

Confidential Study Protocol

Vitamin C in Thermal injury: The VICToRY Trial

A phase III multi-center randomized trial

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Sponsor

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This study will be centrally coordinated at the Clinical Evaluation Research Unit, Kingston, ON Canada with EU support from University of Würzburg, Germany and GCP Services.

THE NEED FOR A TRIAL

1.1 What is the problem to be addressed?

Worldwide, burn injuries represent a significant public health problem and are ranked the seventh most common cause of unintentional injury.¹⁻³ Burn injury strikes mostly young to middle aged working people and is the leading cause of disability adjusted life years in low and middle-income countries.¹⁻⁴ Since the mid 1980's, mortality from burn injuries has plateaued and the leading cause of death from burn injuries continues to be sepsis and multiple organ failure.^{3,5} Burn patients present with up to a 3-fold higher prevalence of sepsis than other trauma patients.⁶ In addition, mortality from sepsis is much higher in burn patients compared to other critically ill patients.⁶ The aim of this trial is to reduce the burden of illness associated with significant burn injury.

In certain disease states, such as those associated with severe burns and other critical illnesses, the relationship between nutrient deficiencies, altered immune status, and acquired infection has been recognized for many years. More than in any other injury, the inflammation and catabolism associated with severe burns can exacerbate nutrient deficiencies, thereby predisposing patients to impaired immune function and increased risk of developing infectious complications, organ dysfunction, and death.⁷ Consequently, over the last few decades numerous trials have evaluated the impact of different nutrition/nutrient strategies in critically ill patients and in particular, severe burns patients.^{8,9} Recently, there has been renewed interest in the role of high dose intravenous vitamin C supplementation in critically ill patients, as summarized below. The origins of vitamin C supplementation in burn patients dates back to research done more than 20 years ago¹⁰ and yet, few centers routinely administer high-dose vitamin C to severely burned patients, suggesting that a high level of evidence is warranted.

The objective of this phase III trial is to demonstrate the efficacy and safety of a high-dose intravenous vitamin C administration in 666 severely burned patients (486 funded by the Department of Defence Military Burn Research Program and 180 pilot trial funded from other sources). We hypothesize that the inexpensive therapeutic strategy tested in this randomized controlled trial will be effective in reducing morbidity and mortality in an otherwise disabling injury worldwide.

1.2 What are the principal research questions to be addressed in this Phase III trial?

Primary research question:

In patients with severe, life-threatening burn injury, what is the effect of high dose (50 mg/kg every 6 hrs for 96 hours) intravenous vitamin C in addition to standard of care (SOC) on 28-days composite outcome of Persistent Organ Dysfunction (PODS) and all-cause mortality compared to add-on placebo and SOC?

Secondary Research question:

In patients with severe, life-threatening burn injury, what is the effect of high dose (50 mg/kg every 6 hrs for 96 hours) intravenous vitamin C in addition to SOC on time to discharge alive from hospital, hospital mortality, duration of stay in ICU and hospital, and 6-month mortality, health-related quality of life, and health care resources compared to add-on placebo and SOC?

1.3 Why is the trial needed now?

Burn injuries can lead to significant endothelial damage, capillary leakage, loss of fluid and plasma proteins, and may result in hypovolemic shock and significant systemic

inflammation, manifesting in hypotension, tachycardia, and edema. If persistent and undertreated, it may result in progressive organ dysfunction and even death.¹¹ Consequently, severe burn patients are aggressively fluid-resuscitated to try and maintain adequate circulating volumes. However, this therapeutic necessity may lead to volume overload, which itself is associated with several secondary complications such as pneumonia.¹² Additionally, the excessive production of oxygen-free radicals and reactive oxygen species when previously ischemic tissues are re-perfused with oxygen rich blood may contribute to excessive inflammatory reaction. The overwhelming production of oxidants can exceed the natural antioxidant defense mechanisms, leading to macromolecule-damage and worsening injury which itself is known as a major driver for the development of organ dysfunctions in these patients.¹³

Preclinical and lower level evidence

Vitamin C is an essential, water-soluble micronutrient, which acts as electron donor in multiple reactions and thus exerts many crucial functions in the human body. Vitamin C is required for more than 60 enzymatic reactions, among which are the synthesis of norepinephrine, collagen and carnitine. Vitamin C is involved in peptide amidation and tyrosine and steroid metabolism and in the conversion of cholesterol to bile acids.¹⁴ Vitamin C is known to support the cytochrome P450 driven hydroxylation of aromatic drugs and carcinogens¹⁴ and to promote iron absorption in the small intestine.¹⁵ Vitamin C enhances cell differentiation from somatic cells to induced pluripotent stem cells,^{16,17} which may be an important feature for regenerating processes in critically ill patients. Vitamin C restores vascular responsiveness to vasoconstrictors,¹⁸ ameliorates microcirculatory blood flow, preserves endothelial barriers, augments bacterial defense¹⁹ and prevents apoptosis.²⁰ Based on its redox-potential and powerful antioxidant capacity, vitamin C has been called the most important antioxidant, scavenging free radicals through the formation of the ascorbyl radical and thereby preventing damage to macromolecules, such as lipids or the DNA.²¹⁻²³ Vitamin C showed organoprotective effects in the nervous, cardiovascular, respiratory, gastrointestinal, coagulation and immune systems, as explained in detail in a review led by our group²⁴ and summarized in

Table 1. In addition to the influence of vitamin C on almost every organ system, and especially relevant for burn patients, there is some evidence that vitamin C may benefit wound healing. In a randomized controlled trial (RCT) (Barbosa et al), pediatric burn patients who were given a mixture of antioxidants including vitamin C which had better wound healing compared to the control group.²⁵ Another RCT with 89 patients with electrical burns, compared administration of growth factor plus vitamin C with growth factor alone and observed better wound healing rate and area of granulation tissue growth after 3 treatments.²⁶ Thirdly, an observational study of burn patients in Ghana associated adequate vitamin C levels and vitamin C intake was associated with improved wound healing.²⁷ A more comprehensive description of the underlying biochemical mechanisms and the influences of vitamin C are explained in greater detail elsewhere.^{14,19,24,28,29}

Table 1: Effects of vitamin C in preclinical and clinical trials

Organ	Influence of Vitamin C
Brain	<ul style="list-style-type: none"> Elevated levels (up to 80 times) protecting neurons from oxidative damage³⁰ Reduces the infarct volume after ischemia³¹
Cardiocirculatory System	<ul style="list-style-type: none"> Attenuates myocardial damage and improves myocardial stunning^{32,33} Reduces vasopressor demand³⁴ Reduces rate of atrial fibrillation³⁵⁻³⁷
Lung	<ul style="list-style-type: none"> Reduces intubation time³⁷ Decreases risk for pneumonia and alveolar inflammation³⁸
Kidney	<ul style="list-style-type: none"> Reduces fluid demand and increases urine production³⁹ No significant difference in AKI in a small pilot trial⁴⁰
Coagulation	<ul style="list-style-type: none"> Restores platelet function³⁸ and decreases capillary plugging¹⁸ Attenuates a sepsis-induced drop of thrombocytes¹⁸
Infection	<ul style="list-style-type: none"> Inhibits of bacterial growth³⁹, enhances microbial killing²⁸ Supports endothelial barrier function and promotes antioxidant scavenging²⁸
Wound healing	<ul style="list-style-type: none"> Shortens time to wound healing²⁵⁻²⁷ Improves area of granulation tissue growth²⁶

Clinical Evidence

Vitamin C concentrations are lowered in severe illness⁴¹, in patients recovering from surgery,⁴² in patients after cardiac surgery,³² and in patients developing multi-organ failure.⁴³ These conditions share pathophysiological similarities with patients after thermal injury, such as vasodilation, endothelial barrier dysfunction, edema and coagulation disorders.

ICU Patients

Over the past years, there has been an explosion of new randomized trials of intravenous vitamin C (IVVC). Previously, we had published several papers on vitamin C in critically ill patients including two systematic reviews and meta-analyses of existing studies of vitamin C supplementation in **critically ill patients**.⁴⁴ In our most recent publication, as compared to placebo, IVVC administration was associated with a trend towards reduced overall mortality (RR 0.87, 95% CI 0.75-1.00, $p=0.06$, test for heterogeneity $I^2=6\%$).⁴⁵ High dose IVVC was associated with a significant reduction in overall mortality (RR=0.70, 95% CI 0.52-0.96, $p=0.03$) whereas low dose IVVC had no effect (RR 0.94, 95% CI 0.79-1.07, $p=0.46$, test for subgroup differences, $p=0.14$). IVVC monotherapy was associated with a significant reduction in overall mortality (RR 0.64, 95% CI 0.49-0.83, $p=0.006$) while there was no effect with IVVC combined therapy (RR 1.00, 95% CI 0.85-1.18, $p=0.99$, test for subgroup differences, $p=0.004$). No trial reported an increase in adverse events related to IVVC.⁴⁵

More recently, the “Lessening Organ dysfunction with VITamin C” trial (LOVIT trial), a large, multicenter trial comparing high-dose (50 mg/kg every 6 hrs for 96 hours) IVVC monotherapy to placebo in patients with septic shock found IVVC monotherapy increased the risk of a composite endpoint of death or persistent organ dysfunction (POD) at day 28 (relative risk [RR] 1.21, 95% confidence interval [CI], 1.05 to 1.40; $p=0.01$).⁴⁶ When adjusted for important covariates, this primary outcome lost its statistical significance (RR 1.15, 95% CI 0.98-1.46). As further illustrated by the authors in the supplementary appendix of the study publication, if different statistical methods were used to analyze the primary endpoint, statistical significance was lost demonstrating fragility of the primary outcome.⁴⁶ An explanation as to how or what caused the increase in POD+death was lacking. There was no evidence of increased

incidence of acute kidney injury or any of the individual components of PODS. There was no significant increase in 28-day or 6-month mortality. None of the lab, biomarker or clinical data pointed to the mechanism of harm.⁴⁶ The results of LOVIT are in contrast with our previous meta-analysis that found benefit of IVVC monotherapy.⁴⁵

