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## Supplement 1: Study Protocol

Supplement 1 contains the ACTS clinical trial protocol v2.4. In addition, the published clinical trial protocol and statistical analysis plan can be found: *Moskowitz A, Yankama T, Andersen LW for the ACTS Clinical Trial Investigators, et al Ascorbic Acid, Corticosteroids and Thiamine in Sepsis (ACTS) protocol and statistical analysis plan: a prospective, multicentre, double-blind, randomised, placebo-controlled clinical trial BMJ Open 2019;9:e034406*. All analyses were performed as described in the published statistical analysis plan unless otherwise noted in the manuscript.

Supplement 1 additionally contains the original clinical trial protocol in addition to a summary of changes made over time.

45 **PROTOCOL V2.4**

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48 **Ascorbic Acid, Hydrocortisone, and Thiamine in Sepsis and Septic Shock**  
49 **– A Randomized, Double-Blind, Placebo-Controlled Trial**

50  
51 **Acronym: Ascorbic acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Trial**

52  
53 **CLINICAL TRIAL PROTOCOL**

54  
55 **Version 2.4**  
56 **December 13, 2018**  
57 **IND: 136882**

58  
59  
60 **Clinical Trials.Gov Identifier: NCT03389555**

61  
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172 **SYNOPSIS**

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174 The “Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS)” trial is a multi-center, double-  
175 blind, randomized clinical trial that aims to determine the impact of Vitamin C, Hydrocortisone, and  
176 Vitamin B1 vs. Placebo on organ injury and mortality on participants with sepsis and septic shock.

177 The trial will be conducted in accordance with all applicable national and international laws,  
178 regulations, and guidelines The trial and this protocol is developed in accordance with the  
179 International Conference on Harmonization (ICH) guidelines<sup>1-3</sup> and the Standard Protocol Items:  
180 Recommendations for Interventional Trials (SPIRIT) statement<sup>4,5</sup>. The principal investigator wrote  
181 the protocol with input from the steering committee. Any substantial changes or amendments to the  
182 protocol will be clearly documented and communicated to all relevant parties.

183

**Title** Vitamin C, Hydrocortisone, and Vitamin B1 in Sepsis and Septic Shock – A Randomized, Double-Blind, Placebo-Controlled Trial (The ACTS Trial)

<b>Clinical Trials Number</b>	NCT03389555
<b>Sources of monetary or material support</b>	Open Philanthropy Project ( <a href="https://www.openphilanthropy.org/">https://www.openphilanthropy.org/</a> )
<b>Study Sites</b>	12-sites in the United States
<b>Condition studied</b>	Sepsis and septic shock
<b>Interventions</b>	Vitamin C (1.5g every 6 hours x 4-days), hydrocortisone (50mg every 6 hours x 4-days), and Vitamin B1 (100mg every 6 hours x 4-days)
<b>Comparator</b>	Placebo
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Adult participant (age <math>\geq</math> 18 years)</li> <li>• Suspected (cultures drawn and antibiotic given) or confirmed (via culture results) infection</li> <li>• Receiving vasopressor (norepinephrine, phenylephrine, epinephrine, dopamine, vasopressin, or angiotensin II)</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Member of a protected population (pregnant, prisoner)</li> <li>• Known history of kidney stones within the past 1 year</li> <li>• End stage renal disease (ESRD) requiring dialysis</li> <li>• Known history of G6PD deficiency</li> <li>• Known history of Hemochromatosis</li> <li>• Comfort Measures Only status</li> <li>• Anticipated death within 24-hours despite maximal therapy (as determined by the enrolling physician)</li> <li>• Receiving supplemental vitamin B1 in a dose greater than that contained in a multivitamin (&lt;2mg)</li> <li>• Clinical indication for steroids (e.g. chronic use) as determined by the clinical team providing this drug</li> <li>• Clinical indication for ascorbic acid supplementation in any form</li> <li>• Clinical indication for vitamin B1 as determined by the clinical team providing this drug</li> <li>• Known allergy to vitamin C, hydrocortisone, or vitamin B1</li> </ul>
<b>Study type</b>	Interventional Allocation: Randomized (1:1) Intervention model: Parallel group Masking: Double-blind
<b>Target sample size</b>	200 Participants (100/arm)
<b>Primary outcome</b>	Change in the Sequential Organ Failure Assessment (SOFA) score between enrollment and 72-hours
<b>Key secondary outcomes</b>	Incidence of renal failure during index ICU stay 30-day mortality

186 **STEERING COMMITTEE**

187

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188 **Conflicts of interest**

189 The members of the steering committee have no financial conflicts of interest related to the current  
190 trial.

191

192 \*Stepped down from Steering Committee prior to publication. Was not a site investigator.

193 **TRIAL SITES**

194

195 **Coordinating Center**

196 **Beth Israel Deaconess Medical Center**

197 330 Brookline Avenue

198 Boston, MA 02215

199 Site Investigator: Michael W. Donnino, MD

200

201 **Enrolling Sites\***

202

<b>Hospital Name</b>	<b>Location</b>	<b>Site Principal Investigator</b>
Henry Ford Hospital	Detroit, MI	Junior Uduman, MD
DMC-Detroit Receiving Hospital	Detroit, MI	Rob Sherwin, MD
DMC-Sinai-Grace Hospital	Detroit, MI	Rob Sherwin, MD
Harper Hospital	Detroit, MI	Rob Sherwin, MD
UT Health, The University of Texas Health Science Center	Houston, TX	Pratik Doshi, MD
Mayo Clinic	Phoenix, AZ	Ayan Sen, MD
Beth Israel Deaconess Medical Center	Boston, MA	Ari Moskowitz, MD
Beaumont Hospital	Royal Oak, MI	Ron Otero, MD
Brigham and Women's Hospital	Boston, MA	Peter Hou, MD
Long Island Jewish Hospital Center - Queens	New York, NY	Maksim Korotun, MD; Jonathan Gong, MD
Long Island Jewish Hospital Center - Hyde Park	New York, NY	Ayelet Hilewitz, MD; Jonathan Gong, MD
Mount Auburn Hospital	Cambridge, MA	Jessica McCannon, MD
University of Pittsburgh	Pittsburgh, PA	David Huang, MD
South Shore Hospital	Weymouth, MA	Mark Hershey, MD

203 \*Depending on study progress, sites may be added or removed in the future.

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223 **1. BACKGROUND AND SIGNIFICANCE**

224 **1.1 Scope of the Problem**

225 The worldwide incidence of sepsis has been estimated at more than 23 million cases<sup>6</sup> and sepsis  
226 contributes to more than a third of all hospital deaths in the United States.<sup>7,8</sup> Mortality for those in  
227 septic shock with elevated lactate is more than 40%.<sup>9</sup> In addition to high short-term mortality, sepsis  
228 is associated with significant post-discharge morbidity and mortality.<sup>10-15</sup> The economic burden for  
229 participants suffering from sepsis is staggering with an estimated yearly financial burden of \$17  
230 billion.<sup>16</sup> Treatments are generally limited to antibiotics and intravenous fluids while providing  
231 support to maintain organ function.<sup>17,18</sup>

232

233 **1.2 Existing Interventions**

234 To date, numerous interventions have been tested for participants with sepsis and septic shock with  
235 limited, if any, success.<sup>19-22</sup> Recently, three large studies found no benefit from early goal directed  
236 therapy over usual care in emergency department participants with sepsis.<sup>23-25</sup> Other recent studies  
237 focusing on hemodynamics, fluid therapy, and transfusions have also failed to show a significant  
238 benefit in this participant population.<sup>26-28</sup> Previous studies focusing on immunomodulatory therapies or  
239 drotrecogin alfa have likewise shown disappointing results.<sup>29-35</sup>

240

241 **1.3 The combination of vitamin C, hydrocortisone, and vitamin B1 may improve outcomes**

242 In a before-and-after study exploring the effects of the combination of vitamin C, hydrocortisone, and  
243 vitamin B1 in a cohort of participants with sepsis and septic shock, Marik et. al. found a remarkable  
244 improvement in time to shock reversal ( $18.3 \pm 9.8$  hours vs.  $54.9 \pm 28.4$  hours), organ injury ( $\Delta$ SOFA  
245  $4.8 \pm 2.4$  vs.  $0.9 \pm 2.7$ ), and mortality (8.5% vs. 40.4%) following implementation of the drug 'cocktail'  
246 as compared to before implementation even after adjusting for potential confounders.<sup>36</sup> This study  
247 joins other promising trials of individual elements of this drug combination. In a trial of vitamin B1 in  
248 septic shock, there was a substantial reduction in mortality and organ injury (particularly kidney  
249 injury) in those with vitamin B1 deficiency and septic shock who were given vitamin B1 as compared  
250 to placebo.<sup>37,38</sup> In addition, several studies of vitamin C alone have shown promise in critically ill  
251 populations<sup>39-42</sup> and a recent meta-analysis of corticosteroids in sepsis suggests potential benefit.<sup>43</sup>

252

253 **1.4 Physiologic Rationale**

254 The combination of vitamin C, hydrocortisone, and vitamin B1 is hypothesized to improve outcomes  
255 in sepsis through a number of mechanisms.<sup>36</sup> Vitamin C is an important contributor to endothelial  
256 integrity and severe deficiency states (e.g. scurvy) can result in endothelial breakdown with resultant  
257 vascular leak and edema.<sup>44,45</sup> In addition, vitamin C is a potent anti-oxidant and is integral to  
258 endogenous vasopressor synthesis.<sup>36</sup> Hydrocortisone, a potential adjunctive therapy in septic  
259 shock<sup>46,47</sup>, may act synergistically with vitamin C.<sup>48,49</sup> Vitamin B1, a key cofactor of pyruvate  
260 dehydrogenase, is a critical component of metabolic dysfunction without which a shift towards  
261 anaerobic energy production occurs.<sup>50</sup> Vitamin B1 is also a necessary component of the pentose  
262 phosphate pathway, which plays a role in reducing oxidative stress.<sup>51,52</sup> While the physiologic effects  
263 of these drugs given in combination is not entirely known, we hypothesize that there will be  
264 synergistic effects with respect the metabolic resuscitation of sepsis.

265 **2. TRIAL DESIGN**

266 **2.1 Overview**

267 This will be an investigator-initiated, multicenter, randomized, placebo-controlled, parallel group,  
268 double-blind, superiority trial of vitamin C, hydrocortisone, and vitamin B1 vs. placebo in participants  
269 with sepsis and septic shock. A total of 200 adult participants will be enrolled. The primary outcome  
270 will be the change in SOFA score between enrollment and 72-hours. Key secondary outcomes  
271 include the incidence of renal failure during the index ICU stay and survival at 30 days.

272

273 **2.2 Allocation**

274 Participants will be randomized in a 1:1 ratio to either the combination of vitamin C, hydrocortisone,  
275 and vitamin B1 or placebo in blocks with random sizes of 2 or 4. The randomization will be stratified  
276 according to site.<sup>53</sup> An independent statistician will create the randomization list using a random  
277 number generator. The complete list will only be shared with an independent pharmacy consultant,  
278 who will not be involved in clinical care. The pharmacy consultant and the independent statistician  
279 will both store the randomization list. The research pharmacy at each enrolling site will receive a  
280 site-specific randomization list.

281

282 **2.3 Intervention**

283 *2.3.1 Vitamin C, Hydrocortisone, and Vitamin B1*

284 The study drugs will consist of vitamin C (1.5g every 6 hours x 4-days), hydrocortisone (50mg every 6  
285 hours x 4-days), and vitamin B1 (100mg every 6 hours x 4-days).

286

287 *2.3.2 Placebo*

288 The placebo will consist of matching volumes of normal saline (0.9% NaCl). See below section 4.4  
289 for specifics of drug and placebo preparation.

290

291 **2.4 Blinding**

292 The trial will be double-blind; participants, investigators, and the clinical team will be blinded to the  
293 allocation. Only the pharmacy providing the study drug will be aware of the allocation. The  
294 pharmacy will not be involved with clinical care or outcome evaluation.

295

296 As vitamin C possess a yellow tinge, the bags containing the vitamin C/placebo will be covered with  
297 light-protective bags. In testing, after dilution there is not distinguishing characteristics of the vitamin  
298 C vs. placebo in the IV tubing. Vitamin C, hydrocortisone, and vitamin B1 are not known to have  
299 distinctive rapid effects which could lead to unblinding.

300

301 The decision to unblind will be at the complete discretion of the treating physician and clinical team.  
302 If a clinical team wishes to unblind a participant (e.g. if anaphylaxis occurs), they will contact the  
303 research pharmacy who will reveal the study group to the clinical team (but the research team will  
304 remain blinded). However, we do not expect many scenarios where emergency unblinding will be  
305 necessary. In case unblinding occurs, the reason(s) will be clearly documented in the case report  
306 form. The patient will no longer receive study medications, but will be followed for outcomes.

307

308 **2.5 Regulatory Issues**

309 An Investigational New Drug (IND) application was submitted to and approved by the Food and  
310 Drug Administration (FDA) for the study of vitamin C, hydrocortisone, and vitamin B1 in sepsis and  
311 septic shock (IND # 136882).

312

313 The trial has been registered on ClinicalTrials.gov: NCT03389555

314

315

316 **3. SETTING AND PARTICIPANT POPULATION**

317 **3.1 Setting**

318 The trial will be conducted at approximately 13 hospitals in the United States. Additional sites might  
319 be recruited if needed.

320

321 **3.2 Inclusion criteria**

322 Inclusion criteria:

- 323 1) Adult participant (age  $\geq$  18 years)  
324 2) Suspected (cultures drawn and antibiotic given) or confirmed (via culture results) infection  
325 3) Receiving (continuous infusion) vasopressor (norepinephrine, phenylephrine, epinephrine,  
326 dopamine, angiotensin II, or vasopressin)  
327 a. Hypotension related primarily to sepsis as opposed to another cause of hypotension  
328 (e.g. bleed, cardiogenic shock)

329

330 **3.3 Exclusion criteria**

331 Exclusion criteria:

- 332 1) Member of a protected population (pregnant, prisoner)  
333 2) Known history of kidney stones within the past 1 year (not including incidentally noted stones  
334 noted on imaging studies)  
335 3) End stage renal disease requiring dialysis (hemodialysis or peritoneal dialysis)  
336 4) Known history of G6PD deficiency  
337 5) Known history of Hemochromatosis  
338 6) Comfort Measures Only status  
339 7) Anticipated death within 24-hours despite maximal therapy (as determined by the enrolling  
340 physician)  
341 8) Receiving supplemental vitamin B1 in a dose greater than that contained in a multivitamin  
342 (<2mg)  
343 9) Clinical indication for steroids (e.g. chronic use) as determined by the clinical team providing  
344 this drug  
345 10) Clinical indication for ascorbic acid supplementation in any form  
346 11) Clinical indication for vitamin B1 as determined by the clinical team providing this drug  
347 12) Known allergy to vitamin C, hydrocortisone, or vitamin B1

348

349 Justification of Inclusion and Exclusion Criteria: The inclusion criteria were chosen to isolate a septic  
350 participant population with high risk of organ injury and death. The exclusion criteria were chosen to  
351 minimize the risk of potential harm and to ensure that participants enrolled do not already have  
352 chronic end-stage renal failure with a high likelihood of early need for renal replacement therapy. By  
353 evaluating this high-risk population (i.e., most likely to die), we will target those most likely to benefit  
354 and therefore increase the probability of showing efficacy.<sup>19</sup>

355

356 **3.4 Pregnancy**

357 Hydrocortisone is considered pregnancy class C on the basis of animal studies showing an  
358 association between prenatal parenteral hydrocortisone use and risk of cleft-palate. In addition,  
359 there are concerns about effects of hydrocortisone on fetal growth and the possibility of neonatal  
360 adrenal insufficiency. The effects of high-dose vitamin C and thiamine in pregnancy are not entirely  
361 known. As such, participants who are pregnant will be excluded from the study. Prior to enrollment,  
362 all participants of potentially child-bearing potential (women aged <45 years<sup>54</sup>) will be required to  
363 have a negative serum or urine HCG test (generally performed as standard-of-care).

