*Confidential Study Protocol*

# The VICToRY Trial

## VItamin C in Thermal injuRY: The VICToRY Pilot Trial

## A feasibility study for a seamless adaptive phase II/III multi-center randomized trial

Clinical trials.gov ID #NCT04138394

**Sponsor**

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This study will be centrally coordinated at the Clinical Evaluation Research Unit, Kingston, ON Canada (The same coordinating center for the RE-ENERGIZE trial).

## 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 fourth most common injury.[1] 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.[1,2] 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.[3,4] Burn patients present with up to a 3-fold higher prevalence of sepsis than other trauma patients.[5] In addition, mortality from sepsis is much higher in burn patients compared to other critically ill patients.[5] 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. 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.[6,7] 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 ago and yet, few centers routinely administer high-dose vitamin C to severely burned patients, suggesting that a high level of evidence is warranted. Ultimately, we aim to conduct a large-scale, multi-center randomized trial of high-dose intravenous vitamin C.

**The objective of this pilot trial is to demonstrate feasibility and safety of a high-dose intravenous vitamin C administration in 180 severely burned patients. Furthermore, this study´s purpose is a) to gain first information about the safety and pharmacokinetics of high-dose intravenous vitamin C in this patient population, b) determine possible endpoints for a definitive study, and c) to evaluate the oxidation-reduction potential as a new biomarker for oxidative stress.** If feasibility is demonstrated in the pilot, a larger phase II/III component will be conducted and aimed at lowering morbidity and mortality and reducing health care costs in an otherwise very devastating and disabling injury worldwide. However, before proceeding to such a large trial, we propose to conduct a smaller pilot trial aimed at assessing the feasibility and fidelity of implementation of the larger trial protocol. We hypothesize that the inexpensive therapeutic strategy tested in this randomized controlled trial will be feasible to conduct with high fidelity of implementation. This trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

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

*Primary research question:*

In patients with severe, life-threatening burn injury, what is the effect of high dose (200mg/kg/day x 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 (200mg/kg/day x 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?

**1.2.1 What are the principal research questions to be addressed in the Phase II stage of the adaptive seamless design?**

*Primary research question:*

In patients with severe, life-threatening burn injury, what is the effect of high dose (200mg/kg/day x 96 hours) intravenous vitamin C in addition to SOC on the Oxidation-Reduction Potential (ORP), a global marker of redox state compared to add-on placebo and SOC?

**1.2.2 What are the principal research questions to be addressed in this feasibility pilot trial?**

The VICToRY trial will be conducted in a North American and European part of the already established RE-ENERGIZE network of burn centres. The feasibility of this study will be judged by a high degree of compliance with the study protocol (>90% compliance with study investigational product (IP), <5% Lost-to-Follow up [LTFU]), low amounts of consent failure (<30%), and adequate enrollment rates to support the larger confirmatory phase II/III trial. We will also use this feasibility pilot study to assess the distribution of ORP within treated and untreated burn patients at sites that choose to participate in the laboratory sub-study. This will help us determine if ORP is a suitable primary outcome for the (phase II part) of the phase II/III trial and will provide estimates to support sample size determination of the confirmatory trial.

**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.[8] 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.[9] 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.[10]

## *Preclinical 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.[11] Vitamin C is known to support the cytochrome P450 driven hydroxylation of aromatic drugs and carcinogens [11] and to promote iron absorption in the small intestine.[12] Vitamin C enhances cell differentiation from somatic cells to induced pluripotent stem cells [13,14], which may be an important feature for regenerating processes in critically ill patients. Vitamin C restores vascular responsiveness to

vasoconstrictors[15], ameliorates microcirculatory blood flow, preserves endothelial barriers, augments bacterial defense[16] and prevents apoptosis [17]. 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 .[18,19,20] 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 group [21] and summarized in Table 1. A more comprehensive description of the underlying biochemical mechanisms and the influences of vitamin C are explained in greater detail elsewhere. [11, 16, 21,22,23]