A concurrently published meta-analysis, which included the LOVIT trial, also found IVVC may be associated with a significant mortality benefit (RR 0.80 [95% CI, 0.68 to 0.93]) in patients with severe infections.⁴⁷ Notably, even with the inclusion of the LOVIT trial, they demonstrated similar results as our previous meta-analysis whereby the beneficial effect was still attributed to the subgroup of IVVC monotherapy (RR 0.65, 95% CI 0.50-0.86, $p=0.002$) rather than the IVVC combined therapy (RR 0.94, 95% CI 0.74-1.19, $p=0.58$), and there was still evidence for a significant test for subgroup differences ($p=0.04$).⁴⁷ However, this meta-analysis included a quasi-randomized trial, a study that excluded extubated patients and a study that published in abstract form only, which limit the confidence in the overall results. Furthermore, they concluded with moderate certainty that IVVC increased 90-day mortality based on a meta-analysis of 5 trials with low risk of bias, where 3 out of 5 of these trials investigated IVVC combination therapy.⁴⁷

These disparate findings from the meta-analysis of RCTs and a well-conducted landmark RCT of IVVC are difficult to reconcile. It is possible that a type-1 error may have occurred in the subgroup analyses of IVVC monotherapy from previous meta-analyses. Further, it has been criticized that the false positive risk for the LOVIT trial (calculated from the published summary data using uniform priors for the parameter values) is 70% and that the received findings should be interpreted cautiously as further there was no prior evidence for a harmful effect of high-dose vitamin C.⁴⁸

Furthermore, other important effect modifiers are not robustly explored in previous subgroup analyses of SRMAs. Consequently, we performed an updated meta-analysis with IVVC with a focus on those trials of critically ill patients that used IVVC as monotherapy.⁴⁹ We were also interested in further exploring whether the effect of IVVC monotherapy was modified by the dose, timing, treatment duration, the included patient population, or trial quality. In addition, a type-1 error may explain the observed significant mortality benefit for IVVC in the prior SRMA and we wanted to evaluate the impact of type 1 error using trial sequential analysis (TSA). Sixteen RCTs evaluating IVVC in adult critically ill patients and reporting ≥ 1 clinical outcomes were included. IVVC monotherapy was associated with significant reduction in overall mortality (risk ratio [RR] 0.73, 95% confidence interval [CI] 0.60-0.89; $p=0.002$; $I^2=42\%$) (See Figure in Appendix A). No subgroup differences were found except there may be evidence of a subgroup effect favoring trials with sicker (control group mortality \geq median of 37.5%) compared to trials with less sick patients (control group mortality of $<37.5\%$, $p=0.06$). TSA confirmed the benefits of Vitamin C among sicker patients but highlighted that more trials may be needed to confirm its treatment effect in less sick patients. The reported safety events were infrequent and equal in distribution between treated and untreated groups. Of note, one single center RCT administered high dose IVVC continuously for 72 hours and showed an increase in use of renal replacement therapy⁵⁰; no such observations were made in trials of intermittent dosing. Based on the current evidence, we conclude that IVVC monotherapy is safe and may still be associated with mortality benefit in critically ill patients, especially in sicker patients.⁴⁹ It may remain as an open question whether IVVC monotherapy improves mortality in a 'less sick' population (such as burn patients).

Burn patients

Burn injury results in a significant release of free radicals leading to vascular endothelial injury and capillary leakage, which in turn leads to burn edema. IVVC can possibly scavenge these free radicals limiting endothelial injury and hence limiting capillary leakage, which in turn leads to reduction in fluid requirement to resuscitate the burn patient. In addition, burn patients also suffer from “after burn,”-the delayed increase of tissue injury resulting from high-dose vasopressors, which may be helped by the microperfusion-enhancement of vitamin C supplementation. Patients with severe burns are also at risk of organ injury and like other critically ill patients, the organo-protective strategies of vitamin C may apply. In addition, oral supplementation of nutritional dosages of vitamin C as monotherapy or in combination with other micronutrients or growth factors may improve wound healing, which represents a major determinant for the patients outcomes.^{25,26,51}

Although they share some similarities with other critical illnesses, burn patients are very different from critically ill patients with sepsis. Time from onset of injury to onset of treatment, volume of distribution, associated concomitant fluids and medications, and risk of organ injury and death vary considerably between these 2 disease states. Studies in burn patients offer the advantage that exact information about the onset of critically illness are well-known and a timely initiation of a rescue therapy is possible, when compared to, for example, septic patients. We would not apply therapies shown to be efficacious in septic patients without studying their safety/efficacy to burns and vice versa. Of note, while the updated systematic review shows no difference in the positive treatment effect of IVVC in sepsis and non-sepsis patient population,⁴⁹ there are no trials of burn patients included in these prior reviews. In addition, the mortality rate in severe burns is much lower than what is observed in critically ill patients and thus, it remains an open question whether IVVC is efficacious in this low mortality risk patient population.

Clinical Evidence of IVVC in Burns

A high-dose intravenous vitamin C regimen of **66 mg/kg/hour for 24 hours** was proposed over 20 years ago and used by Tanaka et al in a prospective pseudo-randomized controlled clinical trial in severe thermally injured patients (n=37).¹⁰ This therapy of vitamin C seemed to be beneficial in the resuscitation phase as it was shown to reduce fluid requirements ($p<0.01$), improved oxygenation ($p<0.01$) and shortened duration of mechanical ventilation ($p<0.05$). In 2018, a small, pseudo-randomized trial of 30 burn patients using this same dosing structure of IVVC confirmed these earlier observations by Tanaka et al and showed that IVVC led to less fluids to achieve hemodynamic stability, greater urine output and consequently, less fluid retention in the first 24 hours.⁵² This trial also showed biological plausibility as they observed lower markers of oxidative stress (malondialdehyde) at 36 hours after resuscitation started (10

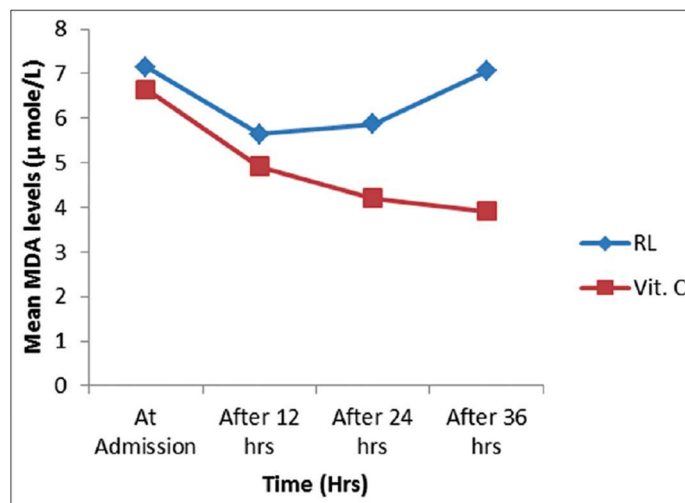


Figure 1: Malondialdehyde levels in both groups in the first 36h

hours after stopping the IVVC infusion) (see Figure 1). The investigators also noted that vitamin C levels in the plasma fell rapidly after stopping the infusion.

Several retrospective evaluations of IVVC of the same dosing structure evaluated in burn patients have also been published. In a retrospective analysis, the same intervention led to a reduction of resuscitation fluid volume ($p < 0.01$), increased urine output ($p < 0.05$) and trends towards decreased and shortened ($p = 0.2$) overall vasopressor requirement ($p = 0.07$) with no increase in renal failure.³⁹ However, in one retrospective case-control study, this therapy was associated with higher urine output/ day and per hour ($p = 0.002$), but also with an increased risk of renal failure (OR 5.4; CI 1.1-26, $p = 0.06$).⁵³ In another retrospective case-control study, IVVC was associated with a reduced fluid requirement in the first 24 hours and no increased risk of renal failure.⁵⁴ Finally, a recently published retrospective analysis using propensity score matching using a large database of burned patients in Japan ($n = 157$ patients who received vitamin C and 628 controls) demonstrated improved hospital survival using high dose vitamin C (>10 grams/day- risk ratio, 0.79; 95% confidence interval, 0.66–0.95; $p = 0.006$; >24 grams/day- risk ratio, 0.83; 95% confidence interval, 0.68–1.02; $p = 0.068$).⁵⁵

A recent review of IVVC in burn patients published in 2022 concludes, “Vitamin C is a promising antioxidant candidate that has been evaluated in burn studies. Without any doubt, the current enthusiasm about the high-dose vitamin C infusion is well justified, based on the fact that many clinical trials, to date, have demonstrated the beneficial role of vitamin C after thermal injury in decreasing total resuscitative volumes”.⁵⁶ We agree with this assertion, that the role of IVVC in burn patients warrants further evaluation. This is the purpose of the VICToRY trial; however, we next must discuss the optimal dose, duration, and method of administration for this evaluation.

Optimal Dose, Duration, and Means of Administering IVCC

Dr. Berry Fowler has done pioneering work establishing the potential safety and efficacy of a dose of 50 mg/kg every 6 hrs for 96 hours. In a phase I dose finding trial, this dose of intravenous vitamin C was associated with higher levels of plasma vitamin C, greater resolution of organ dysfunction, and lower levels of markers of inflammation and coagulation compared to a lower dose and to placebo.⁵⁷ Subsequently, Dr. Fowler and colleagues finished a multicenter phase II RCT of this dosing structure in patients with sepsis and lung injury and the trial did not show a difference in change of SOFA scores, a marker of vascular injury (thrombomodulin) or a marker of inflammation (CRP), the co-primary outcomes.⁵⁸ Nevertheless, they did demonstrate a remarkable survival advantage for these patients. At day 28, mortality was 46.3% (38/82) in the placebo group vs 29.8% (25/84) in the vitamin C group (between-group difference, 16.58% [95% CI, 2% to 31.1%], $P = .03$). As mortality was not considered as the primary outcome but one of 46 other secondary outcomes, these results are provocative but inconclusive. They do, however, confirm the safety of this dose as there were no adverse events noted with this dosing strategy. In another recent pharmacokinetic study of critically ill patients, investigators demonstrated how quickly vitamin C levels return to low levels following the termination of 48-hour dosing schedule suggesting that longer (at least 72 hrs) duration is warranted (not 24 hrs).⁵⁹ In fact, there is little or no justification for the high dose (66 mg/kg/hr for 24 hrs) used in the original Tanaka trial. Vitamin C is very hydrophilic and as such, it is promptly excreted by the kidneys with a resultant increase in osmotic diuresis and excretion of calcium oxalate, potentially leading to acute kidney injury which has been described in some trials.^{50,60}