364

365 We will additionally inform all women of child-bearing potential who are randomized in this study  
366 that we recommend they remain abstinent or use two forms of birth control during the study period  
367 and for a period of 48-hours after the last dose of study drug.

368

## 369 **4. TRIAL PROCEDURES**

### 370 **4.1 Participant Identification**

371 Screening will be performed in the emergency department and intensive care units (ICUs) with the  
372 assistance of electronic screening mechanisms . Detailed screening logs, with reason(s) for  
373 exclusion will be kept at each site and reported in the final publication.

374

375 We anticipate that all patients, as part of standard-of-care for the septic patient, will have a urine or  
376 serum HCG test performed (if a female of child-bearing age). If this test is not sent as part of  
377 standard-of-care, it should be sent prior to consent.

378

### 379 **4.2 Consent procedures**

380 Informed, written consent will be obtained for all participants prior to enrollment.

381

382 After it is determined that they meet all inclusion criteria and no exclusion criteria, the participant (or  
383 legally authorized representative [LAR] if the participant is not able to provide consent) will be  
384 approached for written informed consent by a physician co-investigator from the team. The  
385 investigator will provide the participant/representative information regarding the background and  
386 significance of the study, eligibility criteria, and a description of the protocol. To ensure we are  
387 correctly identifying the potential participant's LAR, we communicate with members of the clinical  
388 team. The consent process may need to be modified based on site-specific IRB recommendations.

389

390 The name of the study investigator obtaining consent will be clearly documented, and this person  
391 will sign the informed consent document and provide the date and time of their signature. If a  
392 physician is performing remote consent, then a copy of the consent form will be signed as soon as  
393 he/she is physically present. Signed copies of the consent form will be given to the  
394 participant/surrogate, and the original consent document will be stored in the secure study file. In  
395 obtaining and documenting informed consent, each investigator will comply with the applicable  
396 regulatory requirements and adhere to the ethical and Good Clinical Practice principles that have  
397 their origin in the Declaration of Helsinki.

398

### 399 **4.3 Randomization**

400 After consent is obtained, the research team will notify the local research pharmacy. The research  
401 pharmacy will be in possession of the randomization list and will determine which arm (intervention  
402 vs. placebo) the participant will be enrolled in.

403

404 Patients should be randomized, consented, and enrolled in the study as soon as possible after  
405 meeting inclusion criteria. Patients should not be *consented* if it has been >24hours since the  
406 patient met inclusion criteria (i.e. start of vasopressors). At the time of randomization and study drug  
407 administration, the patient should still be receiving a vasopressor. The patient should not be given  
408 study drug if the vasopressor has been stopped (e.g. patient met inclusion criteria overnight but  
409 could not be consented for logistical reasons and then improves to the point of no longer requiring a  
410 vasopressor). In this scenario, the patient will be entered into the database as consented but not  
411 enrolled.

412

### 413 **4.4 Drug preparation and administration**

414 The vitamin C and vitamin B1 will be mixed together in 100ml of normal saline and administered  
415 intravenously over 45-60 minutes. The hydrocortisone will be given intravenously as a push-dose in  
416 1ml of saline over 1-2 minutes. The placebo will be given using techniques and volumes matching  
417 those of the study medications.

418  
419 All study medications will be continued for 4-days or until the participant expires or leaves the  
420 intensive care unit.

421  
422 **4.4.1 Contingencies and Participant Withdrawal**

- 423 • In the unlikely event that a participant is discharged alive from the hospital prior to 4 days after  
424 enrollment, all study medications will be stopped. The participant will remain in the study and will  
425 be followed for outcomes.
- 426 • Hydrocortisone is occasionally used for refractory septic shock. If the clinical team opts to provide a  
427 participant hydrocortisone, the hydrocortisone will be given open-label but the vitamin C/B1 will  
428 remain randomized and blinded. In this case, the research team will ensure that study  
429 hydrocortisone/placebo is replaced by open-label hydrocortisone. The participant will remain in  
430 the study and will be followed for outcomes.
- 431 • If the clinical team decides to give the participant vitamin B1 for clinical purposes, the study drug  
432 will be continued (including thiamine) as long as the total maximum dose of vitamin B1 is  
433  $\leq 1,500\text{mg/day}$ . 1,500mg day is a standard dose for Wernicke's encephalopathy at many  
434 institutions and has not been associated with any increased harm.
- 435 • If the clinical team decides to give the participant vitamin C for clinical purposes, further  
436 administration of study meds will be stopped. The participant will remain in the study and will be  
437 followed for outcomes.
- 438 • If a participant withdraws from the study, further administration of study meds will be stopped.  
439 Data collected prior to withdrawal will be maintained but additional data will not be collected.

440  
441 **4.5 Specimen collection procedures**

442 **4.5.1 Timing and volume of blood draw**

443 All participants will have a blood samples collected at four time-points and urine samples at two  
444 time-points (if not already available as part of routine clinical care). Blood will be obtained by  
445 venipuncture, or from an existing venous or arterial catheter. Urine will be collected via clean catch  
446 urine or via catheter.

447  
448 **Specimen Collection Time Points**

- 449 1. T1=0 hrs (just before study drug administration)
- 450 2. T2=24 hrs (+/- 2 hrs)
- 451 3. T3=72 hrs (+/- 2 hrs)
- 452 4. T4=120hrs (+/- 12hrs)

453  
454 **4.5.2 Specimen samples**

455 At the T1, T2, T3, and T4 time points, blood will be sent for complete blood count (including  
456 hemoglobin, white blood cell count, platelet count), a serum chemistry (including sodium,  
457 potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, aspartate transaminase,  
458 alanine transaminase, and total bilirubin), and a venous blood gas to measure lactate. These tests  
459 will be performed by the clinical laboratory at each site. As many of these laboratory tests are  
460 commonly obtained for clinical purposes, these tests do not need to be repeated if a result is  
461 available from the clinical care of the participant within 2 hours of the time point (or within 12 hours  
462 of the T4 time-point).

463  
464 In addition to traditional clinical markers, blood will be obtained for future biomarker analysis  
465 (including inflammatory biomarkers, markers of endothelial function, and markers of mitochondrial  
466 function), and measurement of vitamin C, vitamin B1, and cortisol levels. The total volume of blood  
467 that may be drawn for a participant at each time point will not exceed 60mls. Levels of vitamin C,  
468 vitamin B1, and cortisol will be measured at time T1 and time T3 only. 20ml of urine will be collected  
469 for future biomarker analysis at T1, T2, and T3.

470

471 If performed as part of standard-of-care, results of urinalysis and urine sediment testing will be  
472 collected prior to enrollment.

473

#### 474 4.5.3 Biomarker tube initial processing and shipping

475 Please see accompanying blood collection standard operating procedure for full details. In brief,  
476 15ml of blood will be drawn into EDTA tubes and 10ml of blood will be drawn into a corvac tube.  
477 From one of the EDTA tubes, 3ml of whole blood will be initially drawn and separated into 3x 1ml  
478 aliquots. Plasma will then be isolated from the EDTA tube(s) and aliquoted into cryovials as follows:  
479 4x 0.5ml aliquots and the remainder in 1ml aliquots. Serum will then be isolated from the corvac  
480 tube, and separated into 1ml aliquots. Cryovials will be protected from light and frozen at -80°C until  
481 processing. An additional 20ml of urine will also be collected, centrifuged, and separated into 1ml  
482 aliquots then frozen at -80°C until processing.

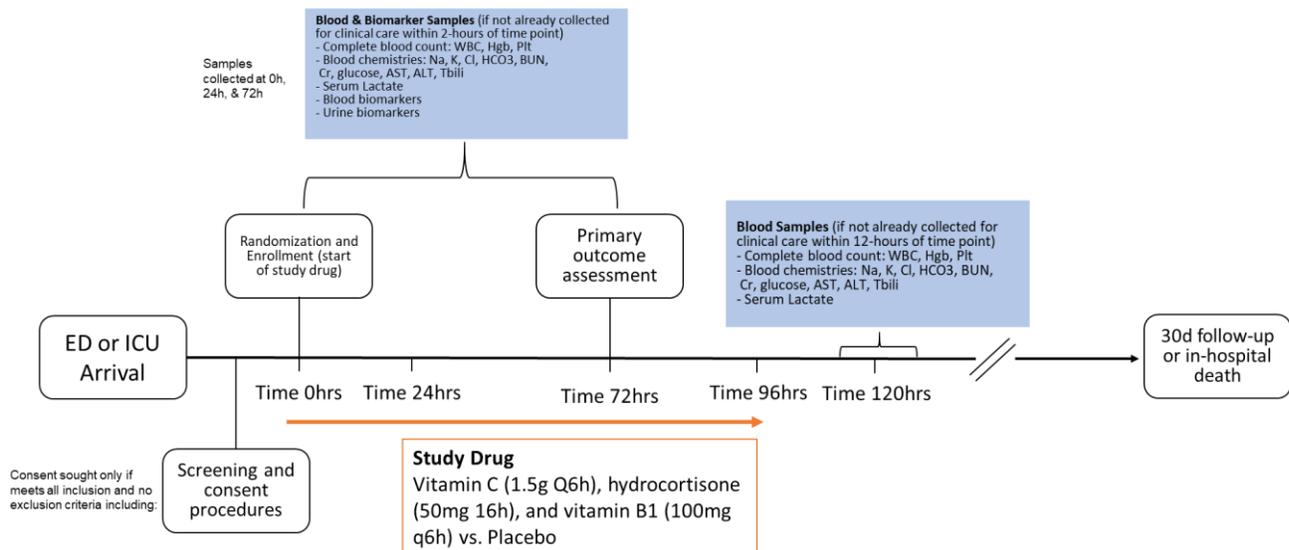
483

484 Sites will be expected to ship frozen samples to the coordinating center after every 5 enrollments.  
485 The coordinating center will assist with all shipping procedures.

486

#### 487 4.6 Study flow diagram

488



489

490

#### 491 4.7 General Sepsis Management

492 Investigators should follow local sepsis management guidelines. No specific sepsis bundle is  
493 required by this study, however the early administration of antibiotics, maintenance of a mean  
494 arterial pressure  $\geq 65$ mmHg with a combination of volume resuscitation and vasopressors, and early  
495 source control are recommended—as detailed in the Surviving Sepsis Guidelines.<sup>55</sup> Elements of  
496 sepsis care should be reported on the online case report form (CRF).

497

#### 498 4.8 Glucometer use during the study period

499 High dose vitamin C has been shown to falsely elevate glucose level readings when measured with  
500 certain point-of-care glucometers employing glucosedehydrogenase-pyrroloquinoline quinone  
501 amperometric methods<sup>56</sup>. Some commonly used glucometer brands using this approach include  
502 Accu-Chek (Roche Diagnostic) and Optium (Abbott Diabetes Care) (but not StatStrip; Nova  
503 Biomedical). While the effects of high-dose vitamin C on glucometer readings have been seen  
504 primarily at higher doses of vitamin C than are intended for use in this trial,<sup>56</sup> we recommend that  
505 sites explore what glucometers are in use in local ICUs. If locally used glucometers may be

506 impacted by high serum concentrations of vitamin C (as determined by the manufacturer), we  
 507 recommend that clinical teams caring for enrolled participants be alerted to the possibility of falsely  
 508 elevated blood-glucose levels when measured by glucometer. If there is a clinical concern about a  
 509 glucose reading obtained via glucometer, a serum glucose should be obtained which will not be  
 510 impacted by vitamin C. In the event of an emergency related to suspected hypoglycemia, glucose  
 511 should be immediately given while a serum glucose level is pending.  
 512

## 513 5. OUTCOMES

### 514 5.1 Definitions

#### 515 5.1.1 Primary Outcome

516 The primary outcome will be the absolute change in the Sequential Organ Failure Assessment  
 517 (SOFA) score from enrollment (time=0) to 72 hours after drug administration. The SOFA score will  
 518 be defined using a modification in which the SaO<sub>2</sub>/FiO<sub>2</sub> ratio is substituted for the PaO<sub>2</sub>/FiO<sub>2</sub> ratio  
 519 as has been previously described.<sup>57,58</sup> This modified score will be used so that participants without  
 520 an existing arterial catheter can be spared arterial puncture.  
 521

Points	SaO <sub>2</sub> */FiO <sub>2</sub> <sup>§</sup>	Blood Pressure	GCS <sup>  </sup>	Bilirubin (mg/dL)	Creatinine (mg/dL)	Platelets (x10 <sup>3</sup> µL)
1	<400	< 70 mm/Hg	13–14	1.2–1.9	1.2 – 1.9	<150
2	<326	dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	10–12	2–5.9	2.0 – 3.4	<100
3	<236 (and receiving invasive or non-invasive mechanical ventilation)	dopamine > 5µg/kg/min, epinephrine/norepinephrine ≤ 0.1 µg/kg/min	6–9	6–11.9	3.5 – 4.9 Or UOP <sup>†</sup> <500ml/day	<50
4	<151 (and receiving invasive or non-invasive mechanical ventilation)	dopamine > 15, epinephrine/norepinephrine > 0.1 µg/kg/min	<6	>12	> 5.0 UOP <sup>†</sup> <200ml/day Or receiving renal replacement therapy	<20

522 \*SaO<sub>2</sub>=Oxygen saturation (%); § = Fraction of inspired oxygen (%); || = Glasgow Coma Scale; † = Urine Output

523 FiO<sub>2</sub> will be determined by using either the set FiO<sub>2</sub> (for patients receiving invasive or non-invasive  
 524 mechanical ventilation) or by adding 3% FiO<sub>2</sub> for each liter/minute of supplemental oxygen added  
 525 up to 100% FiO<sub>2</sub> (for patients not receiving mechanical ventilation). Patients with an SaO<sub>2</sub>/FiO<sub>2</sub>  
 526 ratio <236 who are not receiving invasive or non-invasive mechanical ventilation, will be assigned a  
 527 score of 2.  
 528

#### 529 5.1.2 Key Secondary Outcomes

530 Incidence of Acute Renal Failure – Renal failure will be defined as the development of Kidney  
 531 Disease Improving Global Outcomes [KDIGO] Stage 3 acute kidney injury during the index ICU stay  
 532 after study enrollment.<sup>58</sup>  
 533

KDIGO Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 µmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg per hour for more than 6 hours
2	Increase in serum creatinine to more than 200% to 300% (> 2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 hours
3	<b>Increase in serum creatinine to more than 300% (&gt; 3-fold) from baseline (or serum creatinine of</b>	<b>Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours OR</b>

	more than or equal to 4.0 mg/dl [ $\geq$ 354 $\mu$ mol/l] with an acute increase of at least 0.5 mg/dl [44 $\mu$ mol/l])	New renal replacement therapy (RRT)
--	--	-------------------------------------

534

535 30-Day Mortality – Mortality at 30-days. This will be assessed by review of the medical records if the  
536 participant remains in the hospital or if the participant expired while in the hospital. If the participant  
537 was discharged, 30-day mortality will be assessed by contacting the participant by phone or by  
538 searching the National Center for Health Statistics (NCHS) National Death Index (NDI) consistent  
539 with a recent multicenter phase III trial in sepsis.<sup>23</sup> Phone calls will be made by the research team at  
540 each site.