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

| Organ | Influence of Vitamin C |
|---|---|
| **Brain** | • Elevated levels (up to 80 times) protecting neurons from oxidative damage [24]<br>• Reduces the infarct volume after ischemia [25] |
| **Cardiocirculatory System** | • Attenuates myocardial damage and improves myocardial stunning [26, 27]<br>• Reduces vasopressor demand [40, 28]<br>• Reduces rate of atrial fibrillation [29, 30, 31] |
| **Lung** | • Reduces intubation time [32]<br>• Decreases risk for pneumonia and alveolar inflammation [33] |
| **Kidney** | • Reduces fluid demand and increases urine production [31]<br>• No significant difference in AKI in a small pilot trial [33,34] |
| **Coagulation** | • Restores platelet function [35]and decreases capillary plugging [15]<br>• Attenuates a sepsis-induced drop of thrombocytes [15] |
| **Infection** | • Inhibits of bacterial growth [36], enhances microbial killing [22]<br>• Supports endothelial barrier function and promotes antioxidant scavenging [22] |

## *Clinical Evidence*

Vitamin C concentrations are lowered in severe illness, in patients recovering from surgery [36], in patients after cardiac surgery [26] and in patients developing multi-organ failure.[37] 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, we have conducted a narrative and two systematic reviews and meta-analyses of existing studies of vitamin C supplementation in **critically ill patients** and **cardiac surgery patients** [21,38], one meta-analysis [in preparation], as well as an observational study of antioxidant vitamins in cardiac surgery. In the general ICU population, vitamin C was not associated with an overall reduced risk of mortality (risk ratio [RR] 0.72, 95% confidence interval [CI]: 0.43–1.20, P = .21). No effect was found on infections, ICU or hospital length-of-stay, or duration of mechanical ventilation in the generally critically ill patients. However, we did observe a tendency towards a mortality reduction (RR 0.21; 95% CI: 0.04–1.05; P = .06) when intravenous high dose vitamin C monotherapy was administered. In the population of cardiac surgery patients, vitamin C significantly decreased the ventilation time (P<0.00001), ICU- length-of stay (P=0.004) and hospital-length of stay (P<0.0001) and the incidence of atrial fibrillation (P=0.008). However, a range of intravenous doses, timings and routes have been used in published trials.

1) A recent high-profile pre-post single-center observational study (n=94) found a dramatic effect of 1.5 grams q6h of vitamin C on reduction of vasopressor requirements, organ failure, and

hospital mortality when administered to patients with septic shock (mortality 8.5% [vitamin C] vs. 40.4% [control]; adjusted OR 0.13, 95% confidence interval [CI] 0.04-0.48).[39]
2) In a small single-centered trial of 28 patients with sepsis, Zabet et al. demonstrated in 2016 a significantly reduced mean vasopressor demand and shorter duration of vasopressor therapy and reduced mortality in septic patients receiving 25mg/kg q6h x 72 hours of intravenous vitamin C.[40]
3) Dr. Berry Fowler has done pioneering work establishing the potential safety and efficacy of a dose of 200 mg/kg/day in divided doses (50 mg/kg every 6 hours) 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.[41] Recently, 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.[42] 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 and further confirmation is encouraged and required by ongoing large-scale trials in sepsis. They do, however, confirm the safety of this dose as there were no adverse events noted with this dosing strategy.
4) A recent pharmacokinetic study demonstrated how quickly vitamin C levels return to low levels following the termination of 48 hrs dosing suggesting that longer (at least 72 hrs) duration is warranted (not 24 hrs).[43]

### *Burn patients*

Burn patients often 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. Oral supplementation of nutritional dosages of vitamin C as monotherapy or in combination with other micronutrients improved wound healing.[44,45] A high-dose intravenous vitamin C regimen of **66 mg/kg/hour for 24 hours** was proposed over 20 years ago and used in a prospective pseudo-randomized controlled clinical trial in severe thermally injured patients (n=37).[46] 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 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 ($p=0.07$).[31] In a 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 ($p=0.06$; OR 5.4; CI 1.1-26).[47] 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; $p = 0.068$).[48]

Recent unpublished data of a prospective clinical trial of 39 patients with burn injuries > 20% TBSA who received either high (66 mg/kg/hour x24 hours) or low (3500 mg/d) doses of

vitamin C delivered intravenously and continuously for the first 24 hours indicated safety of the high dose regimen with comparable rates of acute kidney injury, metabolic acidosis and alkalosis and overall mortality.[49] 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 (Figure 1).[50] This finding is in concordance with Fowler's trial in sepsis that found patients to exhibit similarly reduced vitamin C levels at study entry (Figure 1).[41] Fowler et al. saw an increase of serum ascorbic acid (AA) to over 3000 µmol/L on day 4 which corresponds to a 175-fold increase from baseline.[41] This was achieved by administration of 200mg/kg/d for 4 days which amounts to a cumulative dose of 64g in an 80kg patient. In the unpublished study in burn patients, high dose vitamin C administration Tanaka's dose of 66mg/kg/h continuously for 24 hours elevated the average concentration of AA in patient serum 150-fold to 2600µmol/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.