One of our co-investigators recently published a dosing study in burn patients (the only one we are aware of). In this retrospective analysis of 38 patients with burn injuries > 20% TBSA, 19 patients who received high (66 mg/kg/hour x24 hours) were compared to 19 patients who received low (3500 mg/d) doses of vitamin C delivered intravenously and continuously for the first 24 hours.⁶⁰ The high-dose treatment maintained increased serum vitamin C levels significantly longer than the low-dose treatment. At baseline post burn injury, vitamin C concentrations in serum are lower than normal in both groups.⁶⁰ This finding is in concordance with Fowler's trial in sepsis that found patients to exhibit similarly reduced vitamin C levels at study entry (see Figure 2). Fowler et al. saw an increase of serum ascorbic acid (AA) to over 3000 $\mu\text{mol/L}$ on day 4 which corresponds to a 175-fold increase from baseline.⁵⁷ This was achieved by administration of 50 mg/kg every 6 hrs for 96 hours which amounts to a cumulative dose of 64g in an 80kg patient. In the study in burn patients, high dose vitamin C administration using Tanaka's dose of 66mg/kg/h continuously for 24 hours elevated the average concentration of AA in patient serum 150-fold to 2600 $\mu\text{mol/L}$ after 24 hours, while the low dose of 3.5 g/d elevated serum levels 10-fold. An 80kg subject in the high dose group of this study received 126g AA within 24 hours per and yet, overall increase in serum levels was comparatively lower than what Fowler et al. described as therapeutic serum concentration. One possible explanation for this discrepancy might be the more severely disturbed fluid balance in acute severe burn injury, which leads to higher resuscitation volumes and increased dilution effects due to increased capillary permeability with subsequent loss of fluid and active low-molecular agents such as AA into the interstitial space. It may therefore be necessary to administer higher doses of AA during burn shock resuscitation than to patients in septic shock but the safety of giving higher doses is not known. It also means that concerns about safety of high-dose IVVC following the LOVIT trial,⁴⁶ which also used 50 mg/kg every 6 hrs for 96 hours, will be reduced by the fact that the therapeutic concentrations in burn patients will be less than those observed in sepsis.

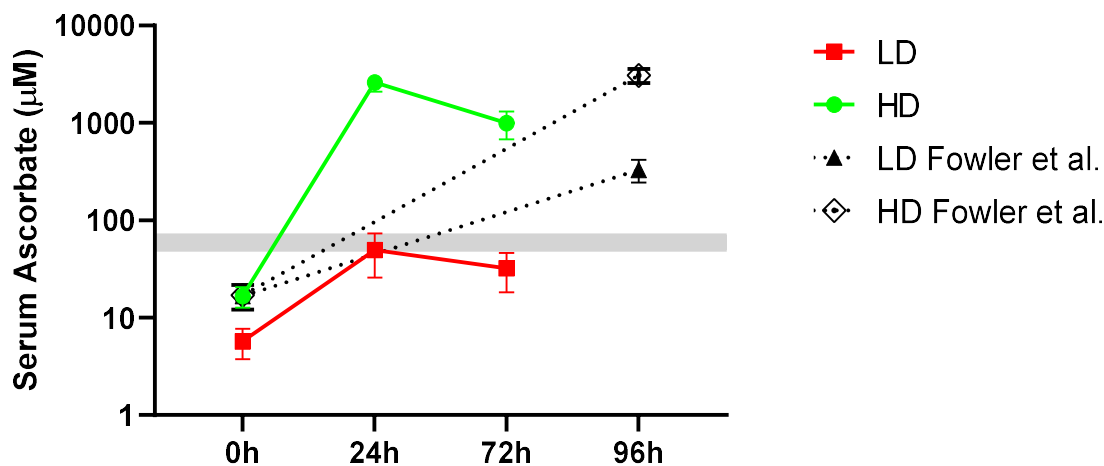


Figure 2. Ascorbic Acid levels in German study⁶⁰ compared to Fowler trial⁵⁷.

Grey bars represent normal values. LD: low dose ascorbic acid (3500mg/24h for 24h); HD: high dose ascorbic acid (66mg/kg/h for 24h). LD Fowler et al.: low dose ascorbic acid: 50mg/kg/24h for 96h. HD Fowler et al.: 50 mg/kg every 6 hrs for 96 hours)

This dosing study of vitamin C in burn patients demonstrated a significant decrease in the need for colloid fluids ($p < 0.05$) during the first 24 hours of acute volume resuscitation and the data trended towards lower requirements of crystalloids and overall fluids, as well as decreased

need for vasoactive catecholamines during the first 24 hours of treatment. The data pattern of this study suggested a considerable effect on several circulatory parameters during the first 24 hours while vitamin C was continuously administered at a high dose suggesting that it has the potential to impact resuscitation outcomes and possibly long-term related outcomes related to perfusion and organ function. At 72h postburn, these effects were partially reversed suggesting that extending the treatment window of vitamin C for the entire period of acute burn shock resuscitation (up to 4 days) may yield the full potential of beneficial clinical results postburn. That this higher intensity of treatment can be safely achieved is supported by the findings of this study which found no increased serum creatinine, risk of renal failure or the need for hemodialysis, as well as no disruptions of the metabolic acid-base-balance associated with high dose vitamin C.

In summary, the biologic rationale and clinical trial data we have systematically reviewed shows plausible mechanistic hypotheses and potential clinically significant benefits, thus clearly justify moving forward with a large double-blind randomized controlled trial. We believe such a trial of intravenous vitamin C supplementation in burn patients is needed now for the following reasons: **First**, as previously stated, the evidence to date suggests that intravenous vitamin C has a favourable effect on clinical outcomes. However, this signal comes almost entirely from non-burn patients. The safety and efficacy of high-dose vitamin C in burn patients are positive but focus on resuscitative outcomes and not more clinically important outcomes. A larger multicenter trial to confirm a signal of benefit is required. **Second**, there is considerable uncertainty, and thus, practice variability with respect to intravenous vitamin C administration in this patient population. Recent unpublished audit of a multi-center database of over 500 severe burn patients (RE-ENERGIZE dataset) shows less than 5% of patients are receiving high dose intravenous vitamin C. Vitamin C is widely available, inexpensive and easy to administer. There are a few safety concerns regarding high doses administered continuously in severe burn patients as there have been some reports of increased risk of renal failure associated with this supranormal dose.^{50,53} Seemingly, a higher level of evidence demonstrating its safety/efficacy is needed before practitioners are ready to embrace this novel therapy. **Third**, our team recently completed the RE-ENERGIZE trial, a large, multi-center, multi-national trial of enteral glutamine in 1200 severely burn injured patients.⁶¹ Currently, we have more than 60 burn centers from all around the world that have participated in the RE-ENERGIZE trial and are ready to collaborate on this project. We have conducted the RE-ENERGIZE trial with high degree of quality with respect to the implementation (more than 90% of study product doses delivered, less than 5% lost to follow up, and high levels of data completeness). To keep this highly functioning burn research network alive and generate new knowledge, we launched the feasibility pilot trial in the final year of enrollment of the RE-ENERGIZE trial and have now obtained funds for the confirmatory phase III VICToRY trial now that the RE-ENERGIZE trial has finished. By doing so, we can leverage the trial infrastructure from RE-ENERGIZE to, in a very cost-effective way, launch the VICToRY trial. Delays in moving forward with the VICToRY trial would cause loss of momentum, which may threaten our ability to finalize the large-scale vitamin C trial in a timely fashion.

1.4 How will the results of this trial be used?

If the phase III trial is positive, we need to ensure that all thermally injured patients receive intravenous vitamin C. If negative or no effect, we need to ensure that patients no longer receive such therapy, even if it works in other diseases such as sepsis. As it relates to critical care

nutrition practice in general, we have a long history of practice-changing initiatives that can be tailored or adapted for use in local burn centers. We have a process of synthesizing (in the form of evidence-based clinical practice guidelines) and disseminating best practice ideas (in the form of web-based repository of tools and information [see www.criticalcarenutrition.com]). In addition, we have conducted several large cluster RCTs⁶²⁻⁶⁴ to introduce system-changing practices in ICUs in North America and several large-scale quality improvement audits of practice to define and improve current practice.^{65,66}

Over the past several years, we have discussed this program of research and this specific protocol at the annual American Burn Association (ABA) meeting with society leaders, researchers, and the burn community at large. We have leveraged our relationships with the ABA to further facilitate our knowledge translation initiatives and increase the likelihood of the uptake of research results across the world. In the fall of 2014, we conducted our latest international nutrition audit and over 200 ICUs and more than 30 burn units worldwide participated in this quality improvement activity. This activity will both strengthen our clinical trials network and enhance our ability to translate findings to other centers worldwide at the completion of this study.

1.5 Describe any risks to the safety of the participants involved in the trial.

The safety profile for vitamin C in ICU patients is remarkably favourable.⁶⁷ Real-time in the field monitoring of safety events has not revealed any safety issues (personal communication, McGuff Pharmaceuticals, Inc., Department of Regulatory Affairs, Ascor® (Ascorbic Acid Injection, USP) PADER Synopsis, Year 5, NDA 209112). However, there are several complications that may develop which will be closely monitored as ‘Events of Interest’ or outcomes in this trial. One of the potential risks is the formation of calcium oxalate crystals in renal tubule. However, this occurs at much higher doses than those being tested in the VICToRY Trial. Cancer patients, for example, sometimes receive vitamin C doses approximately 40-50 times greater than the dose we are planning to administer albeit over a longer period of time.^{68,69} We will nonetheless monitor acute kidney injury (as an outcome in this trial).

Another potential risk, albeit rare, is factitious hyperglycemia as recorded by capillary blood sugar point-of-care devices as the molecular structure of vitamin C and glucose are similar. This phenomenon does not occur with core lab assays and some point-of-care devices.^{70,71} Accordingly, we are going to mandate that glucose can only be measured with one of the 3 following systems up to 7 days after the last dose of the investigational product (even if patient is transferred on ward) : 1) core lab, 2) point-of-care arterial blood gas machine that has been validated in the setting of high plasma concentrations of vitamin C, 3) Nova Biomedical StatStrip glucometer that has been validated to be accurate in the presence of high concentrations of ascorbic acid. Episodes of true hypoglycemia (<3.8 mmol/L) will be captured in the case report form.