541

## 542 **5.2 Rationale for Outcomes**

543 **Change in SOFA score:** Organ failure is highly associated with mortality<sup>60</sup> and improvement in  
544 organ function is a key goal for critical care physicians. In the study by Marik et al.<sup>36</sup>, participants  
545 who received the 3-drug regimen had substantial improvements in the trajectory of organ failure  
546 over the first 72-hours of their ICU stay. If the combination of vitamin C, hydrocortisone, and vitamin  
547 B1 can improve organ function in the first 72-hours following ICU admission, we believe that  
548 clinicians will likely quickly adopt this safe and inexpensive therapy. Importantly, this outcome can  
549 be measured early in the hospital stay and is therefore less likely to be affected by other potential  
550 elements of hospital care that can affect more distal outcomes (e.g., mortality).

551

552 **Kidney Injury:** Renal failure has been estimated to occur in 23% of participants with sepsis and  
553 over 50% of participants with septic shock.<sup>61</sup> In studies of participants with septic shock, there is a  
554 step-wise increase in mortality with worsening acute kidney injury (AKI).<sup>62</sup> In addition, many  
555 participants who experience renal injury during septic shock do not recover renal function prior to  
556 hospital discharge and may require long term dialysis. As both data from the study by Marik et. al.<sup>36</sup>  
557 and a separate study of vitamin B1 in septic shock<sup>38</sup> have shown substantial improvements in renal  
558 outcomes, kidney failure is a natural secondary outcome and one that could change practice  
559 independently from other factors – in other words, many clinicians would likely provide this therapy if  
560 they knew that kidney function could be protected, since this organ is vital to long-term health.

561

562 **Mortality:** Finally, we will measure 30-day mortality. We anticipate that the combination of vitamin  
563 C, hydrocortisone, and vitamin B1 will reduce mortality in this high-risk population.

564

## 565 **5.3 Additional Secondary Outcomes**

### 566 *5.3.1 Additional secondary outcomes*

567 Additional secondary outcomes will include length of ICU stay, length of hospital stay, ventilator-free  
568 days over the first 7-days after enrollment, shock-free days over the first 7-days after enrollment,  
569 and the incidence of delirium on day #3 of the ICU stay (as assessed using the Confusion  
570 Assessment Method [CAM-ICU] system).<sup>63</sup> Sites at which the CAM-ICU is performed daily as part of  
571 standard-of-care should assess whether delirium occurs on any day during the initial ICU stay. See  
572 Appendix #2.

573

### 574 *5.3.2 90-day follow-up for Quality of Life assessment*

575 Sites may choose to participate in a long-term outcomes substudy exploring the effects of ascorbic  
576 acid, hydrocortisone, and thiamine vs. placebo on quality of life following sepsis. If a site chooses to  
577 participate, a trained research assistant/investigator at the site (who is blinded to treatment arm) will  
578 contact all participants who were alive at 30-days, and perform the SF-36 at day 90 following  
579 enrollment. The SF-36 is a 36-Item Short-Form Health Survey (SF-36), a validated survey of  
580 general quality of life in adults, can be administered in person or over the telephone by research

581 personnel. It measures eight different dimensions: physical functioning, bodily pain, role limitations  
582 due to physical health problems, role limitations due to personal or emotional problems, emotional  
583 well-being, social functioning, energy/fatigue, and general health perceptions, as well as one  
584 question asking about perceived changes in health. The telephone version of the 36-Item Short-  
585 Form Health Survey has been validated<sup>64,65</sup> and used in sepsis.<sup>66-69</sup>

## 587 **5.4 Safety**

### 588 *5.4.1 Definitions*

589 The following definitions will be used<sup>70</sup>:

591 Adverse event: any untoward medical occurrence in a participant to whom a medicinal product is  
592 administered and which does not necessarily have a causal relationship with this treatment

594 Serious adverse event: any untoward medical occurrence that at any dose requires inparticipant  
595 hospitalization or prolongation of existing hospitalization, results in persistent or significant disability  
596 or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death

598 Unexpected serious adverse event: a serious adverse reaction, the nature, severity or outcome of  
599 which is not consistent with the reference safety information

### 602 *5.4.2 Specific adverse event data collection*

603 To assess specific and potentially serious adverse events that may be related to the combination of  
604 the study medications, we will collect data on the following:

<b>Serious Adverse Event</b>	<b>Definition</b>
Hyperglycemia	Serum glucose >300mg/dl in the first 120-hours after enrollment
Hyponatremia	Serum sodium (> 150 mmol/L) occurring in the first 120-hours after enrollment
New Infection	As determined by the site principal investigator at each site. Should be a new organism or site of infection and believed to be unrelated to the initial presenting infectious source. Many will have the initiation of new antibiotics or a change in antibiotics.
Catheter-site	
Lung	
Gastrointestinal	
Urinary tract	
Other	
Serious allergic reaction	Anaphylaxis or other allergic reaction requiring systemic corticosteroids. Allergic reaction should be related (or suspected to be related) to the study medication
Renal calculus	Development of a renal calculus between enrollment and 30-day follow-up (based on question asked during follow-up phone call).

606

### 607 *5.4.3 Adverse Event Reporting*

608 All unexpected serious adverse events thought to be related to the study drug, and any  
609 unexpected fatal or life-threatening adverse events thought to be related to the study drug  
610 will be recorded in the online CRF, reported directly to the coordinating center, and reported  
611 to the appropriate IRB shortly following the event per local protocol. In addition, unexpected  
612 serious adverse events related to the study drug will be undergo expedited reporting to the  
613 DSMB within 7 days of the coordinating center becoming aware of the event. The DSMB will  
614 additionally review all adverse events in aggregate after every 50 patients are enrolled.

615

616 Adverse events will additionally be reported to the FDA as outlined in 21CFR312.32 and  
617 summarized below:

- 618 a. All unexpected fatal or life-threatening adverse events thought to be related to the  
619 study drug will be reported to the FDA within 7 calendar-days of when the ACTS  
620 team is made aware of the event.
- 621 b. All unexpected serious adverse events thought to be related to the study drug will be  
622 reported to the FDA within 15 calendar-days of when the ACTS team is made aware.
- 623 c. All serious unexpected adverse events, and any unexpected fatal or life-threatening  
624 events thought to be related to the study drug, will be reported back to all site  
625 investigators within 15 calendar-days of the event.
- 626 d. The ACTS team will periodically review all published information relating to the safety  
627 of each element of the drug combination. Any concerning safety information obtained  
628 from this review, or otherwise obtained (e.g. from unpublished scientific papers), will  
629 be reported to the FDA within 15 calendar-days.

630  
631 **5.4.5 Safety Monitoring Labs**

632 As detailed above, safety monitoring labs will be obtained at 120-hours, after completion of the  
633 study protocol.

634  
635 **6. SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS PLAN**

636 **6.1 Sample size calculation**

637 The study has been powered to have at least 80% power for the primary outcome and all key  
638 secondary outcomes as follows:

639  
640 **SOFA Score:** Based on preliminary data<sup>36</sup>, we conservatively anticipate a decrease in SOFA score  
641 of 6 (standard deviation [SD]: 4) in the treatment group and 4 (SD: 2) in the placebo group. With  
642 these estimates, enrollment of **200 participants (100/arm)** at an alpha of 0.05 and using a t-test  
643 with unequal variance, the trial will provide > 99% power to detect a statistical significant difference  
644 between groups.

645  
646 **Kidney Injury:** Based on preliminary data from our study of vitamin B1 in septic shock,<sup>38</sup> we  
647 anticipate that 30% of participants in the treatment group and 55% in the placebo group will have  
648 renal failure which will result in a 94% power for this outcome. This calculation and following  
649 calculation were performed using the Fisher's exact test.

650  
651 **Mortality:** Based on preliminary data<sup>36,37,71</sup>, we anticipate that the control group will have a mortality  
652 of 40%. We estimate a treatment effect of 50% (risk ratio: 0.50) resulting in a mortality of 20% in the  
653 treatment group. With these estimates, 182 participants will lead to 80% power. To further increase  
654 the trial's power and due to potential loss-to-follow-up, we will aim to enroll 200 participants. These  
655 estimates are conservative compared to the Marik et al. study which found a treatment effect  
656 corresponding to a risk ratio of 0.21 which persisted in adjusted analysis.<sup>36</sup>

657  
658 **Sample Size Adjustment**

659  
660 If after 100 patients are enrolled, the overall change in SOFA score is less than anticipated in the  
661 above power analysis and/or the renal failure event rate or mortality rate is lower than predicted, the  
662 enrollment target of 200 patients may be adjusted accordingly so as to improve power for the  
663 primary outcome and all key secondary outcomes at the end of the trial period. Specifically, we will  
664 aim to maintain ≥90% power to detect a 2-point difference in ΔSOFA score (using variance seen for  
665 the full cohort) and ≥80% power to detect a 50% treatment effect on mortality. Whether to increase  
666 the study sample size, and the degree of sample size increase, will be decided on by the blinded  
667 Steering Committee who will not have access to data stratified by treatment group. The Steering

668 Committee will take into account logistical and financial considerations when updating the  
669 enrollment target.

670

## 671 **6.2 Statistical analysis plan**

### 672 *6.2.1 General considerations*

673 The statistical analyses and reporting will adhere to the CONSORT guidelines.<sup>72,73</sup> All tests will be  
674 two-sided, a p-value < 0.05 will be considered significant, and all confidence intervals will have 95%  
675 coverage. All analyses will be conducted on a modified intention-to-treat basis only including  
676 participants receiving at least the first dose of the study medications. In a double-blind trial, this  
677 approach is unbiased while increasing precision.<sup>74</sup> The two groups will be compared in relation to  
678 baseline characteristics using descriptive statistics.

679

680 The persons conducting the statistical analysis will be blinded to the randomized allocation. Groups  
681 will be designated as “A” and “B” until all pre-specified analyses are performed and shared with all  
682 authors and the Data Safety Monitoring Board.

683

### 684 *6.2.2 SOFA score and renal failure*

685 The change in SOFA score will be calculated and compared between groups using the Wilcoxon  
686 Rank Sum test (if the change is not normally distributed) or by a t-test if the change is approximately  
687 normally distributed. Fisher’s exact tests will be used to compare the incidence of renal failure  
688 during the index ICU stay.

689

690 If a participant expires prior to the 72-hour time point, SOFA scores will be imputed based on a pre-  
691 defined plan as follows. If a participant expires before 24-hours has elapsed, a 20% increase from  
692 baseline will be imputed. If a participant expires between 24-hours and 48-hours, a 15% increase  
693 from the 24-hour time point will be imputed. If a participant dies between 48-hours and 72-hours, a  
694 20% increase from the 24-hour time point will be imputed. Sensitivity analyses will be performed  
695 using various other imputation techniques. Specifically, we will perform 1) a sensitivity analysis in  
696 which the worst possible SOFA score (score of 24) is imputed for those participants who expire, 2) a  
697 sensitivity analysis in which the last SOFA score for participants who expire will be carried forward,  
698 and 3) a sensitivity analysis in which only those patients who survive to 72-hours are included.  
699 These sensitivity analyses were chosen to model ‘worst-possible’ and ‘best-possible’ scenarios. For  
700 the secondary outcome of renal failure, participants who expire during their ICU stay will be  
701 assessed to have developed renal failure if they demonstrated any degree of unresolved KDIGO  
702 acute kidney injury prior to death. If there was no evidence of acute kidney injury prior to death or if  
703 kidney injury had fully resolved, these participants will be assessed as not having developed renal  
704 failure.

705

### 706 *6.2.3 30-day mortality*

707 Survival until 30 days will be analyzed using survival analysis. Participants lost to follow-up will be  
708 censored and the censoring will be assumed non-informative. Results will be presented with  
709 Kaplan-Meier curves and the groups compared using the log-rank test.<sup>75</sup> Hazard ratios with 95%  
710 confidence intervals will be obtained using Cox’s proportional hazards models.<sup>76</sup> The proportional  
711 hazards assumption will be verified by visual inspection of the Kaplan-Meier curves and statistically  
712 by including a product term (i.e. “interaction”) between the treatment group variable and the natural  
713 logarithm of time in the model.<sup>77</sup> If the proportional hazards assumption is not met, only the Kaplan-  
714 Meier curves and the p-value from the log-rank test will be presented.

715

716 Adverse events and other binary outcomes will be presented and analyzed like renal failure.

717

### 718 *6.2.4 Additional Secondary Analyses*

719 Both ICU and hospital length of stay will be compared using Wilcoxon Rank Sum tests. Ventilator  
720 and shock free days over the first 7-days after enrollment will likewise be compared using the

721 Wilcoxon Rank Sum given that the data will likely be not normally distributed. In these latter two  
722 analyses, patients who expire prior to 7-days will be assessed to have 0 ventilator or shock free  
723 days if they had died while on a ventilator or vasopressor respectively. The incidence of delirium will  
724 be compared using the Fisher's exact test. For the quality-of-life outcome (i.e. 90-day SF-36), the  
725 primary analysis will only include patients with available data. As a secondary analysis, multiple  
726 imputation will be used to estimate SF-36 scores in all patients not known to be dead at 90 -days.  
727

### 728 *6.2.5 Subgroup analyses*

729 The analysis will include three pre-defined subgroup analyses for the primary and key secondary  
730 outcomes according to 1) participants with initially high SOFA scores ( $\geq 9$ ). This cut-off was chosen  
731 to represent a population with a  $\geq 50\%$  predicted likelihood of mortality<sup>78</sup> 2) baseline vitamin B1  
732 deficiency and 3) baseline adrenal insufficiency. We will not plan to perform a subgroup analysis  
733 according to vitamin C deficiency, as prior work has shown that the vast majority of participants with  
734 septic shock have vitamin C levels below the reference range.<sup>36</sup> Vitamin B1 deficiency will be  
735 defined as a plasma vitamin B1 level  $\leq 7$  nmol/L as has been previously described.<sup>37</sup> Adrenal  
736 insufficiency will be defined as a cortisol level  $< 10\mu\text{g/dL}$ .<sup>43</sup> The trial is not powered to detect  
737 subgroup differences and these will be considered exploratory and hypothesis generating.  
738

### 739 *6.2.6 Statistical stopping criteria*

740 Since the primary outcome is not mortality, there will be no formal stopping criteria for efficacy.  
741 There will be no predefined stopping criteria for futility since enrollment of the full cohort might allow  
742 for detection of efficacy in subgroups or in other outcomes even if the primary outcome is negative.  
743

## 744 **7. DATA COLLECTION AND MANAGEMENT**

### 745 **7.1 Data collection process**

746 Data collection will be the responsibility of the individual site investigators with oversight from the trial  
747 coordinating center. Most variables (i.e. demographics, sepsis characteristics and laboratory  
748 results) will be obtained prospectively from the electronic medical record. 30-day follow-up  
749 regarding safety and mortality end-points will be obtained via telephone call post-discharge (unless  
750 the participant remains in the hospital at 30-days). Data will be entered directly into the online  
751 database software (see below).  
752

### 753 **7.2 Variables**

754 Will be provided on the online CRF. A PDF version is available upon request.  
755

### 756 **7.3 Data quality and validity**

757 Data quality and validity will be optimized by using a detailed data dictionary which will be  
758 distributed to all sites. Data quality will be monitored both centrally by the coordinating site and  
759 locally by each site principal investigator.  
760

### 761 **7.4 Data storage and security**

762 The database application we will use is REDCap Cloud (<https://www.redcapcloud.com/>). REDCap  
763 Cloud is a professional database that provides a user-friendly interface. The REDCap Cloud data  
764 management system is secure, fully compliant with all regulatory guidelines, and includes a  
765 complete audit-trail for data entry validation. Through these mechanisms, as well as relevant  
766 training for all involved parties, participant confidentiality will be safeguarded. All members of the  
767 research team will be required to complete standardized training in REDCap cloud, which will be  
768 documented within the software.  
769

770 The consent form and other trial documents for each participant will initially be stored in a secure,  
771 locked place at the individual sites. Participating sites will be responsible for maintaining their own  
772 trial documents and study materials (e.g. signed ICFs, site logs etc). Trial documents generated at  
773 the Coordinating Center will be maintained the Coordinating Center. Following completion of the

774 trial, documents will be maintained for a period of at least 2-years at each site per FDA regulations  
775 (or longer depending on local IRB guidelines).