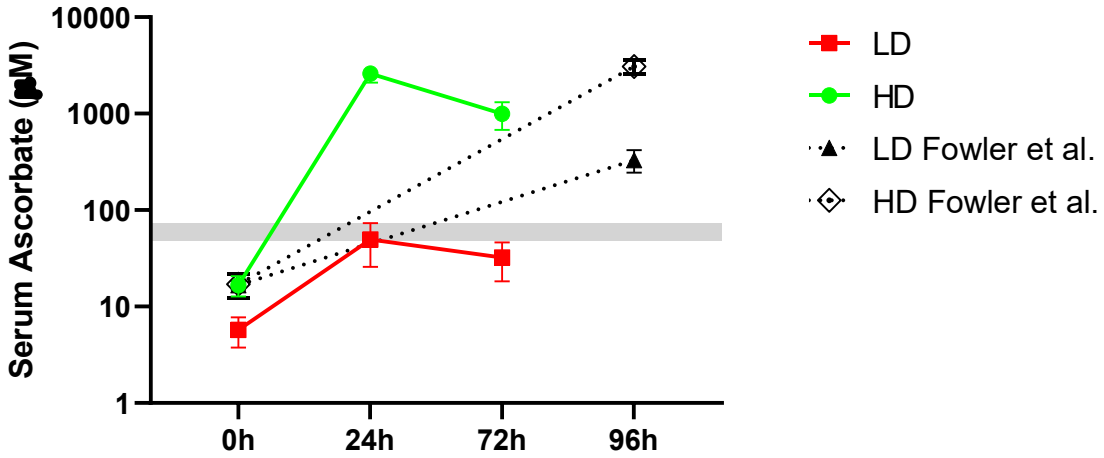


Figure 1. Ascorbic Acid levels in German trial compared to Fowler trial. Grey bars represent normal values. LD: low dose ascorbic acid (3500mg/24h for 24h); HD: high dose ascorbic acid (66mg/kg/h for 24h). LD Fowler et al.: low dose ascorbic acid: 50mg/kg/24h for 96h. HD Fowler et al.: 200mg/kg/24h for 96h.

The unpublished trial of vitamin C in burn patients demonstrated a significant decrease in the need for colloid fluids ($p<0.05$) during the first 24hours of acute volume resuscitation; the data trended towards lower requirements of crystalloids and overall fluids, as well as decreased need for vasoactive catecholamines during the first 24hours 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 prospective trial 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, which had been proposed by statistical trends of a retrospective analysis by Lin et al.[52]

**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. There are more than 20 RCTs registered currently further exploring this work in non-burn ICU patients.[51] The safety and efficacy of high-dose vitamin C in burn patients are conflicting and require a larger multicenter trial to confirm a signal of benefit. But before such a trial is conducted, we need to conduct a small-scale feasibility pilot trial. **Second,** there is considerable uncertainty, and thus, practice variability with respect to intravenous vitamin C administration in this patient population. Recent 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.[52] Seemingly, a higher level of evidence demonstrating its safety/efficacy is needed before practitioners are ready to embrace this novel therapy. Yet, with increasing evidence for vitamin C in sepsis, the window to study vitamin C in burns may be closing. **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. 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 so we are well situated to obtain funds for the confirmatory adaptive seamless phase II/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. By using an adaptive seamless design, we can get the answer to the study question sooner than conventional designs. 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?

The results of this feasibility pilot trial will inform the design of the phase II/III VICToRY trial. 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 RCTs[53,54,55] 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.[56,57]

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 is remarkably favourable. A potential risk 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.[58,59] 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.[60],[61] 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.

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 in Canada is among the lowest in the world and since the trial is designed to facilitate early administration to maximize benefit, we will not screen eligible patients for G6PD deficiency. Of note, existing trials of intravenous vitamin C for sepsis have not screened for G6PD deficiency; no related adverse event has been reported thus far.[15,22] Hemolysis will be monitored and recorded in the case report form (CRF). 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 side effects have been reported in the previous studies on vitamin C used for the treatment of septic patients, we do not anticipate any drugs interactions.