Since the solution containing vitamin C is acidic and contains sodium, acid-base and electrolyte imbalances are theoretically possible,⁷² but its effect on blood pH has been called “negligible” in patients receiving up to 8 g/m².⁷³ and metabolic acidosis has been reported in single-cases when multiple factors such as exsiccosis, acute kidney injury and other metabolic derangements occur simultaneously.^{74,75} Lastly, vitamin C may be associated with hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, who will therefore be excluded from participating in the trial. However, since the prevalence of G6PD deficiency is low in most if not all participating centers and since the trial is designed to facilitate early

administration to maximize benefit, we will not screen eligible patients for G6PD deficiency. Of note, most existing trials of intravenous vitamin C for sepsis have not screened for G6PD deficiency; no related adverse event has been reported thus far.⁴⁹ Hemolysis will be monitored and recorded in the case report form. If hemolysis happens during the intervention period, we will stop the study drug and provide standard supportive care (e.g. monitoring of hemoglobin, red blood cell transfusion as needed). Drug-induced hemolysis resolved when the causative drug is stopped.

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

How will safety concerns be handled?

- 1) We will exclude patients with known G6PD deficiency.
- 2) For individual subjects, the treating physician will have the right to discontinue study product if the enrolled patient develops a new diagnosis of oxalate kidney stones, severe hemolysis, severe acid-base/ electrolyte imbalances or refractory hypoglycemia or any other medical complication such as an SAE that, in the opinion of the treating physician, ongoing use of study product would compromise patient safety.
- 3) We have a Data Monitoring Committee which is charged with the responsibility for ensuring the integrity of the trial. They have and will continue to review all serious adverse events (SAE) and will have the right to trigger an ad hoc safety review if 2 or more similar SAEs are observed that cause concern. In addition, by group (but still blinded) they have and will continue to review events of interest, rates of kidney injury (KDIGO classification of acute kidney injury) and use of renal replacement therapy on an annual basis. In addition, they will review the results of planned interim analyses and provide recommendations regarding the ongoing safety of the VICToRY trial. Two formal interim analysis will be performed to assess increased POD+death in the vitamin C arm after one-third and two-thirds of the patients are enrolled (see section 2.16).

In summary, recent studies provide us with a strong signal that high-dose intravenous vitamin C may be beneficial in septic patients. While the pre-clinical data related to burns are compelling, the clinical data in burn patients are too sparse to convince clinicians of the therapeutic benefits. We aim to conduct a large scale, multi-center trial of intravenous vitamin C in burns to establish the efficacy of our proposed intervention.

2. THE PROPOSED TRIAL

2.1 What is the proposed trial design?

We propose a multicenter, double-blind, randomized controlled trial of 666 patients with severe burns randomly allocated to receive 50 mg/kg every 6 hrs for 96 hours of intravenous vitamin C or placebo. As patients recruited into the pilot trial will also be followed up for the phase III endpoints, the patients from the pilot will also contribute to the confirmatory phase III analysis. This approach will use resources in an efficient manner and will allow us to progress swiftly to make the therapy available to patients as early as possible, if it is safe and efficacious. A Schedule of Assessments is included as Appendix B.

2.2 What are the planned trial interventions?

Patients will be allocated to 2 groups: **Vitamin C group:** patients will receive intravenous vitamin C at 50 mg/kg every 6 hrs for 96 hours. **Control group:** patients will receive a similar

amount of placebo (either D5W or saline) delivered in the same manner as the vitamin C. The vitamin C will be sourced locally and prepared in a blinded manner by local research pharmacies. The vitamin C will be diluted in either 0.9% NaCl or D5W to a concentration of ≤ 92 mg/mL. According to stability testing, vitamin C concentration between 36 and 92 mg/mL, diluted in either normal saline or D5W, and stored protected from light at 2-8°C is physically and chemically stable for at least 14 days.⁷⁶ The volume for dilution will be determined based on the patient's pre-burn dry weight to a maximum of 150 kg. Dosing will be calculated based on a weight of 150 kg for patients weighing ≥ 150 kg. The duration of each infusion will be dependent on infusion rate. The infusion rate will not exceed 100 mg/min. Below is a sample table of infusion volumes and durations based on patients with a pre-burn dry weight between 50 and 175 kg, dosed at a maximum of 150 kg:

	Kg	mg	mg	mL	Minutes
Pre-Burn Dry Weight	Dosing Weight	mg/day based on highest dose (200 mg/kg)	mg/dose (q6h)	Volume/dose (max dose of 92mg/mL)	Duration of infusion (max rate of 100mg/min)
50 kg	50	10000	2500	27	25
75 kg	75	15000	3750	41	37.5
100 kg	100	20000	5000	54	50
125 kg	125	25000	6250	68	62.5
150 kg	150	30000	7500	82	75
175 kg	150	30000	7500	82	75

A missed dose administration will be compensated by a make-up dose within 24 hours of the missed dose. Open-label vitamin C to a maximum of 200 mg/day delivered intravenously or 1,500 mg/day enterally will be allowed in study subjects for the purpose of nutrient repletion. There are no excluded medication treatments before or during the trial other than high dose IV vitamin C. There is no 'rescue' medication for study subjects.

We will provide an inventory Drug Accountability Log (DAL) which will be maintained by the unblinded pharmacist at each participating site to document receipt, distribution, and destruction of the locally sourced IV vitamin C. A participant specific DAL will also be provided for each pharmacy team member to record all doses of study product, active or placebo, prepared and administered to each participant.

2.3 What are the proposed arrangements for allocating participants to trial groups?

To influence clinical outcomes and in particular, resuscitation endpoints, high-dose intravenous vitamin C has to be given as early as possible- within hours of admission to the hospital. This will mean the requirement for obtaining fully informed consent prior to initiation of study procedures may be impractical. Many if not all of the patients will be 'incompetent' to provide consent themselves due to their burn or burn-associated illnesses and medications. Most families or legally appointed representatives are not present during those early hours of resuscitation. Accordingly, we will apply for alteration in informed consent in participating sites, outside of the U.S., that allow for alterations, or where applicable, such as in the UK, Germany,

France, and possibly other countries where permitted by national regulations, sites can use a third-party or professional consent process and follow up with next of kin when available. In the U.S., and all other countries where deferred or third-party consent is not allowed, we will obtain consent from the patient or the legally appointed representative or next of kin, when available, and if not available within the first 24 hours after hospital admission, the patient will not be enrolled in the study. We aim to have patients enrolled as soon as possible after admission to hospital (patients will be excluded if present in hospital for more than 24 hours).

Once consent is obtained, and necessary baseline data collected for qualifying patients, the study co-ordinator will log on to the web-based randomization system at the Clinical Evaluation Research Unit at Queen's University. The system will confirm eligibility prior to allowing randomization. The system will then provide the study co-ordinator with a patient study number and who will then contact the local pharmacist or delegate with notification of randomization. The unblinded pharmacist or delegate will then access the system to determine the treatment assignment. Allocation will be random and concealed and will be blinded to everyone except the pharmacist at each site who will be responsible for preparing study samples and delivering them to the ICU in a blinded fashion in accordance with the documented study operating procedures. The randomization system, which has proven reliable in several prior RCTs, has a robust audit trail, and will maintain concealment and blinding.

The randomization system will use a computer-generated randomization schedule allocating patients 1:1 to either vitamin C or matching placebo by the method of permuted blocks of random undisclosed size stratified by centre. The study statistician will be responsible for generating the randomization codes and will keep these codes in a password protected file on a private drive on the servers at Kingston Health Science Center. Given the large pragmatic nature of the definitive trial, we will not stratify by additional factors such as burn severity. Since there are no antidotes to Vitamin C, there are no unblinding procedures. Study IP stopping rules are articulated in section 1.5.

2.4 What are the proposed methods for protecting against other sources of bias?

All research and clinical personnel at the study site with the exception of the site pharmacist or responsible team member will be blinded to treatment allocations. Vitamin C is colorless and odorless and a saline or D5W placebo will be used to maintain blinding. Given the nature of our study intervention, it is important that we standardize the practice of nutrition therapy in participating units. As per standard of care in these burn units, these patients will be fed enterally and for those fed into the stomach, they will have routine evaluation of gastric residual volume during feeding. We have considerable experience standardizing feeding practices across ICUs using our national nutrition guidelines, pre-printed orders and bedside algorithms (see tools in www.criticalcarenutrition.com). We provide these tools to all participating centers to harmonize practices between centers and to improve compliance. While we have not standardized the selection of feeding solutions for individual patients, we will provide guidance on using standard equations for the determination of energy and protein intakes. We have also harmonized the use of parenteral nutrition when enteral nutrition fails to meet its goal. All other aspects of burn care will not be standardized but we will capture key process of care issues in our minimalistic data collection strategies.

2.5 What are the planned Inclusion/Exclusion criteria?

Inclusion criteria 18 years of age or older with deep 2nd and/or 3rd degree burns, who are assessed as requiring skin grafting, and a minimum burn size $\geq 20\%$ Total Body Surface Area (TBSA). Patients with smaller burns are less likely to require fluid resuscitation and their risk of morbidity and mortality is lower. Burn size will be determined by the attending physician (and confirmed by the attending surgeon if it is not the same person).

Exclusion criteria

1. >24 hours from admission to participating hospital to consent.
2. Patients admitted to burn unit >24 hours from injury or accident.
3. Patients who are moribund (not expected to survive the next 72 hours).
4. Pregnancy (pregnancy will be ruled out as part of standard of care) or lactating.
5. Enrolment in another industry sponsored ICU interventional study
6. Receiving high-dose IV vitamin C already (enteral or oral vitamin C is allowed).
7. Known glucose-6-phosphate dehydrogenase (G6PD) deficiency.
8. Recent history of kidney stones (within the last year).
9. Concomitant use of hydroxocobalamin (vitamin B12) for suspected cyanide poisoning.

