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Resuscitation in Paediatric Septic Shock Using Vitamin C and Hydrocortisone (RESPOND): The RESPOND Randomized Controlled Trial Protocol

OBJECTIVES: Pediatric sepsis results in significant morbidity and mortality worldwide. There is an urgent need to investigate adjunctive therapies that can be administered early. We hypothesize that using vitamin C combined with hydrocortisone increases survival free of inotropes/vasopressors support until day 7 compared with standard care. Here we describe the Resuscitation in Paediatric Septic Shock using Vitamin C and Hydrocortisone (RESPOND) trial protocol, which aims to address this hypothesis.

DESIGN: Randomized, open label, controlled, parallel-group, three-arm trial with integrated economic evaluation.

SETTING: Nine Australia and New Zealand PICUs, with interest from additional international sites.

PATIENTS: Children between 7 days and younger than 18 years old who are treated for suspected or confirmed sepsis and receiving inotropes/vasopressors for greater than 1 hour.

INTERVENTIONS: IV vitamin C (100 mg/kg [maximum 5 g] every 6 hr) and hydrocortisone (1 mg/kg [maximum 50 mg] every 6 hr), or IV hydrocortisone alone (1 mg/kg [maximum 50 mg] every 6 hr) or standard care.

MEASUREMENTS AND MAIN RESULTS: Three hundred eighty-four children will be randomly assigned to receive the interventions, or standard care in a 1:1:1 ratio with stratification by steroid administration pre-randomization and hospital site. The primary outcome is time alive and free of inotropes/vasopressors, censored at 7 days. Secondary outcomes include 28-day mortality, survival free of organ support, PICU length of stay, quality of life, functional status and neurodevelopmental vulnerability at 6 months post-enrollment, and hospitalization-related costs. Statistical analysis will be based on an intention-to-treat principle. The study has ethical approval (HREC/20/QCHQ/69922, dated December 21, 2020), is registered in the Australian New Zealand Clinical Trials Registry (ACTRN12621000247875), commenced recruitment on December 8, 2021, and is expected to finish recruitment by mid-2026.

CONCLUSIONS: Dissemination of the results will occur through publication in peer-reviewed journals, presentations at international conferences, and additional consumer-informed pathways.

KEYWORDS: clinical trial; glucocorticoid; intensive care units, pediatric; sepsis; septic shock; vitamin C

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Sepsis is a leading cause of childhood death (1). Half of sepsis deaths in children occur within 48 hours of presentation (2), implying a need for rapidly applicable interventions to alter the disease trajectory in the pediatric host observed during septic shock. Although outcomes for childhood sepsis have gradually improved, one in six children with septic shock admitted

RESEARCH IN CONTEXT

- This is the first multicenter, multinational randomized controlled trial, informed by a pilot trial and adult studies, powered for clinical endpoints that investigate the effect of vitamin C combined with hydrocortisone in pediatric septic shock.
- Trial outcomes include survival free of inotropes/vasopressors as a combined measure of severity relevant for patients and families, survival, and duration of treatments in hospital, direct healthcare costs, and quality of life and measures of functional status and neurodevelopment 6 months after randomization.
- This multinational collaboration, including high-, low- and middle-income settings, will ensure that the results translate to clinical practice quickly.

to a PICU will die, with even higher numbers in children in less resourced settings (3).

The 2020 pediatric Surviving Sepsis Campaign guidelines do not recommend in favor of or against the use of hydrocortisone in children with septic shock refractory to adequate fluid resuscitation and vasopressor therapy (4). The benefit of steroids in septic shock may be enhanced by vitamin C (5, 6), a strong antioxidant that has been postulated to modulate multiple pathways dysregulated during septic shock (7). Despite the biological plausibility of combining vitamin C based therapies with hydrocortisone in sepsis and initial promising studies, there is low certainty evidence that vitamin C may reduce in-hospital and 30-day mortality in adults, conflicting with moderate certainty evidence suggesting harm toward 90-day mortality in adults (8).

A propensity-matched study in children with septic shock demonstrated the safety of vitamin C, hydrocortisone, and thiamine, and reported decreased 30- and 90-day mortality compared with hydrocortisone alone, and compared with standard care without hydrocortisone (9). We performed a pilot study that confirmed the feasibility of a study protocol of early delivery of vitamin C and hydrocortisone in children admitted to the PICU with septic shock, permitting intervention at a time when a study drug may be more likely to alter the disease trajectory (10, 11). Children with low levels of vitamin C on presentation to the PICU were significantly more likely to have single or multiple organ dysfunction 24 hours later (12). Based on these data and a systematic review confirming safety of high-dose IV vitamin C in children (13), we designed the Resuscitation in Paediatric Septic Shock using Vitamin C and Hydrocortisone (RESPOND) trial to test the primary hypothesis that, in children younger than 18 years with septic shock, using IV vitamin C (100 mg/kg 6 hr) with hydrocortisone (1 mg/kg 6 hr) will result in quicker resolution of shock compared with hydrocortisone alone and compared with standard care. Here we describe the RESPOND trial protocol.