*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 such that, in the opinion of the treating physician, ongoing use of study product would compromise patient safety.

3) We will review in an unblinded manner all safety data after 15 patients have been enrolled per group. The rate of kidney failure in the Lin retrospective study of high dose vitamin C administration in burns patient was 23%.[47] If 5 or more patients in the interventional group patients develop kidney failure, we propose to stop or recruitment to that arm and amend the protocol.

4) For the phase II/III, we plan to have a Data Monitoring Committee which is charged with the responsibility for ensuring the integrity of the trial. They will review all serious adverse events (SAE), biochemical endpoints, and the interim analyses and provide recommendations regarding the ongoing safety of the VICToRY trial. A trial discontinuation plan will be developed at this time.

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 need to conduct a large scale, multi-center trial of intravenous vitamin C in burns but first, we must conduct a feasibility pilot trial to establish the feasibility and support the efficacy of our proposed adaptive seamless phase II/III trial.

## 2. THE PROPOSED TRIAL

### 2.1 What is the proposed trial design?

We propose a multicenter, double-blind, randomized controlled pilot trial of 180 patients with severe burns randomly allocated to receive 200 mg/kg/day x 96 hours of intravenous vitamin C or placebo (90 per group). If the trial is feasible we will move forward into the phase II/III design utilizing an adaptive study design, such as selection of sensitive and clinically relevant endpoints, and sample size re-estimation at the end of the phase II component, which will enable an effective transition from phase II into phase III. As patients recruited into the first stage (phase II) will also be followed up for the phase III endpoints, the patients from the first stage will also contribute to the confirmatory phase III analysis. This approach will use resources in an efficient manner and will allow to progress swiftly to make the therapy available to patients as early as possible, if it is safe and efficacious. Appropriate methodology will be used to maintain the validity and integrity of the trial at a standard required for a phase III confirmatory trial.

### 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 200mg/kg in divided doses, every 6 hrs for 96 hrs. **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 2-8ºC is physically and chemically stable for at least 14 days. 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, injectable vitamin C would not be allowed in study subjects. 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. (see sample in Appendix A).

**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 will 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 that allow for such alterations or, where applicable, sites can use a third-party or professional consent process. 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). If enrolled under an

deferred consent model, where possible, informed consent will subsequently be obtained either timely from the patients themselves, or from legally appointed representatives or next-of-kin in coming days or as soon as possible or in accordance with local ethics committee regulations. If alterations of informed consent are not allowed, sites will have up to 24 hours to enroll patients.

Once consent is obtained (or deferred approval granted), 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 (http://www.ceru.ca/) at Kingston General Hospital. 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 with notification of randomization. The unblinded pharmacist 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 computer. 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 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 2$^{nd}$ and/or 3$^{rd}$ degree burns, who are assessed as requiring skin grafting, and a minimum burn size ≥ 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 ICU or burn unit to assessment.
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).

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. 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.[43,49]

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 outcomes for this pilot trial are feasibility metrics including compliance with the study protocol (>90% compliance with study investigational product (IP), <5% Lost-to-Follow up [LTFU]), low rate of consent failures (<30%), and adequate enrollment rates to support the larger confirmatory phase II/III trial. We will also use this feasibility pilot study to assess the pharmacokinetics and safety of the proposed dosing strategy in this patient population

and the distribution of the oxidative reduction potential (ORP) as a marker of oxidative stress within treated and untreated burn patients. This will help us determine if ORP is a suitable primary outcome for the phase II part of the phase II/III trial and will provide estimates to support sample size determination of the confirmatory trial.

The secondary endpoints of this pilot trial include intensive care unit (ICU) outcomes (e.g. length of stay, duration of mechanical ventilation, and readmission rates); persistent organ dysfunctions including use and duration of renal replacement therapy; hospital outcomes (mortality, length of stay, time-to- discharge alive, time-to-95% graft closure [wound healing], 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, antibiotic utilization, blood transfusions, and other major cost drivers to support our economic evaluation.

The primary outcome for the phase III trial may be persistent organ dysfunction (PODS)+death, a novel composite endpoint that combines being alive and being free of organ support (inotropes or vasopressors, renal replacement therapy and mechanical ventilation).[62] Another possible alternative would be "time to discharge alive from hospital". This composite of mortality and length of stay is similar to "ventilator- free days", which is a widely accepted and commonly used outcome in intensive care research.[63,64] The final decision regarding the primary outcome and sample size for the phase III trial will be made at the conclusion of the phase II trial.