776

## 777 **8. ETHICAL CONSIDERATIONS**

### 778 **8.1 Risks and Benefits**

#### 779 *8.1.1 Potential benefits*

780 **Potential Benefits to Individual Participant:** Assuming our hypothesis is correct and our results are  
781 comparable to those previously published<sup>36</sup>, individual participants enrolled in our study and  
782 randomized to the treatment arm will benefit from a better trajectory of organ failure and improved  
783 mortality. As many participants who survive an initial episode of sepsis will have a future admission for  
784 sepsis, participants participating in this study but randomized to the placebo arm may see a future  
785 benefit from knowledge gained.

786

787 **Potential Benefits to Society:** Septic shock remains a highly morbid clinical condition for which there  
788 is no specific therapy. Our study, assuming our hypothesis is confirmed, will provide strong support for  
789 the widespread adoption of vitamin C, corticosteroids, and vitamin B1 for participants with septic  
790 shock. This, in turn, will significantly improve participant outcomes and reduce the global burden of  
791 death related to septic shock. Thus, even if participants are randomized to the placebo arm, their  
792 involvement with this study has tremendous potential benefits for society as whole. If vitamin C,  
793 corticosteroids, and vitamin B1 are found to be neutral or harmful (the latter being highly unlikely),  
794 society will benefit as the study will likely prevent the widespread dissemination of an ineffective  
795 medication combination.

796

#### 797 *8.1.2 Potential harms*

### 798 **Study Drug**

799 Vitamin C – Ascorbic acid is a water-soluble essential vitamin that is safe even at high doses.  
800 Nevertheless, adverse effects related to high-dose ascorbic acid have been described. These  
801 adverse effects include diarrhea/abdominal bloating, increased oxalate excretion, iron overload in  
802 participants with hemochromatosis, and hemolysis in participants with G6PD deficiency.<sup>79</sup> We  
803 exclude participants with known renal failure, known G6PD deficiency, or known hemochromatosis  
804 to limit these potential risks. We will additionally exclude participants with known allergy to ascorbic  
805 acid. Ascorbic acid has additionally been used in at least 3 clinical trials in critically-ill populations  
806 without major associated adverse effect.<sup>40-42</sup>

807

808 Hydrocortisone – Hydrocortisone is a well-established medication for the treatment of refractory  
809 shock in sepsis. Some studies (e.g. CORTICUS) have found an increased incidence of secondary  
810 infection in participants with septic shock who receive steroids.<sup>46</sup> This finding has not been  
811 replicated in other large trials of corticosteroids for sepsis.<sup>47</sup> Additional hypothetical risks to the  
812 administration of hydrocortisone to participants with septic shock (e.g. increased gastro-intestinal  
813 bleeding, muscle weakness, and delirium) have not been found in clinical trials of corticosteroids in  
814 sepsis.<sup>46,47</sup> Finally, hydrocortisone may increase the risk of hyperglycemia and hyponatremia.

815

816 Hydrocortisone will not be tapered in this study as prior studies have shown benefit with  
817 corticosteroids in septic shock without a taper.<sup>80</sup> In addition, a recent large trial of corticosteroids in  
818 septic shock (ADRENAL, NEJM 2018) randomized patients to 7-days of corticosteroids or placebo  
819 and did not include a taper. In that trial there was no reported difference in rates of recurrent shock.

820

821 Vitamin B1 – The only potential serious side effect that has been reported from vitamin B1  
822 administration is an extremely rare anaphylactic reaction (1:250,000 cases) and this might not even  
823 be of issue with the current manufactured version of vitamin B1 in the United States. The risk of an  
824 anaphylactic reaction was associated with a vitamin complex dispensed in Europe, and whether

825 vitamin B1 was the actual offending agent remains unknown; however, this 0.0004% theoretical  
826 chance of an adverse reaction is incredibly low. In a series of 989 participants in the United States  
827 who received intravenous vitamin B1, none had an anaphylactic reaction and the only reported side  
828 effects were minor consisting of transient local irritation or in one case pruritus (0.093%).<sup>81</sup> Further  
829 safety data comes from the clinical use of intravenous vitamin B1 at our coordinating site. At Beth  
830 Israel Deaconess Medical Center (BIDMC, coordinating center) vitamin B1 is provided liberally for  
831 participants with nutritional deficiency – for example, BIDMC has administered intravenous vitamin  
832 B1 in over 8,000 separate participant encounters from 2002 until present. Despite this heavy usage,  
833 no adverse reactions were reported in any of the 8,000 participant encounters.

834  
835 The combination of vitamin C, hydrocortisone and vitamin B1 – To date, the only study of the  
836 combination of vitamin C, hydrocortisone and vitamin B1 was the above referenced study by Marik  
837 et. al.

838  
839 All procedures will take place at the study site. All research procedures and monitoring will be  
840 conducted by experienced personnel, and participants will be in the ICU given critical illness. This  
841 permits closer observation and more detailed monitoring by clinicians familiar with the care of  
842 participants experiencing and resuscitated from septic shock.

843

#### 844 **Blood Collection**

845 Most participants will have existing venous or arterial catheters in place and we will be able to collect  
846 blood from these ports, essentially eliminating the risks associated with blood collection. In the very  
847 rare case that a participant does not have an indwelling line, the risk of venipuncture is extremely  
848 low, and will not exceed the risk of clinical blood draws the participant will already be receiving.

849

#### 850 **Loss of Confidentiality**

851 All measures will be taken to ensure that no confidential information is released. All participant  
852 information will be stored in a password protected database to which only study investigators will  
853 have access. Additionally, all hard copies of study data will be kept in a locked office accessible only  
854 to study investigators. Thus, the risk of loss of confidentiality is very low.

855

## 856 **9. MONITORING**

### 857 **9.1 Institutional Review Board (IRB)**

858 The study will be reviewed and approved by the IRB at each participating site.

859

### 860 **9.2 Data Safety and Monitoring Board (DSMB)**

861 The DSMB will be responsible for safeguarding the interests of trial participants, assessing the  
862 safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the  
863 clinical trial. The DSMB will consist of three clinicians with critical care experience in the  
864 management of septic participants. An independent biostatistician/epidemiologist will prepare all  
865 DSMB reports. The DSMB members will be chosen such to avoid any financial or intellectual  
866 conflicts of interest. The DSMB will review deidentified data after every 50 participants are enrolled  
867 to assess for safety; unless there are group differences necessitating unblinding (as determined by  
868 the DSMB), the DSMB will be blinded to treatment groups. The trial will continue while the DSMB  
869 review data. After each review, the DSMB will create a short report to the steering committee with  
870 recommendations for continuation, modifications, or termination of the trial. Criteria for  
871 recommending termination will be at the discretion of the DSMB and there will be no formal  
872 statistical criteria for termination due to efficacy or safety. A detailed charter for the DSMB will be  
873 provided.

874

#### 875 DSMB Members

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904 Expertise: Critical Care Medicine

905  
906 **10 CLINICAL MONITORING PLAN**  
907 The detailed clinical monitoring plan has been developed and is available from the Coordinating  
908 Center upon request.

909 **11. TIMELINE AND ENROLLMENT**  
 910 **11.1 Timeline**



911  
 912 **11.2 Screening & Enrollment**

913 Enrollment at each site will be continuously monitored by the site investigator and the principal  
 914 investigator. Each site will be expected to maintain a screening log including all participants who  
 915 meet all eligibility criteria at that site. A standardized screening log will be provided to each site via  
 916 RedCap Cloud—thus allowing for continuous updating of the screening log and will allow capture of  
 917 all screening failures.  
 918

919 Enrollment will be competitive (i.e. without specific enrollment caps). Number of enrollments at each  
920 site will be shared with all sites on a monthly basis. Sites will be expected to complete all elements  
921 of the online CRF within 48-hours of each time point. In the case that a site continuously  
922 underperforms despite troubleshooting and feedback, the steering committee will evaluate whether  
923 enrollment will continue at that site.

924

## 925 **12. FUNDING**

926 Funding for the present trial is provided by the Good Ventures Foundation  
927 (<http://www.goodventures.org/>). The funding agency will have no role in the design and conduct of  
928 the study, collection, management, analysis, and interpretation of the data, preparation, review, or  
929 approval of the manuscript, or the decision to submit the manuscript for publication.

930

## 931 **13. PUBLICATION**

932 The manuscript will adhere to the CONSORT guidelines.<sup>72,73</sup> The principal investigator will be  
933 responsible for assigning authorship position and will follow authorship guidelines from the  
934 International Committee of Medical Journal Editors.<sup>82</sup> At a minimum, all members of the Steering  
935 Committee and all site Principal Investigators (for sites enrolling at least 10 participants) will be  
936 included in the primary author list. The main results will be presented at an international conference.  
937 The trial results will be shared with participating sites and via press releases but not directly with the  
938 participants.

939

## 940 **14. DATA SHARING**

941 Six months after the publication of the last results, all de-identified individual participant data will be  
942 made available for data sharing.<sup>83</sup> Procedures, including re-coding of key variables, will be put in  
943 place to allow for complete de-identification of the data. All relevant trial-related documents,  
944 including the protocol, data dictionary, and the main statistical code, will be shared along with the  
945 data. There will be no predetermined end date for the data sharing. Data will be available for any  
946 research purpose to all interested parties who have approval from an independent ethics review  
947 committee and who have a methodological sound proposal as determined by the steering  
948 committee of the current trial. Interested parties will be able to request the data by contacting the  
949 principal investigator. Authorship of publications emerging from the shared data will follow standard  
950 authorship guidelines from the International Committee of Medical Journal Editors<sup>82</sup> and might or  
951 might not include authors from the steering committee depending on the nature of their involvement.

952

## 953 **15. TASKS AND RESPONSIBILITIES**

954 Principal investigator and sponsor: Overall responsibility for protocol development, funding, budget  
955 overview, data dictionary development, ethical approval, trial registration, daily management, trial  
956 oversight and collection of adverse events, contact to the pharmacy, contact to Good Clinical  
957 Practice monitoring unit and the data and safety monitoring board, assessment of overall  
958 recruitments, potential recruitment of additional sites, data analysis, and dissemination and  
959 presentation of results.

960

961 Steering committee: Protocol development, funding, budget overview, data dictionary development,  
962 trial oversight, dissemination of results, responsibilities as principal investigator for short time  
963 periods.

964

965 Site investigators: Responsible for site-specific enrollment, evaluation of eligible patients not  
966 included, education of personnel at participating sites, reporting of site-specific issues or challenges  
967 to the principal investigator, participant consent for data collection, collecting and reporting data  
968 regarding adverse drug events.

969

970 Clinical team: Administration of the study drug, participant consent for data collection.

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1177 **Appendices**

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1179 **Appendix 1: Abbreviations**

- 1180 ICH.....International Conference on Harmonization
- 1181 SPIRIT.....Standard Protocol Items: Recommendations for Interventional Trials
- 1182 ACT.....Ascorbic Acid, Corticosteroids, and Thiamine
- 1183 ESRD.....End Stage Renal Disease
- 1184 SOFA.....Sequential Organ Failure Assessment
- 1185 IND.....Investigational New Drug
- 1186 FDA.....Food and Drug Administration
- 1187 ICU.....Intensive Care Unit
- 1188 SaO2.....Oxygen Saturation
- 1189 FiO2.....Fraction of Inspired Oxygen
- 1190 GCS.....Glasgow Coma Scale
- 1191 UOP.....Urine Output
- 1192 RRT.....Renal Replacement Therapy
- 1193 CAM.....Confusion Assessment Method
- 1194 NCHS..... National Center for Health Statistics
- 1195 NDI.....National Death Index
- 1196 AKI.....Acute Kidney Injury
- 1197 SD..... standard deviation
- 1198 CRF.....Case Report Form
- 1199 BIDMC.....Beth Israel Deaconess Medical Center (Coordinating Center)
- 1200 IRB.....Institutional Review Board
- 1201 DSMB.....Data Safety and Monitoring Board

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### CAM-ICU Worksheet

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if Present		
<p style="text-align: center;">Is the pt different than his/her baseline mental status? OR</p> <p>Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (i.e., RASS), GCS, or previous delirium assessment?</p>	Either question Yes →	<input type="checkbox"/>		
Feature 2: Inattention				
<p><b>Letters Attention Test</b> (See training manual for alternate Pictures)</p> <p><i>Directions:</i> Say to the patient, "I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand." Read letters from the following letter list in a normal tone 3 seconds apart.</p> <p style="text-align: center;"><b>S A V E A H A A R T</b></p> <p><b>Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."</b></p>			Number of Errors >2 →	<input type="checkbox"/>
Feature 3: Altered Level of Consciousness				
<p>Present if the Actual RASS score is anything other than alert and calm (zero)</p>	RASS anything other than zero →	<input type="checkbox"/>		
Feature 4: Disorganized Thinking				
<p><b>Yes/No Questions</b> (See training manual for alternate set of questions)</p> <ol style="list-style-type: none"> <li>1. Will a stone float on water?</li> <li>2. Are there fish in the sea?</li> <li>3. Does one pound weigh more than two pounds?</li> <li>4. Can you use a hammer to pound a nail?</li> </ol> <p><b>Errors are counted when the patient incorrectly answers a question.</b></p> <p><b>Command</b> Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If pt is unable to move both arms, for 2<sup>nd</sup> part of command ask patient to "Add one more finger"</p> <p><b>An error is counted if patient is unable to complete the entire command.</b></p>			Combined number of errors >1 →	<input type="checkbox"/>
Overall CAM-ICU				
Feature 1 <u>plus</u> 2 <u>and</u> either 3 <u>or</u> 4 present = CAM-ICU positive	Criteria Met →	<input type="checkbox"/> <b>CAM-ICU Positive</b> (Delirium Present)		
	Criteria Not Met →	<input type="checkbox"/> <b>CAM-ICU Negative</b> (No Delirium)		

## 2. PROTOCOL V2.1 (ORIGINAL)

Ascorbic Acid, Hydrocortisone, and Thiamine in Sepsis and Septic Shock  
– A Randomized, Double-Blind, Placebo-Controlled Trial

Acronym: **A**scorbic acid, **C**orticosteroids, and **T**hiamine in **S**epsis (**ACTS**) Trial

### CLINICAL TRIAL PROTOCOL

Version 2.1  
February 2<sup>nd</sup>, 2018  
IND: 136882

Clinical Trials.Gov Identifier: NCT03389555

Principal investigator:  
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Funded By:  
Open Philanthropy Project (<https://www.openphilanthropy.org/>)

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1354 **SYNOPSIS**

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1356 The “Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS)” trial is a multi-center, double-  
1357 blind, randomized clinical trial that aims to determine the impact of Vitamin C, Hydrocortisone, and  
1358 Vitamin B1 vs. Placebo on organ injury and mortality on participants with sepsis and septic shock.