These criteria are designed to include those severe burn injury patients who are likely to benefit from the therapeutic intervention tested in this trial. For the nutrients to have a beneficial effect, particularly on resuscitation outcomes, they have to be delivered as soon after the injury as possible (ideally within 3- 6 hours of admission). However, we acknowledge that it will require some time for research staff to obtain informed consent. We will exclude patients not likely to benefit from the intervention (not likely to survive beyond 72 hours) or those in whom the safety of high dose intravenous vitamin C is uncertain (pregnant patients and patients with G6PD deficiency). High dose vitamin C appears safe in kidney disease except for patients who may have had recent kidney stones or who have received vitamin B12 since it excretes oxalate acid in the kidneys as well. Consistent with other trials of high dose vitamin C, we will recruit patients with kidney injury or failure but exclude patients with recent history of kidney stones.

2.6 What is the proposed duration of treatment period?

96 hours based on Dr. Fowler's trials demonstrating safety and efficacy of this duration. Shorter dosing intervals have demonstrated a reoccurrence of hypovitaminosis after stopping the study intervention.^{25,57}

If a study patient is prematurely withdrawn from the trial (see safety criteria in section 1.5), the timing and reason for the withdrawal from vitamin C administration will be noted and complete study outcomes will continue to be collected. Patients withdrawn from vitamin C/placebo administration will be followed up for 3 days after last administration of the investigational product. If patients withdraw from the entire study, the collected study data will be kept to ensure safety, but no further data will be collected. As we expect this event to be rare, we will not replace such subjects.

2.7 What is the proposed duration of follow-up?

Patient clinical status will be monitored daily during the acute care unit stay for up to 3 days after termination of study IP (maximum 7 days). Hospital outcomes will be abstracted from the chart once the patient is discharged.

2.8 and 2.9 What are the proposed primary and secondary outcome measures?

The primary outcome for this phase III trial is persistent organ dysfunction (POD)+death at 28 days, a novel composite endpoint that combines being alive and being free of organ support (inotropes or vasopressors or mechanical circulatory assistance, renal replacement therapy and mechanical ventilation).⁷⁷

The most important secondary endpoint of this trial will be “time to discharge alive from hospital.” The other secondary outcomes will be the components of 28-day POD which include mortality, use of inotropes or vasopressors or mechanical circulatory assistance, renal replacement therapy and mechanical ventilation and POD-free days in the first 28 days.

Tertiary outcomes will include intensive care unit (ICU) outcomes (e.g. length of stay, duration of mechanical ventilation, and readmission rates); hospital outcomes (hospital mortality, length of stay, bacteremia with gram-negative bacilli, and readmission rates); and 6-month outcomes (mortality, health related quality of life and physical function domain of the Short Form-36 (SF-36) questionnaire, activities of daily living and instrumental activities of daily living). We will also record frequency of operative procedures for burn care, presence of inhalation injury, blood transfusions, and other major cost drivers to support our economic evaluation.

2.10 What is the proposed sample size and what is the justification for the assumptions underlying the power calculation?

The primary outcome for this trial is PODS+death at 28 days after randomization. Based on estimates from currently available pooled data from the RE-ENERGIZE study with $\geq 20\%$ TBSA (n=539), we estimate that the 28-day PODS rate will be 27%. Based on our simulations accounting for two interim analyses (see Tables in Appendix C), we estimate that with 333 subjects per arm, we would achieve 78% power to observe a reduction at a one-sided alpha of 0.025 (or two-sided alpha=0.05) if the rate of PODS at 28 days was reduced from 27% to 18% (RRR=33.3%).

Given the 30-36% relative risk reduction in mortality observed in the meta-analysis reported in section 1.2, we believe this treatment effect to be plausible. The simulated power under various effect sizes accounting for the interim analyses is provided in Appendix C. Based on our several prior studies in this field, we expect to obtain the 28-day PODS status on virtually all patients. Since the randomization is stratified by site and the analysis will control for site, the possible presence of between-site heterogeneity in overall rates will not decrease the power, assuming that the effect of treatment is consistent across sites.

A sample size of 666 patients also provides adequate power for one of our key secondary outcomes, time to discharge from hospital alive. Based on estimates from currently available pooled data from the RE-ENERGIZE study with $\geq 20\%$ TBSA (n=539), we estimate that the median time to hospital discharge is 47 days, by which time no more than 10% would have died. We consider death a competing risk precluding live hospital discharge and, for this outcome, conservatively assume that the intervention has no effect on mortality. With 333 patients per arm followed for up to 182 days and allowing for 5% loss to follow-up, we would achieve 90% power at a two-sided alpha of 0.05 to compare the cumulative incidence of time to alive hospital discharge over 6 months, if the subdistribution hazard ratio of time to live discharge was 1.32. Assuming time to discharge follows an exponential distribution except allowing for the competing risk of death, this effect size would equate to 60% vs. 50% of patients being

discharged alive by day 47 in the intervention and control arm respectively. However, power will decrease due to the interim analysis. The interim analysis will reduce the power by 1% if the RR for PODS+death is 0.667 and the power for time to discharge alive will remain above 80% if the RR of PODS+death is less than 0.85.

We acknowledge that we cannot comment on minimally clinically important differences (MCIDs) in these key endpoints and whether our trial is adequately powered to detect a MCID. This is a problem for all critical-care trials, in which small changes in mortality are important from a patient's perspective; yet detecting such changes would require enrolment of thousands of patients. Rather, we propose a trial that is feasible within the duration of the grant and powered to show a moderate difference in a validated outcome measure. We will be judicious in the interpretation of our results. Thus, if there is a numerical advantage to the study intervention within the range of clinical importance but without statistical significance, our trial results will be "indeterminate".⁷⁸ Fortunately, such trials can be combined statistically with other similar trials, using meta-analysis techniques, to illuminate smaller treatment effects.

2.11 Health service research issues:

Burn care of hospitalized patients is extremely costly, and the cost is related to the severity of the injury.⁷⁹ From the 2013 American Burn Association Repository, the mean hospital charge of burn care was \$US 84,431 per patient (based on 67,115 patients). These charges include patients with minor burns. Patients with burns >20% are much more costly and the charges associated with burn care increase with the severity of burns. Simple interventions, like vitamin C, might result in substantial economic savings from complications averted. If the current trial demonstrates efficacy, we would propose to conduct an economic evaluation using data collected in the phase III trial.

2.12 What is the planned recruitment rate?

Our early real-world experience with fourteen sites over the past 33 months has yielded a recruitment rate of 0.4 patients/site/month. However, based on our experience with the RE-ENERGIZE trial involving over 60 participating sites, our average enrollment rate was closer to 0.3 patients/per site/month. The eligibility criteria for VICToRY are simpler (fewer exclusions) but the time window is shorter, so we will use the same estimate of 0.4 patients/site/month in developing our enrollment plans. With 40 sites around the world participating, we can enroll 16 patients/month and 486 over 2.5 years of the grant. With an additional 180 from the pilot trial, this enables us to reach the desired sample size. We will use the first 9 months of the grant to obtain regulatory and ethics approvals and site activation, and we will need the final 9 months to complete 6 months follow up; to allow for delays in reaching enrollment targets; and to perform data cleaning, analysis, and write up. The total duration of the study is 4 years (2022-2026).

2.13 Are there likely to be any problems with compliance? and 2.14 What is the likely rate of loss to follow up?

In the early experience with the pilot trial (n=15 patients), we have observed 100% compliance with delivery of study product and no patients lost to 28-day follow up. We will continue to monitor and manage compliance issues that emerge through the remaining part of the pilot trial with frequent "touch-base" calls, quality metric reports, and query management. Our experience working with these sites in the RE-ENERGIZE study, in which we observed >90%

compliance with study protocol and less than 4% lost to follow up at 6 months, increases our confidence that there will be no major issues with compliance of this protocol. Moreover, given the short-term duration of the intervention (96 hours) compared to the RE-ENERGIZE trial (3 months), we expect compliance with study medication administration to be even higher than the 90% observed in the RE-ENERGIZE trial. The RE-ENERGIZE trial can be considered as a 'pilot' for all other study procedures as they are essentially the same between the 2 studies.

2.15 How many centers will participate?

We plan to recruit 40+ sites from our existing burn research network to participate in VICToRY. Interested sites to date are from: Canada (Quebec, Ontario, and Nova Scotia); USA (Arizona, Connecticut, Iowa, Maryland, Missouri, Ohio, Texas, Washington, and possibly others); Belgium, Costa Rica, France, Germany, Italy, Mexico, Paraguay, Poland, Portugal, Singapore, Spain, Thailand, and the UK. The inclusion of so many sites from different countries will enhance the generalizability of study results.

2.16 What is the statistical and data analysis plan?

In accordance with the intent-to-treat (ITT) principle, the analysis will include all patients in the arm to which they are randomized regardless of study compliance except patients who do not receive any of the study intervention (modified ITT analysis). In addition, we will conduct a per-protocol analysis of all truly eligible patients who receive all 16 doses. All of the analysis, including reporting of participant flow and patient characteristics by arm, will be presented in accordance with the CONSORT statement. Our primary outcome (alive and PODS free at 28 days) will be compared between groups using by an adjusted relative risk estimated by a modified Poisson regression with robust standard errors clustering by site and controlling for the following baseline covariates: TBSA burn, traumatic brain injury, mechanically ventilated at baseline and injury severity score.⁸⁰ This approach will meet regulatory guidance and best practices suggesting that site and strongly predictive baseline covariates be considered for adjustment in the analysis of multicenter studies.⁸¹⁻⁸³ Binary secondary outcomes will be analyzed similarly.

Based on our substantial prior experience with this population, we expect minimal missing data for all 28-day outcomes. However, details of missing data will be provided, and for the primary outcome, we will perform a sensitivity analysis using a graphical pattern-mixture tipping-point approach demonstrating the treatment effect over the possible range of missing outcomes.^{84,85} Lengths of ICU and hospital stay will be reported by arm using the subdistribution cumulative incidence function (CIF), where death is treated as a competing risk precluding the possibility of discharge. The between-arm difference in time to live discharge will be summarized by the subdistribution hazard ratio with 95% confidence intervals and p-values estimated by the Wald test from the Cox proportional hazards model, with site as a random frailty to account for potential between-site heterogeneity and adjusting for the same baseline covariates as for the primary outcome. For this analysis, survivors will be censored at the earliest of last date known alive or 183 days after randomization. Patients who die prior to discharge will be censored after the end of the follow-up period (i.e. >183 days) to account for the competing risk of death. This will yield virtually the same results as the Fine and Gray approach treating death as a competing risk precluding discharge, except we will have incorporated ICU as a random effect. This outcome is also known as time-to-discharge-alive (TTDA). The distribution of ventilator-free days and PODS-free days up to day 28 will be compared between arms by the

empirical distribution function depicting the proportion of people (y-axis) with at least 1 through 28 free days (x-axis) by arm.