For the phase II portion of the adaptive seamless phase II/III trial, the primary outcome may be the Oxidation-reduction potential (ORP), or redox-status measured at 96 hrs (end of treatment period). Oxidative stress and resulting inflammation represent the major stimuli for the envelopment of organ dysfunctions. Oxidative stress in biological systems is the result of an increased production of reactive oxygen species (ROS)/reactive nitrogen species (RNS), a decrease in levels of endogenous non-enzymatic antioxidants, a decrease in antioxidant enzyme activity (such as superoxide dismutase (SOD)), catalase, and reduced nicotinamide adenine dinucleotide (NADH) peroxidase), and/or an interference with mitochondrial oxidative phosphorylation. [65,66]. Previous studies demonstrated that the extent of oxidative stress serves as a predictor of both severity of disease and future clinical outcomes. Furthermore, additional studies have shown an association between the ORP and outcomes in critically ill patients.[67,68] In a study of multi-trauma patients, ORP longitudinal monitoring appeared to differentiate trauma severity and degree of inflammation.[68] In another study involving multi-trauma patients, increases in ORP correlated with decreases in negative acute phase reactants (i.e. proteins involved in the anti-inflammatory cascade) and total plasma protein levels.[69] Finally, ORP monitoring can be a beneficial clinical tool in assessing the redox-status as well as organ viability for potential transplantation.[70,71] Previous work demonstrated that the ORP is a useful parameter to longitudinally assess oxidative stress in cardiac surgery, where the ischemia and reperfusion injury leads to scheduled oxidative stress (Figure 2). In addition, previous studies demonstrated a close correlation between inflammation and perioperative ORP levels and initial findings revealed that the extent of redox stress may be reduced by the treatment of potent antioxidants (Figure 3)

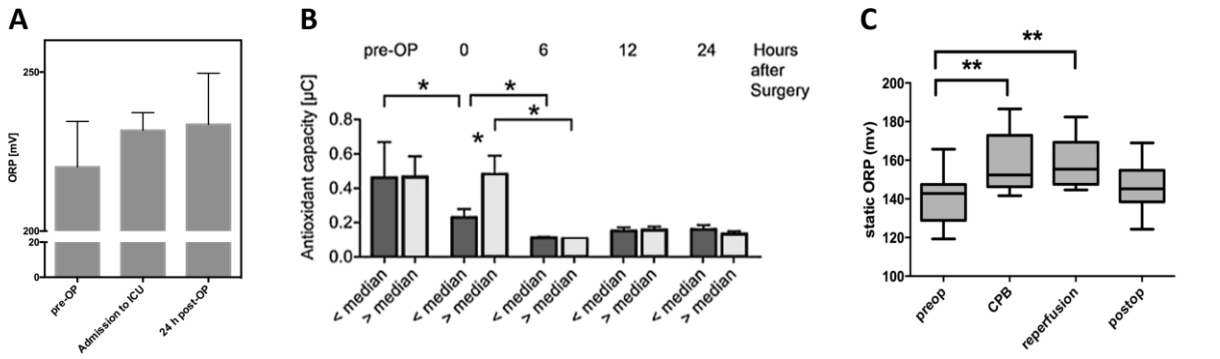


*Figure 2: ORP in Cardiac Surgery, A: time course of ORP during cardiac surgery with sevoflurane anesthesia [72], B: Comparison of ORP in serum samples with high macrophage migration inhibitory factor (MIF) serum levels (> median) with low serum levels (< median) at the corresponding time points [73], C: time course of static ORP during cardiac surgery [74]; CPB= cardiopulmonary bypass*