MATERIALS AND METHODS

The RESPOND trial is an investigator initiated, planned 384-participant international, multicenter, randomized, open-label, standard care-controlled, parallel-group, trial in infants and children younger than 18 years old with septic shock requiring inotropes/vasopressors being conducted in nine Australian and New Zealand (ANZ) PICUs, with additional international sites expected to join (**Fig. 1**).

Ethical Review

Ethical approval has been provided by the Children's Health Queensland Human Research Ethics Committee (HREC/20/QCHQ/69922, dated December 21, 2020) and respective local ethics committees. RESPOND will be conducted in compliance with ethical standards of the responsible committees on human experimentation and the Helsinki Declaration of 1975. Any change to the study documentation will be submitted to approving ethics committees as amendments (**Table S1**, http://links.lww.com/PCC/C580).

Participants

Infants and children with a clinical diagnosis of septic shock, receiving inotropes/vasopressors, and admitted to one of the participating PICUs are eligible (**Table 1**). Specifically, use of antibiotics serves as proxy for infection, and use of inotropes/vasopressors as a proxy for shock. Our pilot study (11)

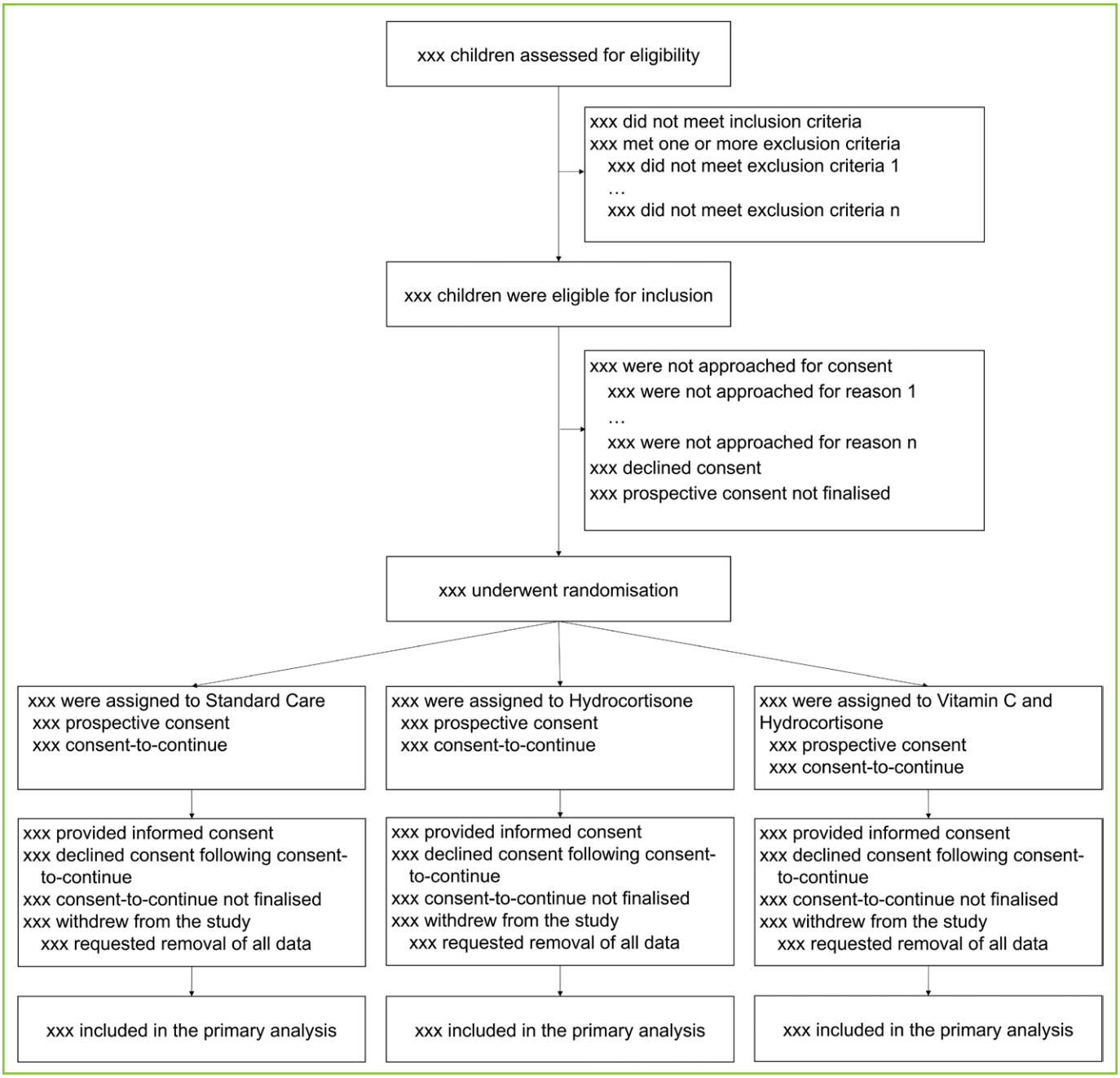

Figure 1. Participant flow diagram.