1359 The trial will be conducted in accordance with all applicable national and international laws,  
1360 regulations, and guidelines The trial and this protocol is developed in accordance with the

1361 International Conference on Harmonization (ICH) guidelines<sup>1-3</sup> and the Standard Protocol Items:

1362 Recommendations for Interventional Trials (SPIRIT) statement<sup>4,5</sup>. The principal investigator wrote  
1363 the protocol with input from the steering committee. Any substantial changes or amendments to the  
1364 protocol will be clearly documented and communicated to all relevant parties.

1365

**TRIAL OVERVIEW**

**Title** Vitamin C, Hydrocortisone, and Vitamin B1 in Sepsis and Septic Shock – A Randomized, Double-Blind, Placebo-Controlled Trial (The ACTS Trial)

<b>Clinical Trials Number</b>	NCT03389555
<b>Sources of monetary or material support</b>	Open Philanthropy Project ( <a href="https://www.openphilanthropy.org/">https://www.openphilanthropy.org/</a> )
<b>Study Sites</b>	12-sites in the United States
<b>Condition studied</b>	Sepsis and septic shock
<b>Interventions</b>	Vitamin C (1.5g every 6 hours x 4-days), hydrocortisone (50mg every 6 hours x 4-days), and Vitamin B1 (100mg every 6 hours x 4-days)
<b>Comparator</b>	Placebo
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Adult participant (age ≥ 18 years)</li> <li>• Suspected (cultures drawn and antibiotic given) or confirmed (via culture results) infection</li> <li>• Receiving vasopressor (norepinephrine, phenylephrine, epinephrine, dopamine, vasopressin, or angiotensin II)</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Member of a protected population (pregnant, prisoner)</li> <li>• Known history of kidney stones within the past 1 year</li> <li>• Known history of chronic kidney disease (CKD stage ≥3b [GFR &lt; 45ml/hr])</li> <li>• Known history of G6PD deficiency</li> <li>• Known history of Hemochromatosis</li> <li>• Comfort Measures Only status</li> <li>• Anticipated death within 24-hours despite maximal therapy (as determined by the enrolling physician)</li> <li>• Receiving supplemental vitamin B1 in a dose greater than that contained in a multivitamin (&lt;2mg)</li> <li>• Clinical indication for steroids (e.g. chronic use) as determined by the clinical team providing this drug</li> <li>• Clinical indication for vitamin B1 as determined by the clinical team providing this drug</li> <li>• Known allergy to vitamin C, hydrocortisone, or vitamin B1</li> </ul>
<b>Study type</b>	Interventional Allocation: Randomized (1:1) Intervention model: Parallel group Masking: Double-blind
<b>Target sample size</b>	200 Participants (100/arm)
<b>Primary outcome</b>	Change in the Sequential Organ Failure Assessment (SOFA) score between enrollment and 72-hours
<b>Key secondary outcomes</b>	Incidence of renal failure during index ICU stay 30-day mortality

1368 **STEERING COMMITTEE**

1369

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1370 **Conflicts of interest**

1371 The members of the steering committee have no financial conflicts of interest related to the current  
1372 trial.

1373 **TRIAL SITES**

1374

1375 **Coordinating Center**

1376 **Beth Israel Deaconess Medical Center**

1377 330 Brookline Avenue

1378 Boston, MA 02215

1379 Site Investigator: Michael W. Donnino, MD

1380

1381 **Enrolling Sites\***

1382

<b>Hospital Name</b>	<b>Location</b>	<b>Site Principal Investigator</b>
Henry Ford Hospital	Detroit, MI	Joseph Miller, MD
DMC-Detroit Receiving Hospital	Detroit, MI	Rob Sherwin, MD
DMC-Sinai-Grace Hospital	Detroit, MI	Rob Sherwin, MD
UT Health, The University of Texas Health Science Center	Houston, TX	Pratik Doshi, MD
Mayo Clinic	Phoenix, AZ	Ayan Sen, MD
Beth Israel Deaconess Medical Center	Boston, MA	Ari Moskowitz, MD
Beaumont Hospital	Royal Oak, MI	Ron Otero, MD
Brigham and Women's Hospital	Boston, MA	Peter Hou, MD
Long Island Jewish Hospital Center - Queens	New York, NY	Maksim Korotun, MD
Long Island Jewish Hospital Center - Hyde Park	New York, NY	Ayelet Hilewitz, MD
Mount Auburn Hospital	Cambridge, MA	Jessica McCannon, MD
University of Pittsburgh	Pittsburgh, PA	David Huang, MD

1383 \*Depending on study progress, sites may be added or removed in the future.

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1406 **3. BACKGROUND AND SIGNIFICANCE**

1407 **1.1 Scope of the Problem**

1408 The worldwide incidence of sepsis has been estimated at more than 23 million cases<sup>6</sup> and sepsis  
1409 contributes to more than a third of all hospital deaths in the United States.<sup>7,8</sup> Mortality for those in  
1410 septic shock with elevated lactate is more than 40%.<sup>9</sup> In addition to high short-term mortality, sepsis  
1411 is associated with significant post-discharge morbidity and mortality.<sup>10-15</sup> The economic burden for  
1412 participants suffering from sepsis is staggering with an estimated yearly financial burden of \$17  
1413 billion.<sup>16</sup> Treatments are generally limited to antibiotics and intravenous fluids while providing  
1414 support to maintain organ function.<sup>17,18</sup>

1415

1416 **1.2 Existing Interventions**

1417 To date, numerous interventions have been tested for participants with sepsis and septic shock with  
1418 limited, if any, success.<sup>19-22</sup> Recently, three large studies found no benefit from early goal directed  
1419 therapy over usual care in emergency department participants with sepsis.<sup>23-25</sup> Other recent studies  
1420 focusing on hemodynamics, fluid therapy, and transfusions have also failed to show a significant  
1421 benefit in this participant population.<sup>26-28</sup> Previous studies focusing on immunomodulatory therapies or  
1422 drotrecogin alfa have likewise shown disappointing results.<sup>29-35</sup>

1423

1424 **1.3 The combination of vitamin C, hydrocortisone, and vitamin B1 may improve outcomes**

1425 In a before-and-after study exploring the effects of the combination of vitamin C, hydrocortisone, and  
1426 vitamin B1 in a cohort of participants with sepsis and septic shock, Marik et. al. found a remarkable  
1427 improvement in time to shock reversal ( $18.3 \pm 9.8$  hours vs.  $54.9 \pm 28.4$  hours), organ injury ( $\Delta$ SOFA  
1428  $4.8 \pm 2.4$  vs.  $0.9 \pm 2.7$ ), and mortality (8.5% vs. 40.4%) following implementation of the drug 'cocktail'  
1429 as compared to before implementation even after adjusting for potential confounders.<sup>36</sup> This study  
1430 joins other promising trials of individual elements of this drug combination. In a trial of vitamin B1 in  
1431 septic shock, there was a substantial reduction in mortality and organ injury (particularly kidney  
1432 injury) in those with vitamin B1 deficiency and septic shock who were given vitamin B1 as compared  
1433 to placebo.<sup>37,38</sup> In addition, several studies of vitamin C alone have shown promise in critically ill  
1434 populations<sup>39-42</sup> and a recent meta-analysis of corticosteroids in sepsis suggests potential benefit.<sup>43</sup>

1435

1436 **1.4 Physiologic Rationale**

1437 The combination of vitamin C, hydrocortisone, and vitamin B1 is hypothesized to improve outcomes  
1438 in sepsis through a number of mechanisms.<sup>36</sup> Vitamin C is an important contributor to endothelial  
1439 integrity and severe deficiency states (e.g. scurvy) can result in endothelial breakdown with resultant  
1440 vascular leak and edema.<sup>44,45</sup> In addition, vitamin C is a potent anti-oxidant and is integral to  
1441 endogenous vasopressor synthesis.<sup>36</sup> Hydrocortisone, a potential adjunctive therapy in septic  
1442 shock<sup>46,47</sup>, may act synergistically with vitamin C.<sup>48,49</sup> Vitamin B1, a key cofactor of pyruvate  
1443 dehydrogenase, is a critical component of metabolic dysfunction without which a shift towards  
1444 anaerobic energy production occurs.<sup>50</sup> Vitamin B1 is also a necessary component of the pentose  
1445 phosphate pathway, which plays a role in reducing oxidative stress.<sup>51,52</sup> While the physiologic effects  
1446 of these drugs given in combination is not entirely known, we hypothesize that there will be  
1447 synergistic effects with respect the metabolic resuscitation of sepsis.

1448 **4. TRIAL DESIGN**

1449 **2.1 Overview**

1450 This will be an investigator-initiated, multicenter, randomized, placebo-controlled, parallel group,  
1451 double-blind, superiority trial of vitamin C, hydrocortisone, and vitamin B1 vs. placebo in participants  
1452 with sepsis and septic shock. A total of 200 adult participants will be enrolled. The primary outcome  
1453 will be the change in SOFA score between enrollment and 72-hours. Key secondary outcomes  
1454 include the incidence of renal failure during the index ICU stay and survival at 30 days.

1455

1456 **2.2 Allocation**

1457 Participants will be randomized in a 1:1 ratio to either the combination of vitamin C, hydrocortisone,  
1458 and vitamin B1 or placebo in blocks with random sizes of 2 or 4. The randomization will be stratified  
1459 according to site.<sup>53</sup> An independent statistician will create the randomization list using a random  
1460 number generator. The complete list will only be shared with an independent pharmacy consultant,  
1461 who will not be involved in clinical care. The pharmacy consultant and the independent statistician  
1462 will both store the randomization list. The research pharmacy at each enrolling site will receive a  
1463 site-specific randomization list.

1464

1465 **2.3 Intervention**

1466 *2.3.1 Vitamin C, Hydrocortisone, and Vitamin B1*

1467 The study drugs will consist of vitamin C (1.5g every 6 hours x 4-days), hydrocortisone (50mg every 6  
1468 hours x 4-days), and vitamin B1 (100mg every 6 hours x 4-days).

1469

1470 *2.3.2 Placebo*

1471 The placebo will consist of matching volumes of normal saline (0.9% NaCl). See below section 4.4  
1472 for specifics of drug and placebo preparation.

1473

1474 **2.4 Blinding**

1475 The trial will be double-blind; participants, investigators, and the clinical team will be blinded to the  
1476 allocation. Only the pharmacy providing the study drug will be aware of the allocation. The  
1477 pharmacy will not be involved with clinical care or outcome evaluation.

1478

1479 As vitamin C possess a yellow tinge, the bags containing the vitamin C/placebo will be covered with  
1480 light-protective bags. In testing, after dilution there is not distinguishing characteristics of the vitamin  
1481 C vs. placebo in the IV tubing. Vitamin C, hydrocortisone, and vitamin B1 are not known to have  
1482 distinctive rapid effects which could lead to unblinding.

1483

1484 The decision to unblind will be at the complete discretion of the treating physician and clinical team.  
1485 If a clinical team wishes to unblind a participant (e.g. if anaphylaxis occurs), they will contact the  
1486 research pharmacy who will reveal the study group to the clinical team (but the research team will  
1487 remain blinded). However, we do not expect many scenarios where emergency unblinding will be  
1488 necessary. In case unblinding occurs, the reason(s) will be clearly documented in the case report  
1489 form. The patient will no longer receive study medications, but will be followed for outcomes.

1490

1491 **4.5 Regulatory Issues**

1492 An Investigational New Drug (IND) application was submitted to and approved by the Food and  
1493 Drug Administration (FDA) for the study of vitamin C, hydrocortisone, and vitamin B1 in sepsis and  
1494 septic shock (IND # 136882).

1495

1496 The trial has been registered on ClinicalTrials.gov: NCT03389555

1497

1498

1499 **3. SETTING AND PARTICIPANT POPULATION**

1500 **3.1 Setting**

1501 The trial will be conducted at 12 hospitals in the United States. Additional sites might be recruited if  
1502 needed.

1503

1504 **3.2 Inclusion criteria**

1505 Inclusion criteria:

1506 4) Adult participant (age  $\geq$  18 years)

1507 5) Suspected (cultures drawn and antibiotic given) or confirmed (via culture results) infection

1508 6) Receiving (continuous infusion) vasopressor (norepinephrine, phenylephrine, epinephrine,  
1509 dopamine, or vasopressin)

1510

1511 **3.3 Exclusion criteria**

1512 Exclusion criteria:

1513 13) Member of a protected population (pregnant, prisoner)

1514 14) Known history of kidney stones within the past 1 year (not including incidentally noted stones  
1515 noted on imaging studies)

1516 15) Known history of chronic kidney disease (CKD stage  $\geq$ 3b [GFR < 45ml/hr])

1517 16) Known history of G6PD deficiency

1518 17) Known history of Hemochromatosis

1519 18) Comfort Measures Only status

1520 19) Anticipated death within 24-hours despite maximal therapy (as determined by the enrolling  
1521 physician)

1522 20) Receiving supplemental vitamin B1 in a dose greater than that contained in a multivitamin  
1523 (<2mg)

1524 21) Clinical indication for steroids (e.g. chronic use) as determined by the clinical team providing  
1525 this drug

1526 22) Clinical indication for vitamin B1 as determined by the clinical team providing this drug

1527 23) Known allergy to vitamin C, hydrocortisone, or vitamin B1

1528

1529

1530 Justification of Inclusion and Exclusion Criteria: The inclusion criteria were chosen to isolate a septic  
1531 participant population with high risk of organ injury and death. The exclusion criteria were chosen to  
1532 minimize the risk of potential harm and to ensure that participants enrolled do not already have  
1533 chronic end-stage renal failure with a high likelihood of early need for renal replacement therapy. By  
1534 evaluating this high-risk population (i.e., most likely to die), we will target those most likely to benefit  
1535 and therefore increase the probability of showing efficacy.<sup>19</sup>

1536

1537 **3.4 Pregnancy**

1538 Hydrocortisone is considered pregnancy class C on the basis of animal studies showing an  
1539 association between prenatal parenteral hydrocortisone use and risk of cleft-palate. In addition,  
1540 there are concerns about effects of hydrocortisone on fetal growth and the possibility of neonatal  
1541 adrenal insufficiency. The effects of high-dose vitamin C and thiamine in pregnancy are not entirely  
1542 known. As such, participants who are pregnant will be excluded from the study. Prior to enrollment,  
1543 all participants of potentially child-bearing potential (women aged <45 years<sup>54</sup>) will be required to  
1544 have a negative serum or urine HCG test (generally performed as standard-of-care).

1545

1546 We will additionally inform all women of child-bearing potential who are randomized in this study  
1547 that we recommend they remain abstinent or use two forms of birth control during the study period  
1548 and for a period of 48-hours after the last dose of study drug.