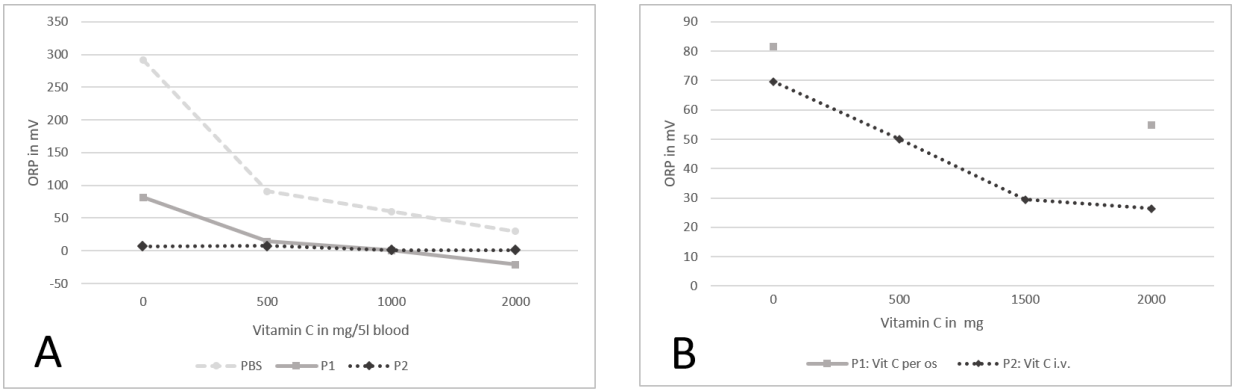


*Figure 3: Influence of vitamin C on ORP; A= in vitro; B= in vivo*

A recently published trial observed an increase of oxidative stress in ICU- patients undergoing major surgery/sepsis or trauma, as well as in patients after cardiac arrest.[75] A strong negative association of ORP and strong positive association between the antioxidative capacity with plasma vitamin C concentrations ($R^2$ >0.8 for ORP and $R^2$=0.842 for antioxidative capacity) and demonstrated a strong concordance between changes in plasma vitamin C concentration and changes in severity of oxidative stress, reflecting that a high dose of vitamin C diminished the oxidative stress in these critically ill patients

Therefore, the amount of oxidative or reductive stress present in plasma after burn injuries, or the efficacy of an antioxidant treatment can theoretically be adequately monitored using an ORP electrode. Our feasibility pilot trial will enable us, for the first time, to obtain measurements of ORP in treated and untreated burn patients. The measures we obtain from the pilot trial will support the estimation of the sample size required for the phase II component of the future trial. Measurement of the ORP will be performed using the RedoxSYS Diagnostic System (AYTU, USA), which measures the overall integrated redox potential of a biological sample from serum samples (20µl). At sites that choose to participate in the laboratory sub-study, samples (15ml blood) will be drawn at baseline (pre-treatment), daily x 4 days while on treatment and then another sample 24 hours post treatment. These samples will be used to measure biomarkers for

inflammation (TNFa, IL6, IL10, determine IL6/IL10 ratio as further marker to evaluate the efficacy), and a panel of other micronutrients (Vit C, Vit B1 [Thiamine], Vitamin A (Retinol), Vit E (α-Tocopherol), Selenium, Seleno P, GPX, Zinc, Vit D, glutamine, Copper). Feasibility outcomes and targets are listed in section 1.2.2. Furthermore, in a sub-study of German sites, we will analyze the resulting effects of the inflammatory response on the immune system, as measured by phorbolmyristate acetate (PMA) ex-vivo stimulation of tumor necrosis factor-alpha (TNF-α) in whole blood. To further characterize the efficacy effect of vitamin C on the body`s immune competence, we aim to perform flow-cytometry (FACS analysis) to assess the immune phenotype and activation of different immune cells (measured in the Department of Immunology, RWTH Aachen University, Prof. L. Rink).

Additional outcomes included in this trial, which will be more important in a confirmatory Phase III trial, include ICU outcomes (length of stay, duration of mechanical ventilation, and readmission rates); hospital outcomes (mortality, length of stay, time-to-discharge alive, time-to-95% graft closure [wound healing], bacteremia with Gram-negative bacilli, and readmission rates); and 6-month outcomes (mortality, quality of life and functional status) as we collected in the RE-ENERGIZE trial. We will also record frequency of operative procedures for burn care, presence of inhalation injury, antibiotic utilization, blood transfusions, and other major cost drivers to support our economic evaluation (see section 2.11). To enable a subgroup analysis of patients with non-burn trauma associated with their injury, we will use the modified Injury Severity Score (which excludes the 'external component' where the burn injury would already be captured) to quantify the extent of trauma present at baseline.[76] In addition, we will record the presence of traumatic brain injury given is impact on outcome in these patients.