Six-month mortality will be reported by group using Kaplan-Meier curves with between-group differences summarized by the hazard ratio and corresponding 95% confidence intervals estimated from the Cox proportional hazards model with site as a random frailty and adjusting for the same baseline covariates as the primary outcome. Survival will be censored at 183 days or time last known alive for patients lost to follow-up. Six-month health-related quality of life and physical-function status will be reported for survivors only since our tools (SF-36 and Katz's ADL index) are not defined for decedents. When interpreting these outcomes, we will only consider results definitive if they are in the same direction as survival. For example, if the intervention arm had both higher survival (regardless of statistical significance) and better SF-36, then we would conclude that health-related quality of life was improved in the intervention arm compared to the control arm. For each of these outcomes we will report the mean scores by arm and estimate the mean difference between arms with 95% confidence intervals. Estimates for these outcomes will be obtained from a linear mixed effects model with our primary predictor of interest being a fixed effect indicator for treatment arm but also including site as a random effect and the following fixed baseline covariates: age, sex, ethnicity, TBSA burn, traumatic brain injury, mechanically ventilated at baseline and injury severity. These estimates will use the augmented inverse probability to minimize bias due to missing data among survivors.⁸⁶

Although the secondary outcomes will play a mostly supportive and exploratory role, result interpretation will consider the multiplicity of tests, and the false discovery rate for correlated tests will be reported if nominal p-values reach ≤ 0.05 for any secondary outcomes.⁸⁷ Tertiary outcomes will be reported without p-values.

There will be two interim analyses for futility/harm after the primary outcome is available on 222 and 444 patients. Both interim analyses will suggest stopping for futility/harm if the adjusted RR of the PODS+death is >1.1 favoring control. The study will not stop early for benefit. Details of the operating characteristics of this study under this futility rule are provided in Appendix C.

2.17 Are there any planned subgroup analyses?

A priori, we plan to explore 5 sources of potential heterogeneity:

- 1) Age
- 2) Severity of burn as judged by TBSA, SOFA, and APACHE.
- 3) Presence of trauma and traumatic brain injury
- 4) Adequacy of prior care/resuscitation as judged by direct arrival vs. transfer from other setting with some prior care.
- 5) early vs. delayed initiation of study IP (based on the observed distribution of times to start study IP).

The rationale for these subgroups is that older patients and patients with more severe burns and more severe trauma will likely be more deficient in vitamin C and, therefore, more likely to benefit from supplementation.^{88,89} As we suspect that earlier treatment with vitamin C, particularly during the resuscitative period, will have the potential for a greater treatment effect, we will explore this source of heterogeneity. The statistical significance of apparent effect modification will be assessed by testing a treatment by covariate interaction term using modified Poisson for mortality and the Cox PH model for time to discharge alive as described above. Due to the increased risk of type I and type II error, subgroup-specific inferences will be considered

exploratory and hypothesis generating. Subgroup-specific effects will be presented by forest plots based on TBSA tertiles and presence of non-thermal trauma, but modelling and tests for interaction will keep TBSA as continuous.

2.18 Ethics and Regulatory Issues

The pilot version of this trial protocol has been approved by Health Canada and a waiver of IND was granted by the FDA. Current regulatory applications are underway in several countries in Europe. All participating institutions will obtain local ethics approval and we will obtain informed consent from patients or their surrogates before starting study procedures. Telephone or e-consent strategies, where allowed by local ethics boards will be acceptable. We justify the use of a placebo as trial participants will receive increased monitoring and follow up, which may translate into improved outcomes. At 6 months, we will be making contact with the patient or their alternative contact. If we detect patients are ‘in need’ of further clinical interventions, local research personnel making the contact will be trained by local investigators to direct the patient back to the referring clinical service or other local service as appropriate.

As this trial was already underway before January 20, 2020 and has already been approved by local IRBs at more than half of the US sites already, using a single IRB is not a cost-effective strategy to activate the remaining US sites. This is consistent with the policy on single IRB exception determinations.⁹⁰

2.19 Confidentiality

Information about study participants will be kept confidential and will be managed in accordance with the following rules:

- All study-related information will be stored securely.
- All study-participant information will be stored in locked file cabinets, or locked room, as applicable, and accessible only to study personnel.
- All paper and eCRFs will be identified only by a coded participant number.
- ***All databases will be password protected and secured within electronic data capture systems (EDCS).***

If a participant revokes authorization to collect or use personal health information, the clinical site retains the ability to use all information collected prior to the revocation of participant authorization unless otherwise specified. Records pertaining to the clinical trial will be retained and maintained for a period of 15 years in compliance with Health Canada requirements.

2.20 Serious Adverse Events and Safety Reporting

In the context of an acute critical illness, all patients eligible for the VICToRY Trial are at risk of adverse events (AEs). Following Canadian guidelines for AE reporting in academic critical care trials, expected AEs were pre-specified as trial outcomes and will not be reported as AEs. These events will be recorded in the electronic data capture system as part of data collection. No other AEs will be reported.

Patients will be monitored daily for SAEs. Clinical sites will document all unexpected SAEs in the EDCS. The local principal investigator, with support from the trial principal investigators and Coordinating Centre, will determine if the SAE is possibly related to the study intervention (see Appendix D for SAE and causality/relatedness definitions). The trial principal investigators and Coordinating Centre will also support the local principal investigator with

determining if the SAE is unexpected. Unexpected SAEs must be reported to the Coordinating Centre via the EDCS within 24 hours of the local principal investigator becoming aware of the unexpected SAE. Unexpected SAEs that are considered to be possibly related to the trial intervention will be reported to all applicable regulatory authorities and participating site principal investigators by the Coordinating Centre in an expedited manner. Clinical sites are also responsible for reporting SAEs to the Institutional Review Board (IRB)/Research Ethics Board (REB) of record as per their IRB/REB of record's reporting requirements.

In accordance with Health Canada requirements for reporting suspected unexpected serious adverse reactions (SUSARS), the Coordinating Centre will inform all applicable regulatory agencies of any unexpected SAEs that are possibly related to the trial intervention within 15 days (if it is neither fatal nor life threatening), or within 7 days after becoming aware of the information (if it is fatal or life threatening). AEs and SAEs that are expected, but not serious, will not be reported to regulatory agencies, but rather monitored and tracked by the Coordinating Centre. The Coordinating Centre will report to applicable regulatory agencies "expected" SAEs, where an increase in the rate of occurrence or severity, was judged to be clinically important.

3. TRIAL MANAGEMENT

3.1 Applicants and Their Role

The research team has all the necessary experience and expertise to successfully conduct this study. Dr. Daren Heyland has been the PI and/or coordinating investigator on more than 20 nutrition RCTs including several NIH-funded studies and three additional non-nutrition ICU multicenter trials. Three of these multicenter trials have been published in the *New England Journal of Medicine*.^{46,61,91} He currently has raised more than \$120 million in research grants including over \$55 million from the Canadian Institutes of Health Research, published over 450 peer-reviewed articles and given over 300 international presentations. Since taking a Faculty position at Queen's University, he has developed and maintained a methodological/clinical research support unit called the Clinical Evaluation Research Unit. CERU has world-class expertise, experience and resources to support the successful completion of the design, conduct, monitoring, and interpretation of Phase II, III, and IV multi-center clinical trials. Currently, the CERU functions as the research coordinating center for several clinical trials.

Dr. Christian Stoppe, Professor at Würzburg University (Germany), has led a burn unit in Aachen for years, is a member of CERU, and has collaborated with Dr. Heyland for almost a decade in the development and execution of clinical trials in the field of burn injuries and critical illness. Together with Dr. Heyland and his international collaborators, he has built up an international clinical research trial group (nutritionCSX network) for several interventional nutrition studies and has received several grants from DFG (German Research Foundation) and other funding agencies. Dr. Stoppe has >190 publications, has given many talks at international congresses and repeatedly serves as lecturer for international courses on nutrition and metabolism. Dr. Stoppe functions as Co-Principal Investigator of this study and EU legal representative.

Dr. Lee Cancio is the Director of the US Army Institute of Surgical Research Burn Center at Fort Sam Houston, TX, the only such unit in the US Department of Defense. He is a retired Colonel, Medical Corps, US Army. While on active duty, he deployed on 6 occasions to diverse theaters of operation, serving at all roles of care from Battalion Aid Station to Combat Support Hospital. He is a Professor of Surgery (Adjoint) at the University of Texas Health

Science Center of San Antonio and is the author/co-author of about 300 peer-reviewed manuscripts and chapters on burns, combat casualty care, acute respiratory distress syndrome, and hemorrhagic shock. He also serves as Co-principal applicant and a member of the executive committee.

Dr. Alexis Turgeon, Professor at Laval University (Canada) is a critical-care physician, epidemiologist and trialist. He leads a large-scale international trial in trauma (HEMOTION trial) and holds a Canada Research Chair in Critical Care Neurology and Trauma. He is funded by the Canadian Institutes of Health Research and published over 260 peer-reviewed articles. He is the chair of Cochrane Canada Francophone.

Dr. Lucy Wibbenmeyer is the Director of a Level-1 ABA Certified Burn Center at the University of Iowa Hospitals and Clinic and has been a Principal Investigator in prior Department of Defense and industry trials. She has over 50 peer-reviewed publications and mentored several students and residents. Dr. Wibbenmeyer has been an active member of the American Burn Association (ABA), and was recently elected as President of the ABA.

Dr. Marc Jeschke has been caring for burn patients for over 20 years and is a global leader in burn care, research, and education. Dr. Jeschke has an essential role in worldwide multicenter clinical trials and is currently engaged in multiple ongoing studies.