1549 **4. TRIAL PROCEDURES**

1550 **4.1 Participant Identification**

1551 Screening will be performed in the emergency department and intensive care units (ICUs) with the  
1552 assistance of electronic screening mechanisms . Detailed screening logs, with reason(s) for  
1553 exclusion will be kept at each site and reported in the final publication.  
1554

1555 We anticipate that all patients, as part of standard-of-care for the septic patient, will have a urine or  
1556 serum HCG test performed (if a female of child-bearing age). If this test is not sent as part of  
1557 standard-of-care, it should be sent prior to consent.  
1558

1559 **4.2 Consent proecdures**

1560 Informed, written consent will be obtained for all participants prior to enrollment.  
1561

1562 After it is determined that they meet all inclusion criteria and no exclusion criteria, the participant (or  
1563 legally authorized representative [LAR] if the participant is not able to provide consent) will be  
1564 approached for written informed consent by a physician co-investigator from the team. The  
1565 investigator will provide the participant/representative information regarding the background and  
1566 significance of the study, eligibility criteria, and a description of the protocol. To ensure we are  
1567 correctly identifying the potential participant's LAR, we communicate with members of the clinical  
1568 team. The consent process may need to be modified based on site-specific IRB recommendations.  
1569

1570 The name of the study investigator obtaining consent will be clearly documented, and this person  
1571 will sign the informed consent document and provide the date and time of their signature. If a  
1572 physician is performing remote consent, then a copy of the consent form will be signed as soon as  
1573 he/she is physically present. Signed copies of the consent form will be given to the  
1574 participant/surrogate, and the original consent document will be stored in the secure study file. In  
1575 obtaining and documenting informed consent, each investigator will comply with the applicable  
1576 regulatory requirements and adhere to the ethical and Good Clinical Practice principles that have  
1577 their origin in the Declaration of Helsinki.  
1578

1579 **4.3 Randomization**

1580 After consent is obtained, the research team will notify the local research pharmacy. The research  
1581 pharmacy will be in possession of the randomization list and will determine which arm (intervention  
1582 vs. placebo) the participant will be enrolled in.  
1583

1584 **4.4 Drug preparation and administration**

1585 The vitamin C and vitamin B1 will be mixed together in 100ml of normal saline and administered  
1586 intravenously over 45-60 minutes. The hydrocortisone will be given intravenously as a push-dose in  
1587 1ml of saline over 1-2 minutes. The placebo will be given using techniques and volumes matching  
1588 those of the study medications.  
1589

1590 All study medications will be continued for 4-days or until the participant expires or leaves the  
1591 intensive care unit.  
1592

1593 *4.4.1 Contingencies and Participant Withdrawal*

- 1594
- 1595 • In the unlikely event that a participant is discharged alive from the hospital prior to 4 days after  
1596 enrollment, all study medications will be stopped. The participant will remain in the study and will  
1597 be followed for outcomes.
  - 1598 • Hydrocortisone is occasionally used for refractory septic shock. If the clinical team opts to provide a  
1599 participant hydrocortisone, the hydrocortisone will be given open-label but the vitamin C/B1 will  
remain randomized and blinded. In this case, the research team will ensure that study

1600 hydrocortisone/placebo is replaced by open-label hydrocortisone. The participant will remain in  
1601 the study and will be followed for outcomes.  
1602 • If the clinical team decides to give the participant either vitamin B1 or vitamin C for clinical  
1603 purposes, further administration of study meds will be stopped. The participant will remain in the  
1604 study and will be followed for outcomes.  
1605 • If a participant withdraws from the study, further administration of study meds will be stopped.  
1606 Data collected prior to withdrawal will be maintained but additional data will not be collected.  
1607

#### 1608 **4.5 Specimen collection procedures**

##### 1609 *4.5.1 Timing and volume of blood draw*

1610 All participants will have a blood samples collected at four time-points and urine samples at two  
1611 time-points (if not already available as part of routine clinical care). Blood will be obtained by  
1612 venipuncture, or from an existing venous or arterial catheter. Urine will be collected via clean catch  
1613 urine or via catheter.  
1614

##### 1615 Specimen Collection Time Points

- 1616 1. T1=0 hrs (just before study drug administration)
  - 1617 2. T2=24 hrs (+/- 2 hrs)
  - 1618 3. T3=72 hrs (+/- 2 hrs)
  - 1619 4. T4=120hrs (+/- 12hrs)
- 1620

##### 1621 *4.5.2 Specimen samples*

1622 At the T1, T2, T3, and T4 time points, blood will be sent for complete blood count (including  
1623 hemoglobin, white blood cell count, platelet count), a serum chemistry (including sodium,  
1624 potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, aspartate transaminase,  
1625 alanine transaminase, and total bilirubin), and a venous blood gas to measure lactate. These tests  
1626 will be performed by the clinical laboratory at each site. As many of these laboratory tests are  
1627 commonly obtained for clinical purposes, these tests do not need to be repeated if a result is  
1628 available from the clinical care of the participant within 2 hours of the time point (or within 12 hours  
1629 of the T4 time-point).  
1630

1631 In addition to traditional clinical markers, 25ml of blood will be obtained for future biomarker analysis  
1632 (including inflammatory biomarkers, markers of endothelial function, and markers of mitochondrial  
1633 function), and measurement of vitamin C, vitamin B1, and cortisol levels. Levels of vitamin C,  
1634 vitamin B1, and cortisol will be measured at time T1 and time T3 only. 20ml of urine will be collected  
1635 for future biomarker analysis at T1, T2, and T3.  
1636

1637 If performed as part of standard-of-care, results of urinalysis and urine sediment testing will be  
1638 collected prior to enrollment.  
1639

##### 1640 *4.5.3 Biomarker tube initial processing and shipping*

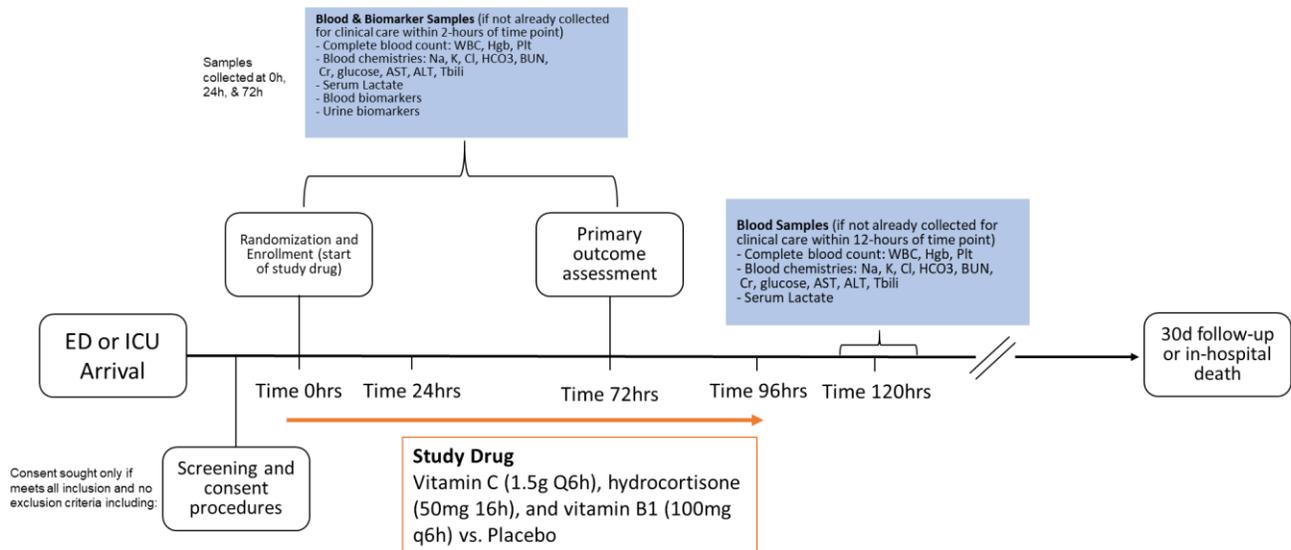
1641 Please see accompanying blood collection standard operating procedure for full details. In brief,  
1642 15ml of blood will be drawn into EDTA tubes and 10ml of blood will be drawn into a corvac tube.  
1643 From one of the EDTA tubes, 3ml of whole blood will be initially drawn and separated into 3x 1ml  
1644 aliquots. Plasma will then be isolated from the EDTA tube(s) and aliquoted into cryovials as follows:  
1645 2x 1ml aliquots and the remainder in 0.5ml aliquots. Serum will then be isolated from the corvac  
1646 tube, and separated into 1ml aliquots. Cryovials will be protected from light and frozen at -80°C until  
1647 processing. An additional 20ml of urine will also be collected, centrifuged, and separated into 1ml  
1648 aliquots then frozen at -80°C until processing.  
1649

1650 Sites will be expected to ship frozen samples to the coordinating center after every 5 enrollments.  
1651 The coordinating center will assist with all shipping procedures.

1652

#### 1653 4.6 Study flow diagram

1654



1655

1656

#### 1657 4.7 General Sepsis Management

1658 Investigators should follow local sepsis management guidelines. No specific sepsis bundle is  
1659 required by this study, however the early administration of antibiotics, maintenance of a mean  
1660 arterial pressure  $\geq 65$ mmHg with a combination of volume resuscitation and vasopressors, and early  
1661 source control are recommended—as detailed in the Surviving Sepsis Guidelines.<sup>55</sup> Elements of  
1662 sepsis care should be reported on the online case report form (CRF).

1663

#### 1664 4.8 Glucometer use during the study period

1665 High dose vitamin C has been shown to falsely elevate glucose level readings when measured with  
1666 certain point-of-care glucometers employing glucosedehydrogenase-pyrroloquinoline quinone  
1667 amperometric methods<sup>56</sup>. Some commonly used glucometer brands using this approach include  
1668 Accu-Chek (Roche Diagnostic) and Optium (Abbott Diabetes Care) (but not StatStrip; Nova  
1669 Biomedical). While the effects of high-dose vitamin C on glucometer readings have been seen  
1670 primarily at higher doses of vitamin C than are intended for use in this trial,<sup>56</sup> we recommend that  
1671 sites explore what glucometers are in use in local ICUs. If locally used glucometers may be  
1672 impacted by high serum concentrations of vitamin C (as determined by the manufacturer), we  
1673 recommend that clinical teams caring for enrolled participants be alerted to the possibility of falsely  
1674 elevated blood-glucose levels when measured by glucometer. If there is a clinical concern about a  
1675 glucose reading obtained via glucometer, a serum glucose should be obtained which will not be  
1676 impacted by vitamin C. In the event of an emergency related to suspected hypoglycemia, glucose  
1677 should be immediately given while a serum glucose level is pending.

1678

### 1679 5. OUTCOMES

#### 1680 5.1 Definitions

##### 1681 5.1.1 Primary Outcome

1682 The primary outcome will be the absolute change in the Sequential Organ Failure Assessment  
1683 (SOFA) score from enrollment (time=0) to 72 hours after drug administration. The SOFA score will  
1684 be defined using a modification in which the SaO<sub>2</sub>/FiO<sub>2</sub> ratio is substituted for the PaO<sub>2</sub>/FiO<sub>2</sub> ratio

1685 as has been previously described.<sup>57</sup> This modified score will be used so that participants without an  
 1686 existing arterial catheter can be spared arterial puncture.  
 1687

Points	SaO <sub>2</sub> */FiO <sub>2</sub> <sup>§</sup>	Blood Pressure	GCS <sup>  </sup>	Bilirubin (mg/dL)	Creatinine (mg/dL)	Platelets (x10 <sup>3</sup> µL)
1	<512	< 70 mm/Hg	13–14	1.2–1.9	1.2 – 1.9	<150
2	<357	dopamine ≤ 5 µg/kg/min or dobutamine (any dose)	10–12	2–5.9	2.0 – 3.4	<100
3	<214	dopamine > 5µg/kg/min, epinephrine/norepinephrine ≤ 0.1 µg/kg/min	6–9	6–11.9	3.5 – 4.9 Or UOP <sup>†</sup> <500ml/day	<50
4	<89	dopamine > 15, epinephrine/norepinephrine > 0.1 µg/kg/min	<6	>12	> 5.0 UOP <sup>†</sup> <200ml/day	<20

1688 \*SaO<sub>2</sub>=Oxygen saturation (%); § = Fraction of inspired oxygen (%); || = Glasgow Coma Scale; † = Urine Output  
 1689

1690 **5.1.2 Key Secondary Outcomes**

1691 Incidence of Acute Renal Failure – Renal failure will be defined as the development of Kidney  
 1692 Disease Improving Global Outcomes [KDIGO] Stage 3 acute kidney injury during the index ICU stay  
 1693 after study enrollment.<sup>58</sup>  
 1694

KDIGO Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 µmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg per hour for more than 6 hours
2	Increase in serum creatinine to more than 200% to 300% (> 2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 hours
3	<b>Increase in serum creatinine to more than 300% (&gt; 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl [≥ 354 µmol/l] with an acute increase of at least 0.5 mg/dl [44 µmol/l])</b>	<b>Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours OR New renal replacement therapy (RRT)</b>

1695  
 1696 30-Day Mortality – Mortality at 30-days. This will be assessed by review of the medical records if the  
 1697 participant remains in the hospital or if the participant expired while in the hospital. If the participant  
 1698 was discharged, 30-day mortality will be assessed by contacting the participant by phone or by  
 1699 searching the National Center for Health Statistics (NCHS) National Death Index (NDI) consistent  
 1700 with a recent multicenter phase III trial in sepsis.<sup>23</sup> Phone calls will be made by the research team at  
 1701 each site.  
 1702

1703 **5.2 Rationale for Outcomes**

1704 **Change in SOFA score:** Organ failure is highly associated with mortality<sup>59</sup> and improvement in  
 1705 organ function is a key goal for critical care physicians. In the study by Marik et al.<sup>36</sup>, participants  
 1706 who received the 3-drug regimen had substantial improvements in the trajectory of organ failure  
 1707 over the first 72-hours of their ICU stay. If the combination of vitamin C, hydrocortisone, and vitamin  
 1708 B1 can improve organ function in the first 72-hours following ICU admission, we believe that  
 1709 clinicians will likely quickly adopt this safe and inexpensive therapy. Importantly, this outcome can  
 1710 be measured early in the hospital stay and is therefore less likely to be affected by other potential  
 1711 elements of hospital care that can affect more distal outcomes (e.g., mortality).

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**Kidney Injury:** Renal failure has been estimated to occur in 23% of participants with sepsis and over 50% of participants with septic shock.<sup>60</sup> In studies of participants with septic shock, there is a step-wise increase in mortality with worsening acute kidney injury (AKI).<sup>61</sup> In addition, many participants who experience renal injury during septic shock do not recover renal function prior to hospital discharge and may require long term dialysis. As both data from the study by Marik et. al.<sup>36</sup> and a separate study of vitamin B1 in septic shock<sup>38</sup> have shown substantial improvements in renal outcomes, kidney failure is a natural secondary outcome and one that could change practice independently from other factors – in other words, many clinicians would likely provide this therapy if they knew that kidney function could be protected, since this organ is vital to long-term health.

**Mortality:** Finally, we will measure 30-day mortality. We anticipate that the combination of vitamin C, hydrocortisone, and vitamin B1 will reduce mortality in this high-risk population.

### **5.3 Additional Secondary Outcomes**

#### *5.3.1 Additional secondary outcomes*

Additional secondary outcomes will include length of ICU stay, length of hospital stay, ventilator-free days over the first 7-days after enrollment, shock-free days over the first 7-days after enrollment, and the incidence of delirium on day #3 of the ICU stay (as assessed using the Confusion Assessment Method [CAM-ICU] system).<sup>62</sup> Sites at which the CAM-ICU is performed daily as part of standard-of-care should assess whether delirium occurs on any day during the initial ICU stay. See Appendix #2.