confirmed the feasibility of this pragmatic operationalization of suspected septic shock. These criteria were chosen given the controversies surrounding the 2005 criteria for sepsis in children, which were still based on systemic inflammatory response syndrome criteria (14). In 2024, the Phoenix Sepsis Criteria (15) were released following commencement of our trial; our included patients meet the Phoenix Sepsis Criteria requirements for both infection and cardiovascular dysfunction.

Interventions

All eligible children will undergo standard initial shock management including fluids and a first IV inotrope/vasopressor as per institutional practice (16) and be randomized to one of three treatment arms (**Table 2**). Regardless of whether full study treatment is continued or not, the follow-up schedule will continue unchanged for all randomized participants.

The drug protocol for the RESPOND trial was changed from the previously published adult

TABLE 1.
Inclusion and Exclusion Criteria

Category	Criterion
Inclusion	Child ≥ 7 d and < 18 yr old and admitted to the PICU
	Treatment of septic shock with inotrope/vasopressor therapy for > 1 hr
Exclusion	Corrected age of < 7 d
	Patients with known glucose-6-phosphate dehydrogenase deficiency
	Patients with known history of oxalate nephropathy
	Patients with known malaria
	Patients receiving cyanocobalamin or deferoxamine
	Receiving ongoing treatment with inotropes/vasopressors for confirmed or suspected sepsis or septic shock for > 24 hr
	Cardiopulmonary arrest in the past two hours requiring CPR > 2 min, or death is deemed to be imminent or inevitable
	Palliative care patient/patient with limitation of treatment (not for inotropes/vasopressors, CPR, extracorporeal life support, intubation, and ventilation)
	Prior enrolment in the Resuscitation in Paediatric Septic Shock using Vitamin C and Hydrocortisone study within the past 6 mo

CPR = cardiopulmonary resuscitation.

TABLE 2.
Study Interventions

Arm	Description
Vitamin C	Patients will receive concomitant treatment with vitamin C and IV hydrocortisone: 1) vitamin C 100 mg/kg IV (maximum 5 g/dose) every 6 hr infused over 1 hr, and 2) hydrocortisone 1 mg/kg (maximum 50 mg/dose) every 6 hr given as a slow IV bolus for a maximum of 3 d post-randomization
Hydrocortisone	Patients receive IV hydrocortisone 1 mg/kg (maximum 50 mg) every 6 hr for a maximum of 3 d post-randomization
Standard care	Patients should receive care as per institutional practice. Patients can receive hydrocortisone only if clinically indicated at the discretion of the attending PICU staff specialist. Hydrocortisone use (or vitamin C use) will be captured as a protocol violation

metabolic resuscitation protocol (17) and our pilot study (10, 11). Informed by component network analyses (18) indicating a dose-response relationship, this study uses a higher vitamin C dose compared with most published adult trials. The dosing of 100 mg/kg/dose (maximum 20 g/d, 30 mg/kg/dose/every 6 hr for 7 d used in RESPOND pilot [11]) for vitamin C was informed by the safety data from our systematic review (13). Thiamine that was part of the pilot study protocol has been removed for this trial because of the signal for potential associated harm in the component network meta-analysis (18).

The ANZ sites will use a sodium ascorbate formulation provided by Biological Therapies (Braeside, VIC, Australia). The same product will be used in international sites if approved by the respective regulatory bodies. Sites in India will use locally sourced ascorbic acid due to the drug import restrictions. Locally available hydrocortisone product formulations will be used.

Treatment Duration

Study treatments will be discontinued after shock resolution—defined as cessation of inotropes/vasopressors for at least 4 hours—or after a maximum of 72 hours.

Attending clinicians are allowed to wean hydrocortisone as per individual PICU practice. We chose this duration of therapy as the severity of pediatric shock and associated metabolic perturbations is highest during the initial 72 hours (19) and given that side-effects related to treatments may increase with prolonged treatment. All other care is provided at the discretion of the treating attending physician.

Study Outcomes

The primary outcome is time alive and free of inotropes/vasopressors, censored at 7 days (168 hr) (**Table 3**). Secondary outcomes include 28-day mortality, survival free of organ support, and PICU length of stay. We will also assess quality of life, functional status and neurodevelopmental vulnerability at 6 months post-enrollment, and hospitalization-related costs.

