharing

As outlined in the statistics section, pre-specified data sharing will occur between this platform and the LOVIT trial. Agreement for sharing of data will be specified in the informed consent and information documents used at participating sites.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the core protocol documents. This domain has not received any additional domain-specific funding but such funding may be obtained during the life-time of the domain.

12.2. Funding of domain interventions and outcome measures

Vitamin C will be acquired by participating hospitals.

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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