#### *5.3.2 90-day follow-up for Quality of Life assessment*

Sites may choose to participate in a long-term outcomes substudy exploring the effects of ascorbic acid, hydrocortisone, and thiamine vs. placebo on quality of life following sepsis. If a site chooses to participate, a trained research assistant/investigator at the site (who is blinded to treatment arm) will contact all participants who were alive at 30-days, and perform the SF-36 at day 90 following enrollment. The SF-36 is a 36-Item Short-Form Health Survey (SF-36), a validated survey of general quality of life in adults, can be administered in person or over the telephone by research personnel. It measures eight different dimensions: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions, as well as one question asking about perceived changes in health. The telephone version of the 36-Item Short-Form Health Survey has been validated<sup>63,64</sup> and used in sepsis.<sup>65-68</sup>

### **5.4 Safety**

#### *5.4.1 Definitions*

The following definitions will be used<sup>69</sup>:

Adverse event: any untoward medical occurrence in a participant to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment

Serious adverse event: any untoward medical occurrence that at any dose requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death

Unexpected serious adverse event: a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information

1762 **5.4.2 Specific adverse event data collection**

1763 To assess specific and potentially serious adverse events that may be related to the combination of  
 1764 the study medications, we will collect data on the following:  
 1765

Serious Adverse Event	Definition
Hyperglycemia	Serum glucose >300mg/dl in the first 120-hours after enrollment
Hypernatremia	Serum sodium (> 150 mmol/L) occurring in the first 120-hours after enrollment
New Infection	As determined by the site principal investigator at each site. Should be a new organism or site of infection and believed to be unrelated to the initial presenting infectious source. Many will have the initiation of new antibiotics or a change in antibiotics.
Catheter-site	
Lung	
Gastrointestinal	
Urinary tract	
Other	
Serious allergic reaction	Anaphylaxis or other allergic reaction requiring systemic corticosteroids. Allergic reaction should be related (or suspected to be related) to the study medication
Renal calculus	Development of a renal calculus between enrollment and 30-day follow-up (based on question asked during follow-up phone call).

1766

1767 **5.4.3 Adverse Event Reporting**

1768 Any Unexpected Serious Adverse Events thought to be related to the study drug (as determined by  
 1769 the site investigator) will be reported to the and all above listed Serious Adverse Events will be  
 1770 reported to the coordinating site, the data safety monitoring board (see below), and the regulatory  
 1771 authorities as applicable (i.e. IRB, FDA). Reporting of Serious Adverse Events will be done in  
 1772 aggregate after every 50 patients are enrolled. Unexpected Serious Adverse Event will additionally  
 1773 be reported to the coordinating site within 72-hours.  
 1774

1774

1775 **5.4.5 Safety Monitoring Labs**

1776 As detailed above, safety monitoring labs will be obtained at 120-hours, after completion of the  
 1777 study protocol.  
 1778

1778

1779 **6. SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS PLAN**

1780 **6.1 Sample size calculation**

1781 The study has been powered to have at least 80% power for the primary outcome and all key  
 1782 secondary outcomes as follows:  
 1783

1783

1784 **SOFA Score:** Based on preliminary data<sup>36</sup>, we conservatively anticipate a decrease in SOFA score  
 1785 of 6 (standard deviation [SD]: 4) in the treatment group and 4 (SD: 2) in the placebo group. With  
 1786 these estimates, enrollment of **200 participants (100/arm)** at an alpha of 0.05 and using a t-test  
 1787 with unequal variance, the trial will provide > 99% power to detect a statistical significant difference  
 1788 between groups.  
 1789

1789

1790 **Kidney Injury:** Based on preliminary data from our study of vitamin B1 in septic shock,<sup>38</sup> we  
 1791 anticipate that 30% of participants in the treatment group and 55% in the placebo group will have  
 1792 renal failure which will result in a 94% power for this outcome. This calculation and following  
 1793 calculation were performed using the Fisher's exact test.  
 1794

1794

1795 **Mortality:** Based on preliminary data<sup>37,70,71</sup>, we anticipate that the control group will have a mortality  
 1796 of 40%. We estimate a treatment effect of 50% (risk ratio: 0.50) resulting in a mortality of 20% in the  
 1797 treatment group. With these estimates, 182 participants will lead to 80% power. To further increase  
 1798 the trial's power and due to potential loss-to-follow-up, we will aim to enroll 200 participants. These

1799 estimates are conservative compared to the Marik et al. study which found a treatment effect  
1800 corresponding to a risk ratio of 0.21 which persisted in adjusted analysis.<sup>36</sup>  
1801

## 1802 **6.2 Statistical analysis plan**

### 1803 *6.2.1 General considerations*

1804 The statistical analyses and reporting will adhere to the CONSORT guidelines.<sup>72,73</sup> All tests will be  
1805 two-sided, a p-value < 0.05 will be considered significant, and all confidence intervals will have 95%  
1806 coverage. All analyses will be conducted on a modified intention-to-treat basis only including  
1807 participants receiving at least the first dose of the study medications. In a double-blind trial, this  
1808 approach is unbiased while increasing precision.<sup>74</sup> The two groups will be compared in relation to  
1809 baseline characteristics using descriptive statistics.  
1810

1811 The persons conducting the statistical analysis will be blinded to the randomized allocation. Groups  
1812 will be designated as “A” and “B” until all pre-specified analyses are performed and shared with all  
1813 authors and the Data Safety Monitoring Board.  
1814

### 1815 *6.2.2 SOFA score and renal failure*

1816 The change in SOFA score will be calculated and compared between groups using the Wilcoxon  
1817 Rank Sum test (if the change is not normally distributed) or by a t-test if the change is approximately  
1818 normally distributed. Fisher’s exact tests will be used to compare the incidence of renal failure  
1819 during the index ICU stay.  
1820

1821 If a participant expires prior to the 72-hour time point, SOFA scores will be imputed based on a pre-  
1822 defined plan as follows. If a participant expires before 24-hours has elapsed, a 20% increase from  
1823 baseline will be imputed. If a participant expires between 24-hours and 48-hours, a 15% increase  
1824 from the 24-hour time point will be imputed. If a participant dies between 48-hours and 72-hours, a  
1825 20% increase from the 24-hour time point will be imputed. Sensitivity analyses will be performed  
1826 using various other imputation techniques. Specifically, we will perform 1) a sensitivity analysis in  
1827 which the worst possible SOFA score (score of 24) is imputed for those participants who expire, 2) a  
1828 sensitivity analysis in which the last SOFA score for participants who expire will be carried forward,  
1829 and 3) a sensitivity analysis in which only those patients who survive to 72-hours are included.  
1830 These sensitivity analyses were chosen to model ‘worst-possible’ and ‘best-possible’ scenarios. For  
1831 the secondary outcome of renal failure, participants who expire during their ICU stay will be  
1832 assessed to have developed renal failure if they demonstrated any degree of unresolved KDIGO  
1833 acute kidney injury prior to death. If there was no evidence of acute kidney injury prior to death or if  
1834 kidney injury had fully resolved, these participants will be assessed as not having developed renal  
1835 failure.  
1836

### 1837 *6.2.3 30-day mortality*

1838 Survival until 30 days will be analyzed using survival analysis. Participants lost to follow-up will be  
1839 censored and the censoring will be assumed non-informative. Results will be presented with  
1840 Kaplan-Meier curves and the groups compared using the log-rank test.<sup>75</sup> Hazard ratios with 95%  
1841 confidence intervals will be obtained using Cox’s proportional hazards models.<sup>76</sup> The proportional  
1842 hazards assumption will be verified by visual inspection of the Kaplan-Meier curves and statistically  
1843 by including a product term (i.e. “interaction”) between the treatment group variable and the natural  
1844 logarithm of time in the model.<sup>77</sup> If the proportional hazards assumption is not met, only the Kaplan-  
1845 Meier curves and the p-value from the log-rank test will be presented.  
1846

1847 Adverse events and other binary outcomes will be presented and analyzed like renal failure.  
1848

### 1849 *6.2.4 Additional Secondary Analyses*

1850 Both ICU and hospital length of stay will be compared using Wilcoxon Rank Sum tests. Ventilator  
1851 and shock free days over the first 7-days after enrollment will likewise be compared using the

1852 Wilcoxon Rank Sum given that the data will likely be not normally distributed. In these latter two  
1853 analyses, patients who expire prior to 7-days will be assessed to have 0 ventilator or shock free  
1854 days if they had died while on a ventilator or vasopressor respectively. The incidence of delirium will  
1855 be compared using the Fisher's exact test. For the quality-of-life outcome (i.e. 90-day SF-36), the  
1856 primary analysis will only include patients with available data. As a secondary analysis, multiple  
1857 imputation will be used to estimate SF-36 scores in all patients not known to be dead at 90 -days.  
1858

#### 1859 *6.2.5 Subgroup analyses*

1860 The analysis will include three pre-defined subgroup analyses for the primary and key secondary  
1861 outcomes according to 1) participants with initially high SOFA scores ( $\geq 9$ ). This cut-off was chosen  
1862 to represent a population with a  $\geq 50\%$  predicted likelihood of mortality<sup>78</sup> 2) baseline vitamin B1  
1863 deficiency and 3) baseline adrenal insufficiency. We will not plan to perform a subgroup analysis  
1864 according to vitamin C deficiency, as prior work has shown that the vast majority of participants with  
1865 septic shock have vitamin C levels below the reference range.<sup>36</sup> Vitamin B1 deficiency will be  
1866 defined as a plasma vitamin B1 level  $\leq 7$  nmol/L as has been previously described.<sup>37</sup> Adrenal  
1867 insufficiency will be defined as a cortisol level  $< 10\mu\text{g/dL}$ .<sup>43</sup> The trial is not powered to detect  
1868 subgroup differences and these will be considered exploratory and hypothesis generating.  
1869

#### 1870 *6.2.6 Statistical stopping criteria*

1871 Since the primary outcome is not mortality, there will be no formal stopping criteria for efficacy.  
1872 There will be no predefined stopping criteria for futility since enrollment of the full cohort might allow  
1873 for detection of efficacy in subgroups or in other outcomes even if the primary outcome is negative.  
1874

## 1875 **7. DATA COLLECTION AND MANAGEMENT**

### 1876 **7.1 Data collection process**

1877 Data collection will be the responsibility of the individual site investigators with oversight from the trial  
1878 coordinating center. Most variables (i.e. demographics, sepsis characteristics and laboratory  
1879 results) will be obtained prospectively from the electronic medical record. 30-day follow-up  
1880 regarding safety and mortality end-points will be obtained via telephone call post-discharge (unless  
1881 the participant remains in the hospital at 30-days). Data will be entered directly into the online  
1882 database software (see below).  
1883

### 1884 **7.2 Variables**

1885 Will be provided on the online CRF. A PDF version is available upon request.  
1886

### 1887 **7.3 Data quality and validity**

1888 Data quality and validity will be optimized by using a detailed data dictionary which will be  
1889 distributed to all sites. Data quality will be monitored both centrally by the coordinating site and  
1890 locally by each site principal investigator.  
1891

### 1892 **7.4 Data storage and security**

1893 The database application we will use is REDCap Cloud (<https://www.redcapcloud.com/>). REDCap  
1894 Cloud is a professional database that provides a user-friendly interface. The REDCap Cloud data  
1895 management system is secure, fully compliant with all regulatory guidelines, and includes a  
1896 complete audit-trail for data entry validation. Through these mechanisms, as well as relevant  
1897 training for all involved parties, participant confidentiality will be safeguarded. All members of the  
1898 research team will be required to complete standardized training in REDCap cloud, which will be  
1899 documented within the software.  
1900

1901 The consent form and other trial documents for each participant will initially be stored in a secure,  
1902 locked place at the individual sites. Participating sites will be responsible for maintaining their own  
1903 trial documents and study materials (e.g. signed ICFs, site logs etc). Trial documents generated at  
1904 the Coordinating Center will be maintained the Coordinating Center. Following completion of the

1905 trial, documents will be maintained for a period of at least 2-years at each site per FDA regulations  
1906 (or longer depending on local IRB guidelines).  
1907

## 1908 **8. ETHICAL CONSIDERATIONS**

### 1909 **8.1 Risks and Benefits**

#### 1910 *8.1.1 Potential benefits*

1911 **Potential Benefits to Individual Participant:** Assuming our hypothesis is correct and our results are  
1912 comparable to those previously published<sup>36</sup>, individual participants enrolled in our study and  
1913 randomized to the treatment arm will benefit from a better trajectory of organ failure and improved  
1914 mortality. As many participants who survive an initial episode of sepsis will have a future admission for  
1915 sepsis, participants participating in this study but randomized to the placebo arm may see a future  
1916 benefit from knowledge gained.  
1917

1918 **Potential Benefits to Society:** Septic shock remains a highly morbid clinical condition for which there  
1919 is no specific therapy. Our study, assuming our hypothesis is confirmed, will provide strong support for  
1920 the widespread adoption of vitamin C, corticosteroids, and vitamin B1 for participants with septic  
1921 shock. This, in turn, will significantly improve participant outcomes and reduce the global burden of  
1922 death related to septic shock. Thus, even if participants are randomized to the placebo arm, their  
1923 involvement with this study has tremendous potential benefits for society as whole. If vitamin C,  
1924 corticosteroids, and vitamin B1 are found to be neutral or harmful (the latter being highly unlikely),  
1925 society will benefit as the study will likely prevent the widespread dissemination of an ineffective  
1926 medication combination.  
1927

#### 1928 *8.1.2 Potential harms*

##### 1929 **Study Drug**

1930 Vitamin C – Ascorbic acid is a water-soluble essential vitamin that is safe even at high doses.  
1931 Nevertheless, adverse effects related to high-dose ascorbic acid have been described. These  
1932 adverse effects include diarrhea/abdominal bloating, increased oxalate excretion, iron overload in  
1933 participants with hemochromatosis, and hemolysis in participants with G6PD deficiency.<sup>79</sup> We  
1934 exclude participants with known renal failure (CKD  $\geq 3b$ ), known G6PD deficiency, or known  
1935 hemochromatosis to limit these potential risks. We will additionally exclude participants with known  
1936 allergy to ascorbic acid. Ascorbic acid has additionally been used in at least 3 clinical trials in critically-  
1937 ill populations without major associated adverse effect.<sup>40-42</sup>  
1938

1939 Hydrocortisone – Hydrocortisone is a well-established medication for the treatment of refractory  
1940 shock in sepsis. Some studies (e.g. CORTICUS) have found an increased incidence of secondary  
1941 infection in participants with septic shock who receive steroids.<sup>46</sup> This finding has not been  
1942 replicated in other large trials of corticosteroids for sepsis.<sup>47</sup> Additional hypothetical risks to the  
1943 administration of hydrocortisone to participants with septic shock (e.g. increased gastro-intestinal  
1944 bleeding, muscle weakness, and delirium) have not been found in clinical trials of corticosteroids in  
1945 sepsis.<sup>46,47</sup> Finally, hydrocortisone may increase the risk of hyperglycemia and hyponatremia.  
1946

1947 Hydrocortisone will not be tapered in this study as prior studies have shown benefit with  
1948 corticosteroids in septic shock without a taper.<sup>80</sup> In addition, a recent large trial of corticosteroids in  
1949 septic shock (ADRENAL, NEJM 2018) randomized patients to 7-days of corticosteroids or placebo  
1950 and did not include a taper. In that trial there was no reported difference in rates of recurrent shock.  
1951

1952 Vitamin B1 – The only potential serious side effect that has been reported from vitamin B1  
1953 administration is an extremely rare anaphylactic reaction (1:250,000 cases) and this might not even  
1954 be of issue with the current manufactured version of vitamin B1 in the United States. The risk of an  
1955 anaphylactic reaction was associated with a vitamin complex dispensed in Europe, and whether

1956 vitamin B1 was the actual offending agent remains unknown; however, this 0.0004% theoretical  
1957 chance of an adverse reaction is incredibly low. In a series of 989 participants in the United States  
1958 who received intravenous vitamin B1, none had an anaphylactic reaction and the only reported side  
1959 effects were minor consisting of transient local irritation or in one case pruritus (0.093%).<sup>81</sup> Further  
1960 safety data comes from the clinical use of intravenous vitamin B1 at our coordinating site. At Beth  
1961 Israel Deaconess Medical Center (BIDMC, coordinating center) vitamin B1 is provided liberally for  
1962 participants with nutritional deficiency – for example, BIDMC has administered intravenous vitamin  
1963 B1 in over 8,000 separate participant encounters from 2002 until present. Despite this heavy usage,  
1964 no adverse reactions were reported in any of the 8,000 participant encounters.