The primary outcome is aligned with the published adult study (17) and serves as a composite surrogate marker, given: 1) it reflects resolution of shock as the primary evidence of treatment effectiveness; 2) it includes mortality; 3) inotrope/vasopressor therapy is a key determinant of escalating organ support, and duration of inotrope/vasopressor therapy is a determinant of PICU length of stay in shocked patients; 4) inotrope/vasopressor therapy duration is associated with brain and organ ischemia, multiple organ failure, and worse short- and long-term outcomes; 5) the outcome is a proxy measure of burden to families and patients (i.e., being confined to PICU with invasive devices, exposed to PICU therapies, fear of death); and 6) correlates with direct healthcare costs.

Sample Size

Based on data from our pilot randomized controlled trial (RCT) in ANZ (11), the average (i.e., mean) time

TABLE 3.
Study Outcomes

Type	Outcome	Definition
Primary	Time alive and free of vasopressors	Duration free of inotropes/vasopressors in the first 7 d (168 hr) post-randomization; patients dying within 7 d of randomization will be censored as zero
Secondary	Alive and free of multiple organ dysfunction	Multi-organ dysfunction measured by a pediatric Sequential Organ Failure Assessment score change in organ-specific subscore of > 0 in at least two organs within 72 hr of randomization
	Survival	PICU-free survival; patients dying within 28 d of randomization will be censored as 0 d to correct for the competing effect of mortality on PICU length of stay
		Survival free of organ support within 28 d of randomization, defined as free of ventilation, inotropes/vasopressors, ECMO, and renal replacement therapy
		Survival free of cardiovascular support within 28 d of randomization, defined as free of inotropes/vasopressors and ECMO
		Survival free of ventilation within 28 d of randomization, defined as free of invasive ventilation
		Death, defined as death occurring within 28 d of randomization
	Length of stay	Length of stay in the PICU
		Length of stay in hospital
	Costs	Direct hospitalization-related costs (starting at time of admission to the PICU) and censored at 6 mo post-randomization
	Neurodevelopmental and functional outcome at 6 mo	Quality of life 6 mo post-randomization
		Functional status 6 mo post-randomization
		Neurodevelopmental vulnerability at 6 mo post-sepsis defined as a score in each developmental domain > 1 SD below the normative mean or specified impairment cutoffs. These domains include physical development, cognitive skills, emotional wellbeing and social competence

ECMO = extracorporeal membrane oxygenation.

alive and free of inotropes/vasopressors in the control group was 96 hours (median 120 hr), associated with a SD of 61 hours. An improvement of a minimum of 1 day (25 hr to ensure at least 1 full day) when comparing the vitamin C and hydrocortisone group, over both the standard care and hydrocortisone only arm, is considered clinically relevant (17). To achieve 80% power, a corrected type I error of 0.025 to allow for two primary comparisons (standard care vs. vitamin C and hydrocortisone; standard care vs. vitamin C and hydrocortisone), attrition of 5% and inflation for a non-normally distributed outcome, 128 participants per group are required (384 total). A blinded analysis will be undertaken after the primary outcome is achieved in 128 patients recruited in ANZ, and after 50 patients are recruited in each additional region to confirm the assumed SD within the study cohort and recalibrate the target sample size if necessary. With a conservative estimate of 50% enrollment rate of eligible patients, we expect a 4-year recruitment period for the study.

Randomization

All children being treated with inotropes/vasopressors for suspected septic shock at the study sites are screened by PICU staff for inclusion. Treatment assignment is performed using a secure, centralized, web-based randomization interface (Research Electronic Data Capture [REDCap]) (20), hosted by The University of Queensland or sealed opaque envelopes. The allocation sequence is generated using computer-generated random numbers. Variable block randomization is being used to allocate children in a 1:1:1 ratio. As our pilot study showed that 27% of participants received pre-randomization steroids for septic shock (11), participants are stratified by administration of steroids before enrollment and hospital site.

Blinding and Allocation Concealment

The interventions are open label, due to the logistical difficulties of blinding two different drugs (specifically, dissolved vitamin C has a characteristic yellowish color) (17). Allocation concealment will be maintained by the randomization system.

Consent Procedures

Two modes of consent are employed in this trial, prospective and consent-to-continue; consent materials have been piloted with consumer representatives (**Appendix S1a** and **Appendix S1b**, http://links.lww.com/PCC/C580). With prospective consent, informed written consent is gained from the parents/carers before randomization. Given the fulminant nature of sepsis (19), our aim is to enroll patients as soon as possible after presentation to PICU. If parents/carers are unavailable or are very distressed, we employ a consent-to-continue approach. Here, we randomize the child (and initiate the intervention) and seek consent from the parents/carers at a more suitable time, aiming to obtain consent within the following 24 hours. Parents/carers have the right to decline ongoing participation as well as withdrawing all collected data.