Dr. Jonathan Pollack is the Associate Director of the Mercy Hospital St Louis Burn Center and has been providing burn care there for over 17 years. Dr. Pollack has had numerous publications relating to burns and plastic surgery, while also being the team leader enrolling burn patients in multi-center clinical trials.

Mr. Andrew Day, senior biostatistician at CERU will be responsible for the statistical analysis of this trial. With over 25 years' experience as a senior biostatistician, Mr. Day has served as the lead statistician for dozens of major international RCTs including other international burn trials and all trials led by Dr. Heyland. Mr. Day has taught several graduate courses in statistics, served on the Canadian Institutes of Health Research RCT Committee for 15 years.

Each of the coinvestigators have provided input on the trial design and study protocol. Throughout the trial, they will function as part of the Steering Committee and provide guidance and advice on key operational issues related to the trial.

3.2 Day-to-day management of the trial:

All CERU staff will be supervised by Dr. Daren Heyland and along with Drs. Stoppe and Cancio, and will form the Executive Committee which will be responsible for the day-to-day management of the trial. They will be responsible for all aspects of coordinating this trial including training, data management, quality assurance and monitoring, and analysis. The team at the CERU will be supported by the Steering Committee that will provide specific scientific and operational input. We have also constituted a Stakeholder Committee, comprised of the Steering Committee and additional site investigators, research coordinators and patient advisors, to obtain input from a broader group of stakeholders.

Appendices

- Appendix A: Results of Most Recent Meta-analysis of Intravenous Vitamin C
- Appendix B: Schedule of Assessments
- Appendix C: Interim Analysis and Sample Size Considerations
- Appendix D: SAE and causality/relatedness definitions
- Appendix E: References

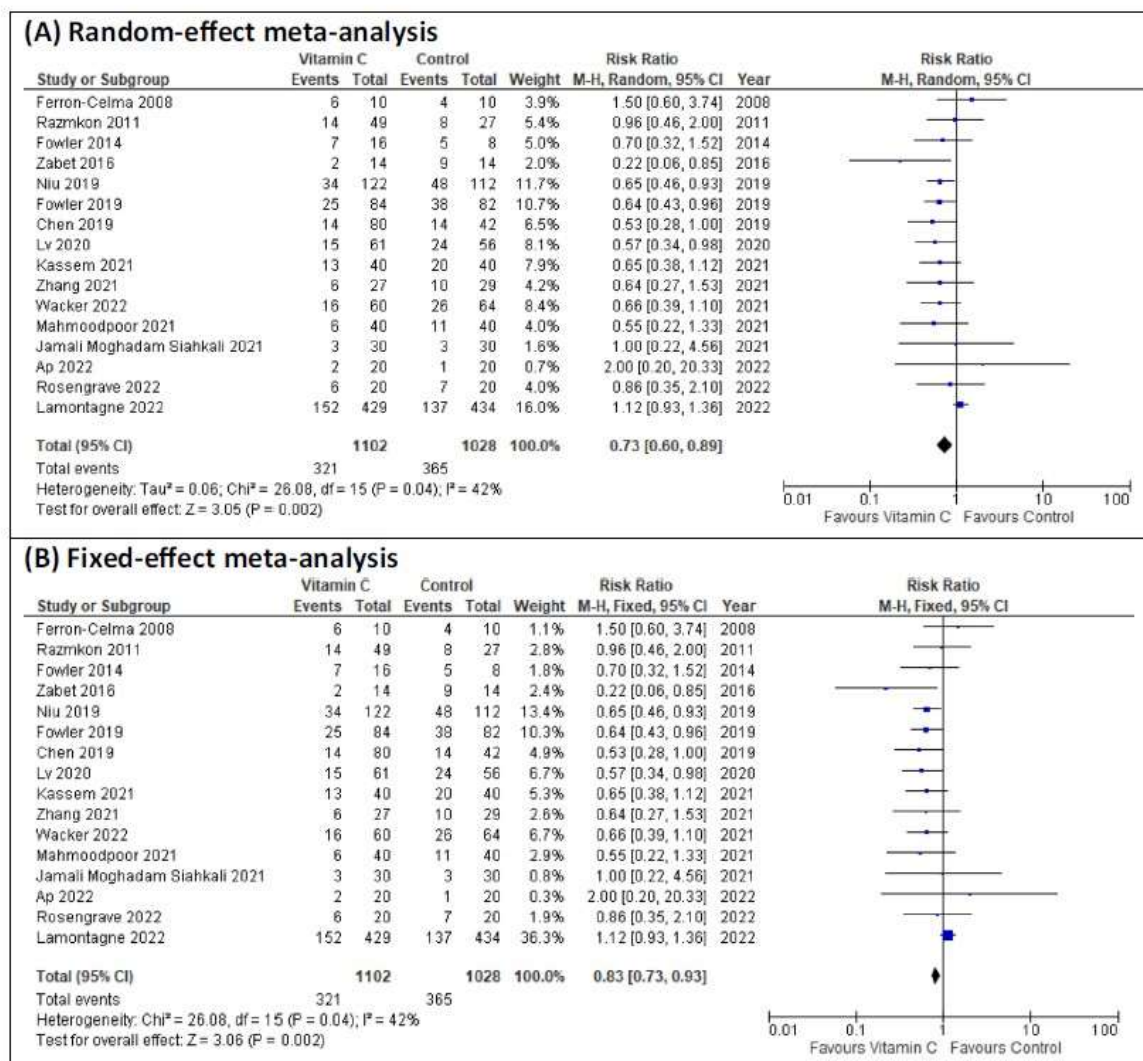
Appendix A: Results of Most Recent Meta-analysis of Intravenous Vitamin C⁴⁹

Fig. 2 Overall mortality. A Random-effect meta-analysis, and B sensitivity analysis with fixed-effect meta-analysis

Appendix B: Schedule of Assessments

SCHEDULE OF ASSESSMENTS	Screening / Baseline Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Ad Hoc	Outcomes (d/c to 90 days max)	6 Month Follow-Up	Early withdrawal
SCREENING/Pre-RANDOMIZATION (collected once)												
Obtain Consent	<input type="checkbox"/>											
Rule-out Pregnancy (if applicable) as SOC	<input type="checkbox"/>											
Inclusion Criteria met (age; burn size)	<input type="checkbox"/>											
Exclusion Criteria - none present	<input type="checkbox"/>											
BASELINE (collected once at beginning of study period)												
Randomization	<input type="checkbox"/>											
Demographics, Comorbidities, APACHE II Score, hospital & ACU admit date/time	<input type="checkbox"/>											<input type="checkbox"/>
Burn Injury Assessment (date/time; type; % TBSA)	<input type="checkbox"/>											<input type="checkbox"/>
Clinical Frailty Scale assessment	<input type="checkbox"/>											<input type="checkbox"/>
TRAUMA (collected once at baseline)												
Traumatic Brain Injury, GCS, other trauma	<input type="checkbox"/>											<input type="checkbox"/>
SOFA (record from ACU admission to 3 days after last dose of IP)												
PaO ₂ /FiO ₂ (lowest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Platelets (lowest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
MAP (lowest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
MICROBIOLOGY (record from >72 hours after ACU admission to ACU discharge for a maximum of 3 months)												
Gram negative bacteremias									<input type="checkbox"/>			<input type="checkbox"/>
VENTILATION/RRT (record data from hospital admission to hospital discharge for a maximum of 3 months)												
Invasive Mechanical Ventilation										<input type="checkbox"/>		<input type="checkbox"/>
Renal Replacement Therapy (dialysis)										<input type="checkbox"/>		<input type="checkbox"/>
VASOPRESSORS and INOTROPES (record from ACU admission to ACU discharge for a maximum of 3 months)												
Vasopressors/Inotropes (highest hourly rate) for each: dobutamine, dopamine, epinephrine, levosimendan, milrinone, norepinephrine, phenylephrine, vasopressin.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		<input type="checkbox"/>		<input type="checkbox"/>
VITAMIN C DOSING (record all doses received)												

SCHEDULE OF ASSESSMENTS	Screening / Baseline Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Ad Hoc	Outcomes (d/c to 90 days max)	6 Month Follow-Up	Early withdrawal
Vitamin C administration (start/stop times; volume infused; interruptions)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>					<input type="checkbox"/>
DAILY LABORATORY (record labs ordered as SOC from ACU admission to 3 days after last dose of IP)												
Creatinine, serum (highest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Bilirubin, Total (highest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Urea (highest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Glucose (closest to 8:00 A.M.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Hypoglycemic events (record up to 3/day)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Lactate Dehydrogenase (LDH) (highest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
pH, arterial (lowest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
HCO ₃ (bicarbonate), serum (lowest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Albumin (lowest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Hemoglobin (lowest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Haptoglobin (highest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Reticulocyte count (highest)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Clinical suspicion of hemolysis? (yes/no)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
FLUID BALANCE (record from ACU admission to 3 days after last dose of IP)												
Were blood products given? (yes/no)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Packed RBCs (volume)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Plasma (volume)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Albumin, 5%, 20%, 25%, other (volume)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Urine output (mL)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Total fluid volume IN (mL)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
Total fluid volume OUT (mL)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
BURN RELATED PROCEDURES (record from hospital admission to hospital discharge for a maximum of 3 months)												
Date, planned or unplanned, location of procedure, and type of procedure									<input type="checkbox"/>			<input type="checkbox"/>
PROTOCOL VIOLATIONS (record from randomization to 3 days after last dose of IP)												
Type of violation, SI awareness, action taken	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>				<input type="checkbox"/>
EVENTS OF INTEREST (record related events that result in stopping IP early, from start of IP to stop of IP)												
New diagnosis of oxalate kidney stone										<input type="checkbox"/>		<input type="checkbox"/>
Severe hemolysis										<input type="checkbox"/>		<input type="checkbox"/>
Severe acid-base imbalance										<input type="checkbox"/>		<input type="checkbox"/>