1965  
1966 The combination of vitamin C, hydrocortisone and vitamin B1 – To date, the only study of the  
1967 combination of vitamin C, hydrocortisone and vitamin B1 was the above referenced study by Marik  
1968 et. al.

1969  
1970 All procedures will take place at the study site. All research procedures and monitoring will be  
1971 conducted by experienced personnel, and participants will be in the ICU given critical illness. This  
1972 permits closer observation and more detailed monitoring by clinicians familiar with the care of  
1973 participants experiencing and resuscitated from septic shock.

#### 1974 1975 **Blood Collection**

1976 Most participants will have existing venous or arterial catheters in place and we will be able to collect  
1977 blood from these ports, essentially eliminating the risks associated with blood collection. In the very  
1978 rare case that a participant does not have an indwelling line, the risk of venipuncture is extremely  
1979 low, and will not exceed the risk of clinical blood draws the participant will already be receiving.

#### 1980 1981 **Loss of Confidentiality**

1982 All measures will be taken to ensure that no confidential information is released. All participant  
1983 information will be stored in a password protected database to which only study investigators will  
1984 have access. Additionally, all hard copies of study data will be kept in a locked office accessible only  
1985 to study investigators. Thus, the risk of loss of confidentiality is very low.

### 1986 1987 **9. MONITORING**

#### 1988 **9.1 Institutional Review Board (IRB)**

1989 The study will be reviewed and approved by the IRB at each participating site.

#### 1990 1991 **9.2 Data Safety and Monitoring Board (DSMB)**

1992 The DSMB will be responsible for safeguarding the interests of trial participants, assessing the  
1993 safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the  
1994 clinical trial. The DSMB will consist of three clinicians with critical care experience in the  
1995 management of septic participants. An independent biostatistician/epidemiologist will prepare all  
1996 DSMB reports. The DSMB members will be chosen such to avoid any financial or intellectual  
1997 conflicts of interest. The DSMB will review deidentified data after every 50 participants are enrolled  
1998 to assess for safety; unless there are group differences necessitating unblinding (as determined by  
1999 the DSMB), the DSMB will be blinded to treatment groups. The trial will continue while the DSMB  
2000 review data. After each review, the DSMB will create a short report to the steering committee with  
2001 recommendations for continuation, modifications, or termination of the trial. Criteria for  
2002 recommending termination will be at the discretion of the DSMB and there will be no formal  
2003 statistical criteria for termination due to efficacy or safety. A detailed charter for the DSMB will be  
2004 provided.

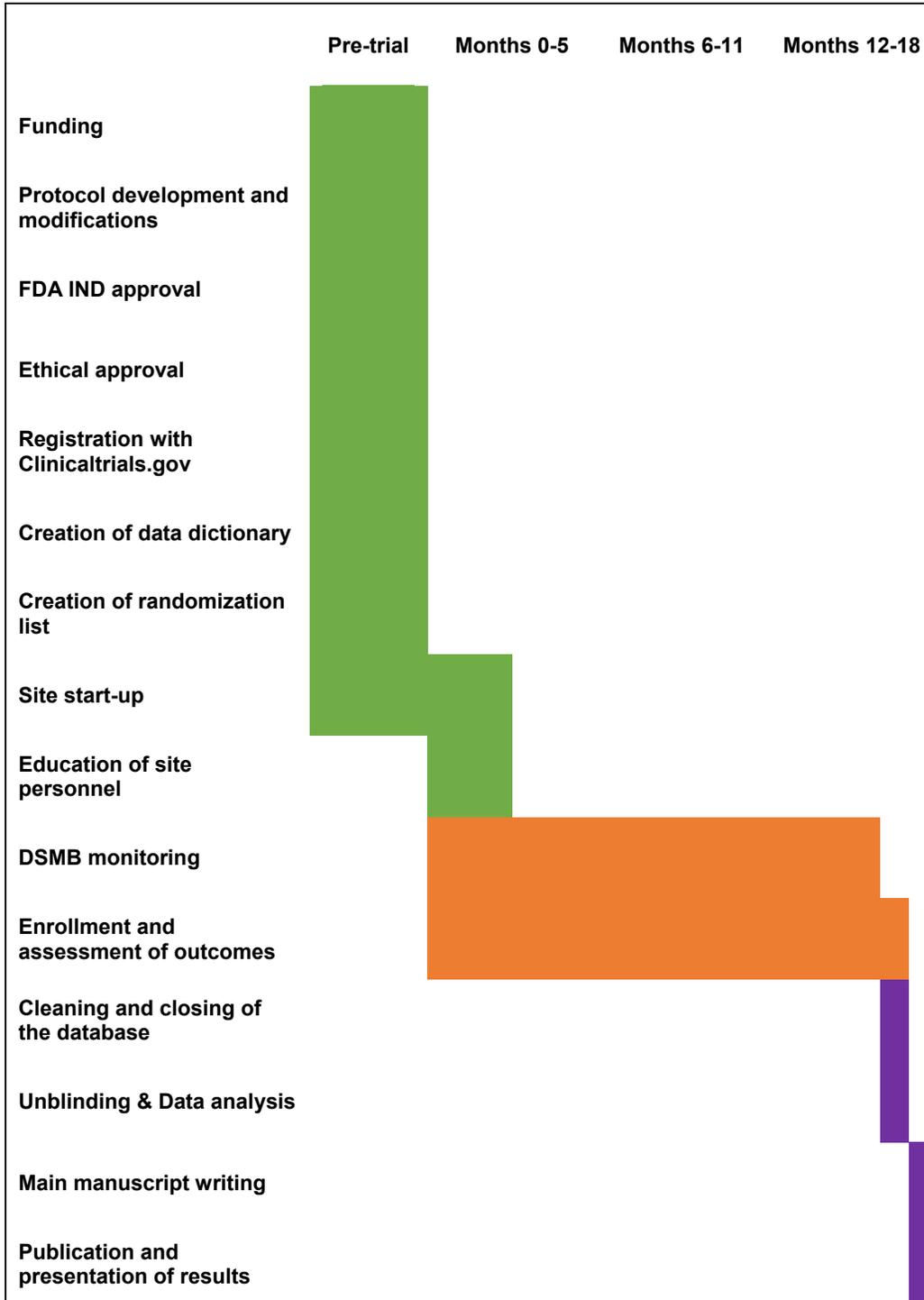
#### 2005 2006 DSMB Members

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2010 Pittsburgh, PA 15260  
2011 (412) 647-8287  
2012 callawaycw@upmc.edu  
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2024 Director, Critical Care Translational Research, Pulmonary/Critical Care Unit, MGH  
2025 Medical Director, ARDS Network Clinical Coordinating Center  
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2038 Principal Statistician, Technomics Research, LLC  
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2041 Expertise: Biostatistics  
2042  
2043 **10 CLINICAL MONITORING PLAN**  
2044 The detailed clinical monitoring plan has been developed and is available from the Coordinating  
2045 Center upon request.

2046  
2047

## 11. TIMELINE AND ENROLLMENT

### 11.1 Timeline



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### 11.2 Screening & Enrollment

Enrollment at each site will be continuously monitored by the site investigator and the principal investigator. Each site will be expected to maintain a screening log including all participants who meet all eligibility criteria at that site. A standardized screening log will be provided to each site via RedCap Cloud—thus allowing for continuous updating of the screening log and will allow capture of all screening failures.

2056 Enrollment will be competitive (i.e. without specific enrollment caps). Number of enrollments at each  
2057 site will be shared with all sites on a monthly basis. Sites will be expected to complete all elements  
2058 of the online CRF within 48-hours of each time point. In the case that a site continuously  
2059 underperforms despite troubleshooting and feedback, the steering committee will evaluate whether  
2060 enrollment will continue at that site.  
2061

## 2062 **12. FUNDING**

2063 Funding for the present trial is provided by the Good Ventures Foundation  
2064 (<http://www.goodventures.org/>). The funding agency will have no role in the design and conduct of  
2065 the study, collection, management, analysis, and interpretation of the data, preparation, review, or  
2066 approval of the manuscript, or the decision to submit the manuscript for publication.  
2067

## 2068 **13. PUBLICATION**

2069 The manuscript will adhere to the CONSORT guidelines.<sup>72,73</sup> The principal investigator will be  
2070 responsible for assigning authorship position and will follow authorship guidelines from the  
2071 International Committee of Medical Journal Editors.<sup>82</sup> At a minimum, all members of the Steering  
2072 Committee and all site Principal Investigators (for sites enrolling at least 10 participants) will be  
2073 included in the primary author list. The main results will be presented at an international conference.  
2074 The trial results will be shared with participating sites and via press releases but not directly with the  
2075 participants.  
2076

## 2077 **14. DATA SHARING**

2078 Six months after the publication of the last results, all de-identified individual participant data will be  
2079 made available for data sharing.<sup>83</sup> Procedures, including re-coding of key variables, will be put in  
2080 place to allow for complete de-identification of the data. All relevant trial-related documents,  
2081 including the protocol, data dictionary, and the main statistical code, will be shared along with the  
2082 data. There will be no predetermined end date for the data sharing. Data will be available for any  
2083 research purpose to all interested parties who have approval from an independent ethics review  
2084 committee and who have a methodological sound proposal as determined by the steering  
2085 committee of the current trial. Interested parties will be able to request the data by contacting the  
2086 principal investigator. Authorship of publications emerging from the shared data will follow standard  
2087 authorship guidelines from the International Committee of Medical Journal Editors<sup>82</sup> and might or  
2088 might not include authors from the steering committee depending on the nature of their involvement.  
2089

## 2090 **15. TASKS AND RESPONSIBILITIES**

2091 Principal investigator and sponsor: Overall responsibility for protocol development, funding, budget  
2092 overview, data dictionary development, ethical approval, trial registration, daily management, trial  
2093 oversight and collection of adverse events, contact to the pharmacy, contact to Good Clinical  
2094 Practice monitoring unit and the data and safety monitoring board, assessment of overall  
2095 recruitments, potential recruitment of additional sites, data analysis, and dissemination and  
2096 presentation of results.  
2097

2098 Steering committee: Protocol development, funding, budget overview, data dictionary development,  
2099 trial oversight, dissemination of results, responsibilities as principal investigator for short time  
2100 periods.  
2101

2102 Site investigators: Responsible for site-specific enrollment, evaluation of eligible patients not  
2103 included, education of personnel at participating sites, reporting of site-specific issues or challenges  
2104 to the principal investigator, participant consent for data collection, collecting and reporting data  
2105 regarding adverse drug events.  
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2107 Clinical team: Administration of the study drug, participant consent for data collection.

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2. ICH Harmonised Tripartite Guideline. General Considerations for Clinical Trials E8. 1997; [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E8/Step4/E8\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf). Accessed June 30, 2017.
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2315 **Appendices**

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2317 **Appendix 1: Abbreviations**

- 2318 ICH.....International Conference on Harmonization
- 2319 SPIRIT.....Standard Protocol Items: Recommendations for Interventional Trials
- 2320 ACT.....Ascorbic Acid, Corticosteroids, and Thiamine
- 2321 CKD.....Chronic Kidney Disease
- 2322 SOFA.....Sequential Organ Failure Assessment
- 2323 IND.....Investigational New Drug
- 2324 FDA.....Food and Drug Administration
- 2325 ICU.....Intensive Care Unit
- 2326 SaO2.....Oxygen Saturation
- 2327 FiO2.....Fraction of Inspired Oxygen
- 2328 GCS.....Glasgow Coma Scale
- 2329 UOP.....Urine Output
- 2330 RRT.....Renal Replacement Therapy
- 2331 CAM.....Confusion Assessment Method
- 2332 NCHS..... National Center for Health Statistics
- 2333 NDI.....National Death Index
- 2334 AKI.....Acute Kidney Injury
- 2335 SD..... standard deviation
- 2336 CRF.....Case Report Form
- 2337 BIDMC.....Beth Israel Deaconess Medical Center (Coordinating Center)
- 2338 IRB.....Institutional Review Board
- 2339 DSMB.....Data Safety and Monitoring Board

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### CAM-ICU Worksheet

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if Present		
<p style="text-align: center;">Is the pt different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (i.e., RASS), GCS, or previous delirium assessment?</p>	Either question Yes →	<input type="checkbox"/>		
Feature 2: Inattention				
<p><b>Letters Attention Test</b> (See training manual for alternate Pictures)</p> <p><i>Directions:</i> Say to the patient, "I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand." Read letters from the following letter list in a normal tone 3 seconds apart.</p> <p style="text-align: center;"><b>S A V E A H A A R T</b></p> <p><b>Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."</b></p>			Number of Errors >2 →	<input type="checkbox"/>
Feature 3: Altered Level of Consciousness				
<p>Present if the Actual RASS score is anything other than alert and calm (zero)</p>	RASS anything other than zero →	<input type="checkbox"/>		
Feature 4: Disorganized Thinking				
<p><b>Yes/No Questions</b> (See training manual for alternate set of questions)</p> <ol style="list-style-type: none"> <li>1. Will a stone float on water?</li> <li>2. Are there fish in the sea?</li> <li>3. Does one pound weigh more than two pounds?</li> <li>4. Can you use a hammer to pound a nail?</li> </ol> <p><b>Errors are counted when the patient incorrectly answers a question.</b></p> <p><b>Command</b> Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If pt is unable to move both arms, for 2<sup>nd</sup> part of command ask patient to "Add one more finger"</p> <p><b>An error is counted if patient is unable to complete the entire command.</b></p>			Combined number of errors >1 →	<input type="checkbox"/>
Overall CAM-ICU				
Feature 1 <u>plus</u> 2 <u>and</u> either 3 <u>or</u> 4 present = CAM-ICU positive	Criteria Met →	<input type="checkbox"/> <b>CAM-ICU Positive</b> (Delirium Present)		
	Criteria Not Met →	<input type="checkbox"/> <b>CAM-ICU Negative</b> (No Delirium)		

### 3. SUMMARY OF PROTOCOL CHANGES

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2369 **v2.1** – Original trial protocol. v1.0 of the protocol was a draft protocol that was updated following the  
2370 initial investigator meeting.

2371 **v2.2** – Added external study sites. Modifications to protocol at coordinating center (reflected in v2.3  
2372 for all sites).

2373 **v2.3** – Change in exclusion criteria from CKD  $\geq 3b$  [GFR < 45ml/hr] to receiving renal replacement  
2374 therapy. Clarification that sepsis should be the likely cause of hypotension resulting in vasopressor  
2375 requirement and that consent/enrollment should be within 24-hours of meeting inclusion criteria.

2376 Change in contingency should open label thiamine be prescribed by the clinical team. Allowance for  
2377 a consideration of sample size adjustment should the SOFA score and/or mortality for the full study  
2378 cohort (examined without consideration of study group) fall below that anticipated in the power  
2379 analysis. Clarification of adverse event reporting procedures.

2380 **v2.4** – Addition of study site. Correction of oversight in exclusion criteria with respect to clinical  
2381 ascorbic acid supplementation. Clarification of SOFA scale to assign a renal SOFA score of 4 if a  
2382 patient is started on renal replacement therapy.

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