DATA COLLECTION, MANAGEMENT, AND ANALYSIS

Data Collection

The trial data dictionary is informed by the pilot study database (11). We prospectively record demographic variables, comorbid status, type of infection, severity at baseline, primary endpoints, secondary endpoints, predetermined physiologic variables of interest, process of care, safety, and long-term outcome measures. All data are collected by trained staff at each study site and entered into the purpose-built REDCap database, available only to approved investigators and site staff. Administration of study drugs, duration, doses, amount of drug received, adverse events, protocol deviations, and reason for protocol violations are also recorded. Randomized patients are followed up to 28 days post-randomization (or death, whichever occurs first) and again at 6 months. Long-term outcome measures are parent/carer reported. The follow-up questionnaires for collecting long-term outcome measures are administered by a secure web link provided to parents in an email.

Child and Parent Long-Term Follow-Up

Parent-reported screening questionnaires using validated tools will collect child and parent outcomes (**Table S2**, http://links.lww.com/PCC/C580). The screening questionnaire was designed in consultation with the multidisciplinary study team and consumer representatives, considering the measure's reliability and validity and relevance to the sepsis literature.

Assessments will be prospectively performed at baseline, hospital discharge, 28 days, and 6 months post-randomization (**Table S3**, http://links.lww.com/PCC/C580). At 6 months, parents will be contacted to complete the online screening questionnaire using a secure link to their electronic questionnaire and contact details of their recruiting site. The 6-month questionnaire takes approximately 45–60 minutes to complete. In the case of parent comorbidity or circumstances limiting completion of the online screeners, questionnaires will be administered via telephone interview by the research coordinator. Parents/carers of the child will have the option of receiving a report following completion of the 6-month questionnaire that outlines their child's progress, which can be used to aid discussions with primary care and education providers (ANZ sites only). This report was co-designed with consumers and piloted in two other research studies (21, 22).

Monitoring

An independent monitor for each site will perform data monitoring. The monitoring plan has been successfully trailed in the pilot study and includes source data verification for 100% of enrolled patients for fields relating to eligibility criteria, interventions, consent forms, serious adverse events (SAEs), and primary outcomes and monitoring of a subset of other key data fields (identified through risk assessment) in 10% of enrolled patients. Additionally, centralized monitoring will be used to evaluate recruitment statistics; evaluate completeness and rates of critical data within and across study sites; and review automated range and logic discrepancies in the REDCap study database. Site visits, independent audits, and regular monitoring of the blood sample storage will be performed. At completion of the study, the monitor will ensure that there are plans for long-term storage of all relevant data and source documentation.

Biobanking

Blood is collected at, or shortly after randomization, including 1–2 mL of EDTA blood (for DNA), 2.5 mL of PAXgene blood (for gene expression markers), and 1–2 mL of serum. The samples are processed, stored, shipped, and batch analyzed for future biomarker studies (23).

Analysis Plan

Descriptive statistics will be used to report on the baseline characteristics of the total study cohort and each group. The primary outcome will be analyzed using quantile regression, comparing the two intervention groups with standard care. Stratification variables (administration of steroids before enrollment and hospital site [also accounting for difference in vitamin C formulation]) will be accounted in the model. Analysis of secondary outcomes will be undertaken using a similar approach using appropriate regression models for the outcome under investigation. 95% CIs will be used as the major method of presentation. If there are greater than 10% missing data for the primary outcome, multiple imputation will be performed and reported as a sensitivity analysis. Main analyses will be performed according to the intention-to-treat principle; per-protocol analyses will also be performed. An exploratory analysis will compare the two intervention groups to each other, as well as the vitamin C and hydrocortisone group with the hydrocortisone and standard care groups combined. Predefined subgroup analyses will focus on severity upon presentation measured by organ dysfunction scores, age, previously healthy children vs. children with comorbidities, community-acquired vs. hospital-acquired sepsis, vitamin C formulation, and patient with pre-randomization treatment with hydrocortisone. As the trial started before the Phoenix Sepsis Criteria (15) became available, sensitivity analyses on children meeting Phoenix Sepsis Criteria for septic shock at enrollment will be performed. The statistical analysis plan will be submitted for publication with lodgment of the full code for analysis on GitHub (San Francisco, CA) before completion of recruitment.