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

The larger confirmation phase II/III trial will likely require a sample size of 1000-1400 patients. However, this estimate will be reconsidered after completion of the feasibility trial and re-estimated in the interim analysis of the adaptive seamless phase II/III trial. The first stage (phase II component) of the adaptive seamless phase II/III trial will likely require between 200-400 patients (as part of the overall sample size of 1000-1400 patients). However, the design will be fine-tuned as part of the feasibility study and a further blinded sample size recalculation will be included in the first stage of the adaptive phase II/III design to determine the exact timepoint of the interim analysis (phase II analysis).

For this feasibility pilot trial, we propose to recruit 180 patients from several centers across North, Central and South America and Europe to establish the feasibility and fidelity of the trial protocol. With this sample size, our observed estimate of a binary feasibility outcome with a true population rate of 95% would have a 90% chance of falling between 90% and 98%. If the true rate is ≥98% then we will have over a 95% chance of observing a rate ≥95%. If the true rate is ≤ 83% then we will have a 95% chance of observing a rate below 90%.

**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.[77] 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 is feasible, we would propose to conduct an economic evaluation using data collected in the adaptive seamless phase II/III trial.

**2.12 What is the planned recruitment rate?**

Based on our experience with the RE-ENERGIZE trial, participating sites should be able to enroll 0.3-0.5 patients/per site/ month. Moreover, the eligibility criteria are less strict and if granted an alteration to informed consent, it may be easier to enroll patients in VICToRY. We aim to have 12-15 sites from Germany, Canada and the United States participating in this pilot trial and the rest of the network will get activated once funds for the phase II/III are available. We will allow for 6-12 months for study start up and 2 years of recruitment (7-8 patients/month x 24 months=180 patients).

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

We have not piloted this study protocol but have worked extensively with our burn research network in the context of the RE-ENERGIZE trial to ensure high quality implementation and compliance with the study protocol, as previously reported. Given the short-term duration of the intervention (96 hrs) compared to the RE-ENERGIZE trial (3 months), we expect compliance with study medication administration to be even higher than the 90% observed in RE-ENERGIZE trial. The RE-ENERGIZE trial can be considered as a 'pilot' for all other study procedures as they are exactly the same between the 2 studies.

**2.15 How many centers will participate?**

We plan to recruit 10-15 sites from our existing burn research network to participate in VICToRY. Interested sites to date include: Canada (Montreal, and Quebec City); USA (Iowa, Mercy St. Louis, Arizona, Seattle, Ohio, Dallas, and possibly others); Germany (Aachen, Ludwigshafen, Cologne), the UK (Birmingham, Chelsea and Westminster and Liverpool), and Latin America (Mexico, Paraguay, and possibly Brazil). The inclusion of so many sites from different countries will enhance the generalizability of study results and reduce the study activation time for phase II/III.

**2.16/17: What is the proposed frequency and type of analyses?**

The feasibility outcomes will be assessed descriptively using proportions with exact Clopper-Pearson 95% confidence intervals. The distribution of ORP will be examined by arm in detail using boxplots and descriptive statistics in including quartiles, means and standard deviations. The data will also feed into computer simulations to assess various design options for the adaptive seamless phase II/III design as part of a so-called clinical scenario evaluation (CSE) exercise.[78,79] The adaptive seamless II/III design will use appropriate statistical techniques to maintain characteristics associated with confirmatory phase III clinical trials such as control of the type I error rate.[80,81] Interim analyses for the phase II/III design will be proposed at this stage of the trial. A priori, we plan to explore 4 sources of potential heterogeneity that may need in the context of the adaptive design that may lead to revise the patient eligibility criteria:
1) Severity of burn as judged by TBSA, ABI, SOFA, or APACHE.

2) Mechanically (invasive or non-invasive) ventilation or not
3) Adequacy of prior care/resuscitation as judged by direct arrival vs. transfer from other setting with some prior care.
4) early vs. delayed initiation of study IP (based on the observed distribution of times to start study IP).

**2.18 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 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. The local principal investigator, with support from the trial principal investigators and Coordinating Centre, will also determine if the SAE is unexpected.

Unexpected SAEs that are considered to be possibly related to the trial intervention must be reported to the Coordinating Centre via the EDCS within 24 hours of the local principal investigator becoming aware of the unexpected SAE. Clinical sites are also responsible for reporting SAEs to the Research Ethics Board (REB) of record as per their 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 after becoming aware of the information 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.