SCHEDULE OF ASSESSMENTS	Screening / Baseline Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Ad Hoc	Outcomes (d/c to 90 days max)	6 Month Follow-Up	Early withdrawal
Severe electrolyte imbalance										<input type="checkbox"/>		<input type="checkbox"/>
Refractory hypoglycemia										<input type="checkbox"/>		<input type="checkbox"/>
SERIOUS ADVERSE EVENTS (recorded within 24 hrs of awareness, from randomization to 3 days after the last dose of IP)												
Event description, seriousness, outcome, expectedness, relationship to IP, action taken with IP, action taken to treat event									<input type="checkbox"/>			<input type="checkbox"/>
HOSPITAL OVERVIEW (recorded once after hospital discharge to a maximum of 3 months)												
ACU – date of discharge, death, or consent withdrawal.										<input type="checkbox"/>		<input type="checkbox"/>
Hospital – date of discharge, death, or consent withdrawal.										<input type="checkbox"/>		<input type="checkbox"/>
Location discharged to or cause of death.										<input type="checkbox"/>		<input type="checkbox"/>
COVID-19 (collected once and recorded at hospital discharge, or 3 months after admission)												
COVID-19 Status, negative, positive, presumed positive, not tested/unknown and date of result or determination										<input type="checkbox"/>		<input type="checkbox"/>
SURVIVAL ASSESSMENT (collected once at 6 months after admission (+/- 14 days))												
Alive or deceased, date, source of data.											<input type="checkbox"/>	<input type="checkbox"/>
If data not obtained, record efforts made, and date last known to be alive.											<input type="checkbox"/>	<input type="checkbox"/>
HEALTH RELATED QUALITY OF LIFE ASSESSMENTS (collected once at 6 months after admission (+/- 14 days))												
SF-36 questionnaire											<input type="checkbox"/>	
Katz ADL questionnaire											<input type="checkbox"/>	
Lawton IADL questionnaire											<input type="checkbox"/>	
Data Query Resolution (resolve after data entry milestones: hospital overview and survival/6-month assessments)												
Data query checks are built into the EDCS and will generate queries to address missing, inconsistent, and illogical data.									<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Data Quality Management and Source Verification/Monitoring

- The study management team will review recruitment reports monthly to identify and address slow enrollment and areas of concern.
- Monitoring visits to conduct source verification and confirm compliance with the protocol and regulatory processes will be conducted throughout the course of the study.
- A Touch Base webinar to debrief will be scheduled after enrollment of the first 2 subjects.
- An initial monitoring visit, either onsite or remote, will be conducted after data entry through hospital discharge has been completed for at least 2 enrolled patients.
- Ongoing monitoring and visits will be risk based and determined by the Executive Committee after review of the findings of the initial monitoring visit.

Glossary of Terms

ACU Acute Care Unit

ADL Activities of Daily Living

EDCS Electronic Data Capture System

GCS Glasgow Coma Scale

IADL Instrumental Activities of Daily Living

IP Investigational Product

mL millilitre, milliliter, millilitres, milliliters

% percentage

SF Short Form

SI Site Investigator

SOC Standard of Care

Appendix C: Interim Analysis and Sample Size Consideration

We plan to conduct formal interim analyses once 28-day PODS+death is available for one-third ($n=222$) and two-thirds ($n=444$) of the full study ($n=666$). Given the conflicting literature with regards to the direction a vitamin C effect, we plan for one-sided interim analyses which would suggest stopping for harm/futility if a signal increased PODS+death is observed in the vitamin C arm. We have examined the study characteristics of various stopping rules using 10,000 simulations for each treatment effect scenario. A relative risk (RR) of 1 equates to the null hypothesis, an $RR < 1$ favours Vitamin C, and in all scenarios, we assume a 27% 28-day PODS+death rate in the control arm. With 10,000 simulations, the estimates of all percentages will have at least a 95% chance of being estimated to within 1% and the mean RR and Bias have more than a 95% chance of being accurate to the second (and final) decimal reported. All simulations were analyzed according to the analysis plan by using modified Poisson regression clustering for site and controlling for: age, sex, ethnicity, TBSA burn, traumatic brain injury, mechanically ventilated at baseline and injury severity. However, the data generated assumed that each observation was independent, so that there was no clustering by site and none of the covariates were related to the outcome. It may be noted that the actual number of simulations is up to 0.7% less than 10,000. This is due to the generalized estimating equations (GEE) algorithm used for the modified Poisson model not converging. We chose the modified Poisson over the log-binomial model because the log-binomial model did not converge in over 30% of the simulations and we chose modified Poisson over logistic regression due to the preference of estimating relative risks rather than odds ratio.

We wanted to have a high probability of stopping at the interim if vitamin C was harmful, but a low probability of stopping if vitamin C was not harmful. We also wanted the stopping rule to cause minimal type I error inflation, minimal loss of power and minimal bias in the final estimate – which would come from the interim analysis if the study stopped early. Finally, we could not choose a rule that would guide the DMC to recommending continuing the study at an uncomfortably large RR. Based on these criteria and simulation results, we choose a stopping threshold of $RR > 1.1$ (in the direction of harm) regardless of statistical significance at either of two interim analyses. This stopping rule only trivially reduced power for detecting benefit of vitamin C and did not meaningfully increase the type I error compared to no interim analysis. The simulation results with this stopping rule are presented in table B. Under the null hypothesis, the $RR > 1.1$ stopping rule would have a 33.3% and 8% chance of stopping at the first and second interim respectively. The expected RR would be 1.08 (a bias of 0.08), but the 95% confidence intervals would contain the true value of one 94% of the time which is the same as obtained without a stopping rule. The trivial type I error inflation and corresponding sub-nominal 95% confidence interval coverage appears even without an interim analysis due to using the modified Poisson approach which uses robust standard errors. With the $RR > 1.1$ rule, if the true $RR=1.2$ there will be a 67% chance of stopping at the first interim, and a 14% chance of stopping at the 2nd interim. With a true $RR=1.333$ there would be an 83% and an 11% chance of stopping at the 1st and 2nd interim analysis respectively. Under the assumed effect size of $RR=0.666$ we would maintain 78% power with only a 1% chance of stopping a study early that would otherwise have gone on to be statistically significant.

In summary, the one-sided futility/safety stopping rule has only trivial impact on the study characteristics if vitamin C is meaningfully beneficial. However, if vitamin C is harmful, there is a high probability that the study will stop at one-third the way through the study which will greatly reduce the power to detect a statistically significant harm; also, this will slightly bias the RR towards greater harm, but the 95% confidence intervals will still maintain near nominal coverage of the correct RR. We believe this is a worthwhile trade-off to save patients from unnecessary harm and to save resources from being used to complete a study that had virtually no chance of detecting a significant benefit of vitamin C.

Table B: Operating Characteristics of Trial Under RR>1.1 Stopping Rule at 1/3 and 2/3 Enrollment

		Stopped at 1st interim (n=222) for futility/harm			Stopped at 2nd interim (n=444) for futility/harm			Completed study									
Control 28-day PODS Rate 27%	N	p>=0.05	p<0.05	Total	p>=0.05	p<0.05	Total	p>0.05	benefit at p<=0.05	harm at p<=0.05	Total	RR	Bias		Coverage of 95% CI	Average 95% CI Width	Stopped at Interim but would have shown significant benefit at final
		%	%	%	%	%	%	%	%	%	%	Mean	Mean	Std			
Scenario																	
I 18% RR=0.666	9929	2.7	0.0	2.7	0.1	0.0	0.1	19.1	78.1	0.0	97.2	0.68	0.02	0.13	92%	0.41	0.9%
I 20.25% RR=.75	9949	5.7	0.1	5.8	0.5	0.0	0.5	40.0	53.6	0.0	93.6	0.78	0.03	0.16	92%	0.46	0.6%
I 21.6% RR=.8	9964	9.7	0.3	10.0	1.0	0.0	1.0	50.8	38.2	0.0	89.0	0.84	0.04	0.18	91%	0.51	0.6%
I 24.3% RR=.9	9965	19.4	1.1	20.5	3.4	0.0	3.4	62.5	13.5	0.0	76.0	0.96	0.06	0.20	93%	0.61	0.3%
I 27% RR=1	9963	30.2	3.1	33.3	8.0	0.0	8.0	55.9	2.9	0.0	58.8	1.08	0.08	0.21	94%	0.72	0.0%
I 29.7% R=1.1	9962	41.5	8.1	49.6	12.2	0.0	12.2	37.5	0.4	0.2	38.1	1.19	0.09	0.21	94%	0.84	0.0%
I 32.4% RR=1.2	9969	51.2	16.2	67.4	13.8	0.0	13.8	18.3	0.0	0.6	18.9	1.29	0.09	0.23	94%	0.96	0.0%
I 33.75% RR=1.25	9958	51.6	21.9	73.5	13.4	0.0	13.4	12.6	0.0	0.4	13.0	1.33	0.08	0.24	95%	1.00	0.0%
I 36% RR=1.333	9948	50.6	32.1	82.7	11.4	0.0	11.4	5.2	0.0	0.6	5.8	1.40	0.07	0.26	95%	1.07	0.0%

Appendix D: SAE and causality/relatedness definitions

A **Serious Adverse Event (SAE)** is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an event in which the study participant was, in the opinion of the qualified investigator (QI), at risk of death from the event if medical intervention had not occurred. NOTE: This does not include an event that hypothetically had it occurred in a more serious form, might have caused death).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (i.e. a substantial disruption in an individual's ability to conduct normal life functions).
- Is a congenital anomaly or birth defect.
- Other medically important condition (Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious events when, based on medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above).

Relationship of Study Intervention to event (The determination of the relationship of the SAE to the investigational product must be made by the Site Investigator or trained sub-Investigator. To assist the Investigator in making this assessment, the following definitions have been provided (select **only** one):

- **Not related:** A serious adverse event that is clearly due to extraneous causes (disease, environment, etc.) and does not meet the criteria for drug relationship listed under 'Possibly' or 'Probably'.
- **Unlikely related:** A serious adverse event that is more likely due to other causes than the study intervention.
- **Possibly related:** Suggests that the association of this SAE with the study intervention is unknown and the event is not reasonably supported by other conditions.
- **Probably related:** Suggests that a reasonable temporal sequence of this SAE with study intervention administration exists and the association of the event with the study intervention seems likely.

If the SAE is considered to be related to the investigational product, please provide the pertinent clinical features that, in the opinion of the Investigator, made her/him think that the event was related to the study intervention vs. the progression of underlying disease.

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