Health Economic Evaluation

A within trial economic evaluation will compare the cost and benefits of the trial treatments, censored at 6 months, comparing costs and benefits in terms of resource use and quality adjusted life years gained, derived from the Pediatric Quality of Life questionnaire. To estimate health utilities, we will use a previously described mapping algorithm (24). To provide longer-term analysis, cost-effectiveness will be estimated following a Markov Chain modeling approach. Models will include sensitivity analysis methods including bootstrapping to account for uncertainty in

our estimates. Outputs will include cost-effectiveness acceptability curves to display the probability of cost-effectiveness at varying thresholds of net monetary benefit (NMB). Probabilistic sensitivity analysis will be provided to give the probability of cost-effectiveness at each threshold level of NMB. This will allow to capture the impact of sepsis on direct and indirect costs, including disability-adjusted life years, loss of parental productivity, and ongoing support needs.

SAFETY MONITORING

Adverse Events

The critically ill child with sepsis has life-threatening organ dysfunction. The severity of dysfunction may have several contributors less responsive to optimal treatment such as underlying comorbidities, microbe pathogenicity, and delay in treatment initiation. Therefore, aligned with accepted practice in PICU trials (25), events that are considered to result from the natural history of the primary disease process or which represent expected complications related to critical illness will not be reported as SAEs in this study. All adverse events considered as potentially causally related to the study intervention will be reported unless they are prespecified study outcomes. Specific adverse events related to RESPOND include the following: hyperglycemia, hypoglycemia, hypernatremia, new hospital-acquired microbiologically confirmed infection within 28 days after randomization, oxalate nephropathy, hemolysis, and worsening of liver function (**Table 4**). Events that are collected as study outcomes will not be reported as adverse events. However, death will be reported as an SAE and recorded as a study outcome.

Safety Data Monitoring

The Data and Safety Monitoring Board (DSMB) charter and procedures have been trialed in the pilot study (11). The DSMB members consist of two intensivists (one local; one international), emergency physician, and statistician. The DSMB monitor safety and quality of the study, review adverse events, and monitor recruitment progress. Interim analyses for safety will be performed after 33, 66, and 100 patients have complete primary outcome data. Given the difference in formulation used, similar safety analyses will also be undertaken after 33, 66, and 100 patients have been recruited to Indian sites and have complete primary outcome data. Additionally, after 100 patients have complete primary outcome data, and after 50 patients recruited in each non-ANZ country have primary outcome data, a blinded analysis will be undertaken to confirm the SD of the primary outcome.

PATIENT AND PUBLIC INVOLVEMENT

The acceptability of questionnaires and reporting was informed by consumer focus groups using a similar set of tools (21). A consumer representative is a member of the trial steering committee, contributing to the design of study education materials, conduct, interpretation, article writing, and dissemination. Extensive consumer consultation occurred after the publication

TABLE 4.
List of Adverse Events

Adverse Event Definition
Hyperglycemia within 7 d of randomization, defined as treated with IV insulin for high blood glucose or higher than usual requirement of insulin dose, if a known diabetic
Hypoglycemia within 7 d of randomization, defined as blood glucose concentration < 2.6 mmol/L
Hypernatremia within 7 d of randomization, defined as serum sodium concentration > 155 mmol/L
Hospital-acquired microbiologically confirmed infection within 28 d of randomization
Oxalate nephropathy within 28 d of randomization, as reported by treating medical team
Hemolysis within 7 d of randomization, as reported by the treating medical team and if not explained by other factors such as extracorporeal membrane oxygenation
Worsening of liver function, defined as a > two-fold increase in alanine transferase from baseline to day 7 post-randomization; and/or an increase in total bilirubin of more than 68 μmol/L from baseline to day 7 post-randomization as per 2005 International Pediatric Sepsis Consensus Criteria (15)

of Lessening Organ Dysfunction with Vitamin C (LOVIT) trial results (26) to ensure consumer perspectives were incorporated. Additionally, a doctoral student is undertaking a series of related studies to elevate and guide ongoing consumer involvement.

DISCUSSION

Evidence for adjunctive therapies in pediatric septic shock is scarce. The RESPOND trial will provide robust evidence that is urgently needed to inform pediatric critical care practice. RESPOND is the first trial powered for patient-centered endpoints in children with septic shock investigating high-dose vitamin C, based on our multicenter pilot RCT. The trial is run across all major PICUs in ANZ and is scalable to include additional international sites.