Clinical sites are responsible for reporting SAEs to the REB of record as per their REB of record's reporting requirements. AEs and SAEs that are expected, but not serious, will not be reported to the regulatory agency, 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 Day-to-day management of the trial**:

The Clinical Evaluation Research Unit (CERU, see www.ceru.ca), under the Direction of Dr. Daren Heyland, will be the coordinating center for this trial protocol and will continue to be the coordinating center for this larger trial. This research unit has considerable experience with conducting large scale, multicenter, multinational trials including the RE-ENERGIZE Trial and prior trials published in the New England Journal of Medicine.[82,83] As the Methods Center, CERU will be responsible for the coordination of all aspects of the trial including activities related to Start-up, Implementation, Data Management, Data Monitoring, Data Analysis, serious adverse event reporting and the close out phase of the trial. Dr. C. Stoppe and team in Wurzburg, Germany will be responsible for adequate conduct of the study in Europe (Dr. C. Stoppe exec. lead) and handle the European regulatory (including BfArM) and ethics applications. Dr. C. Stoppe has established a strong collaboration with CERU as part of the so called sustainCSX study (EudraCT-No.: 2016-004284-39) in Europe and Canada. Both centers have staff with

experience and resources to support the completion of all phases of the design, conduct, monitoring, and interpretation of multicenter clinical studies.
In extension, Wurzburg will take over the lead for shipment, storing of blood samples and will coordinate the planned translational sub-analyses (e.g. measurements of inflammation, redox-stress vitamin C and vitamin E).

**3.2 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 EDC systems.

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 25 years in compliance with Health Canada requirements.

**3.3 Role of each applicant**

The research team has all the necessary experience and expertise to successfully conduct this study, as demonstrated by our prior track record. All CERU staff will be supervised by Dr. Daren Heyland and they will form the Executive Committee which will be responsible for the day-to-day management of the trial. They will be supported by the Steering Committee that will provide specific scientific and operational input. Mr. Andrew Day, senior biostatistician at CERU will be responsible for the statistical analysis of this trial. Mr. Tim Friede, Professor of biostatistics at the University Medical Center Göttingen (UMG), will oversee the design and implementation of the adaptive seamless phase II/III trial.

# Appendices

Appendix A: Drug Accountability Log sample

Appendix B: References

# VICToRY Trial

Principal Investigator: _____Site Name: _____ Site ID: _____

**Participant Initials: ___ ___ Location: _____ CRS Randomization ID**: __ __ __ __ __ __ __ __

**Treatment Assignment**: Select One

( ) Ascorbic Acid 200mg ( ) Placebo

| Transaction Date | ____- ____-_____ | Product Lot Number & Expiry | Ppd by/ Chk by | Dose Returns | Comments |
|---|---|---|---|---|---|
| **Day 1** | IV Infusion - Bag 1 | | | | |
| | IV Infusion - Bag 2 | | | | |
| | IV Infusion - Bag 3 | | | | |
| | IV Infusion - Bag 4 | | | | |

| Transaction Date | ____- ____-_____ | Product Lot Number & Expiry | Ppd by/ Chk by | Dose Returns | Comments |
|---|---|---|---|---|---|
| **Day 2** | IV Infusion - Bag 5 | | | | |
| | IV Infusion - Bag 6 | | | | |
| | IV Infusion - Bag 7 | | | | |
| | IV Infusion - Bag 8 | | | | |

| Transaction Date | ____- ____-_____ | Product Lot Number & Expiry | Ppd by/ Chk by | Dose Returns | Comments |
|---|---|---|---|---|---|
| **Day 3** | IV Infusion - Bag 5 | | | | |
| | IV Infusion - Bag 6 | | | | |
| | IV Infusion - Bag 7 | | | | |
| | IV Infusion - Bag 8 | | | | |

| Transaction Date | ____- ____-_____ | Product Lot Number & Expiry | Ppd by/ Chk by | Dose Returns | Comments |
|---|---|---|---|---|---|
| **Day 4** | IV Infusion - Bag 9 | | | | |
| | IV Infusion - Bag 10 | | | | |
| | IV Infusion - Bag 11 | | | | |
| | IV Infusion - Bag 12 | | | | |

| Transaction Date | ____- ____-_____ | Product Lot Number & Expiry | Ppd by/ Chk by | Dose Returns | Comments |
|---|---|---|---|---|---|
| **Supplemental Dose Preparation** | IV Infusion - Bag __ | | | | |
| | IV Infusion - Bag __ | | | | |
| | IV Infusion - Bag __ | | | | |
| | IV Infusion - Bag __ | | | | |

Additional Notes:

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