Several limitations need to be considered. First, rather than using Phoenix Sepsis Criteria (15) for enrollment, which were published after the initiation of this trial, we chose a pragmatic entry point defined by the interventions clinicians apply in children with septic shock. We acknowledge that different clinicians may apply variable thresholds to initiate inotrope/vasopressor treatment; however, given uncertainty surrounding blood pressure thresholds (27), we believe our approach allows inclusion of the population of children exposed to these treatments at the study sites. Second, while we aimed for a pragmatic inclusion strategy, we excluded patients with malaria or those with glucose-6-phosphate dehydrogenase deficiency. Third, the intervention is open label given the logistic and feasibility challenges with blinding several drugs. Fourth, patients may have received hydrocortisone for septic shock before enrollment, which is why we apply a stratification for this situation. Fifth, the vitamin C dose is based on preclinical data, a systematic review, and the adult literature, and we are not performing a dose-finding trial nor pharmacological substudies. Sixth, the three-arm design permits comparison of hydrocortisone plus vitamin C vs. hydrocortisone alone, and vs. standard care, but does not compare vitamin C alone vs. standard care. Seventh, the primary outcome of survival free of inotropes/vasopressors censored at 1 week may not capture later effects related to immunomodulation of the interventions; however, the secondary outcomes should capture these later effects. Finally, if the trial recruits a sizeable proportion of patients from low- and middle-income resource settings, this—albeit improving generalizability—may add additional heterogeneity related to difference in drug formulation, practices of drug use, local epidemiology, and risk factors such as malnutrition.

The RESPOND trial will test the hypothesis that combination of IV hydrocortisone with vitamin C will improve survival free of inotropes/vasopressors support in children admitted to the PICU with septic shock. The trial will provide information on secondary outcomes, the effect of hydrocortisone treatment alone compared with standard care, and information on healthcare costs and long-term outcomes in children with septic shock.

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The Resuscitation in Paediatric Septic Shock using Vitamin C and Hydrocortisone (RESPOND) Study Group are listed in ***Appendix 1****.*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/pccmjournal).

The study protocol first draft was designed by Drs. Raman, Gibbons, and Schlapbach based on the previous pilot study design established by Drs. Schlapbach and Bellomo. Dr. Gibbons wrote the section on statistical analyses. Dr. Blythe wrote the section on health economic analyses. Dr. Long wrote the section on long-term follow-up. The present study protocol has been revised with input from Drs. Jayashree, Butt, Erickson, Ganu, Festa, Singh, Lister, George, Buckley, Cho, de Souza, Lalitha, Johnson, Cree, Venkatesh, Long, and Ms. Wall. Drs. Raman, Gibbons, and Schlapbach prepared the final protocol article, which was reviewed and approved by all authors. The Trial Steering Committee is formed of Drs. Raman, Gibbons, Schlapbach, Bellomo, Butt, Erickson, Festa, George, Venkatesh, Jayashree, Long, de Souza, and Ms. Wall.

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Drs. Raman, Gibbons, and Schlapbach contributed equally.

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Trial registration: ACTRN12621000247875; Protocol Version: 1.6, September 14, 2022.

The trial is overseen by a Trial Steering Committee, comprising Chief Investigators, Site and Region Representatives, Statistician, Trial Research Coordinator, and a Consumer. Additionally, the trial in monitored by an independent Data and Safety Monitoring Board.

REFERENCES

1. Schlapbach LJ, Kissoon N: Defining pediatric sepsis. *JAMA Pediatr* 2018; 172:312–314
2. Weiss SL, Balamuth F, Hensley J, et al: The epidemiology of hospital death following pediatric severe sepsis: When, why, and how children with sepsis die. *Pediatr Crit Care Med* 2017; 18:823–830
3. Tan B, Wong JJ, Sultana R, et al: Global case-fatality rates in pediatric severe sepsis and septic shock: A systematic review and meta-analysis. *JAMA Pediatr* 2019; 173:352–362
4. Weiss SL, Peters MJ, Alhazzani W, et al: Executive summary: Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Crit Care Med* 2020; 21:186–195
5. Schlapbach LJ, Oliveira CFD, Raman S, et al: Metabolic resuscitation in pediatric sepsis: A narrative review. *Transl Pediatr* 2021; 10:2678–2688
6. Fujii T, Deane AM, Nair P: Metabolic support in sepsis: Corticosteroids and vitamins: The why, the when, the how. *Curr Opin Crit Care* 2020; 26:363–368
7. Moskowitz A, Andersen LW, Huang DT, et al: Ascorbic acid, corticosteroids, and thiamine in sepsis: A review of the biologic rationale and the present state of clinical evaluation. *Crit Care* 2018; 22:283
8. Agarwal A, Basmaji J, Fernando SM, et al: Administration of parenteral vitamin C in patients with severe infection: Protocol

for a systematic review and meta-analysis. *JMIR Res Protoc* 2022; 11:e33989

9. Wald EL, Sanchez-Pinto LN, Smith CM, et al: Hydrocortisone-ascorbic acid-thiamine use associated with lower mortality in pediatric septic shock. *Am J Respir Crit Care Med* 2020; 201:863–867
10. Schlapbach LJ, Gibbons K, Ridolfi R, et al; RESPOND PICU study investigators and the Australian New Zealand Intensive Care Society Paediatric Study Group (ANZICS PSG): Resuscitation in paediatric sepsis using metabolic resuscitation—a Randomized Controlled Pilot Study in the Paediatric Intensive Care Unit (RESPOND PICU): Study protocol and analysis plan. *Front Pediatr* 2021; 9:663435
11. Schlapbach LJ, Raman S, Buckley D, et al; Resuscitation in Paediatric Sepsis Randomized Controlled Pilot Platform in the Paediatric Intensive Care Unit (RESPOND PICU) Study Investigators and the Australian and New Zealand Intensive Care Society Paediatric Study Group: Resuscitation with vitamin C, hydrocortisone, and thiamin in children with septic shock: A multicenter randomized pilot study. *Pediatr Crit Care Med* 2024; 25:159–170
12. McWhinney B, Ungerer J, LeMarsey R, et al; Rapid Acute Paediatric Infection Diagnosis in Suspected Sepsis (RAPIDS) Study Investigators: Serum levels of vitamin C and thiamin in children with suspected sepsis: A prospective observational cohort study. *Pediatr Crit Care Med* 2024; 25:171–176
13. Yanase F, Raman S, Naorungroj T, et al: Efficacy and safety of parenteral high-dose vitamin C therapy in pediatric patients: A scoping review. *Pediatr Crit Care Med* 2021; 22:561–571
14. Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis: International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; 6:2–8
15. Schlapbach LJ, Watson RS, Sorce LR, et al; Society of Critical Care Medicine Pediatric Sepsis Definition Task Force: International consensus criteria for pediatric sepsis and septic shock. *JAMA* 2024; 331:665–674
16. Davis AL, Carcillo JA, Aneja RK, et al: The American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: Executive summary. *Pediatr Crit Care Med* 2017; 18:884–890
17. Fujii T, Luethi N, Young PJ, et al; VITAMINS Trial Investigators: Effect of vitamin C, hydrocortisone, and thiamine vs hydrocortisone alone on time alive and free of vasopressor support among patients with septic shock: The VITAMINS randomized clinical trial. *JAMA* 2020; 323:423–431
18. Fujii T, Salanti G, Belletti A, et al: Effect of adjunctive vitamin C, glucocorticoids, and vitamin B1 on longer-term mortality in adults with sepsis or septic shock: A systematic review and a component network meta-analysis. *Intensive Care Med* 2022; 48:16–24
19. Schlapbach LJ, MacLaren G, Festa M, et al; Australian & New Zealand Intensive Care Society (ANZICS) Centre for Outcomes & Resource Evaluation (CORE) and Australian & New Zealand Intensive Care Society (ANZICS) Paediatric Study Group: Prediction of pediatric sepsis mortality within 1 h of intensive care admission. *Intensive Care Med* 2017; 43:1085–1096
20. Harris PA, Taylor R, Minor BL, et al; REDCap Consortium: The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 2019; 95:103208
21. Long D, Anderson VA, Crossley L, et al: Longitudinal cohort study investigating neurodevelopmental and socioemotional outcomes in school-entry aged children after open heart surgery in Australia and New Zealand: The NITRIC follow-up study protocol. *BMJ Open* 2023; 13:e075429
22. Long D, Gibbons K, Dow B, et al: Effectiveness-implementation hybrid-2 randomised trial of a collaborative shared care model for detecting neurodevelopmental impairments after critical illness in young children (DAISY): Pilot study protocol. *BMJ Open* 2022; 12:e060714
23. Schlapbach LJ, Ganesamoorthy D, Wilson C, et al; EUCLIDS consortium: Host gene expression signatures to identify infection type and organ dysfunction in children evaluated for sepsis: A multicentre cohort study. *Lancet Child Adolesc Health* 2024; 8:325–338
24. Khan KA, Petrou S, Rivero-Arias O, et al: Mapping EQ-5D utility scores from the PedsQL™ generic core scales. *PharmacoEcon* 2014; 32:693–706
25. Cook D, Lauzier F, Rocha MG, et al: Serious adverse events in academic critical care research. *CMAJ* 2008; 178:1181–1184
26. Lamontagne F, Masse MH, Menard J, et al; LOVIT Investigators and the Canadian Critical Care Trials Group: Intravenous vitamin C in adults with sepsis in the intensive care unit. *N Engl J Med* 2022; 386:2387–2398
27. Darnell R, Brown A, Laing E, et al; Protocolised Evaluation of Permissive Blood Pressure Targets Versus Usual Care (PRESSURE) Trial Investigators on behalf of the U.K. Paediatric Critical Care Society Study Group (PCCS-SG): Protocol for a randomized controlled trial to evaluate a permissive blood pressure target versus usual care in critically ill children with hypotension (PRESSURE). *Pediatr Crit Care Med* 2024; 25:629–637

APPENDIX 1.

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