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Original Article

Statistical analysis plan for the SQUEEZE trial: A trial to determine whether septic shock reversal is quicker in pediatric patients randomized to an early goal-directed fluid-sparing strategy vs. usual care (SQUEEZE)

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ABSTRACT

Background: The SQUEEZE trial is a multicentred randomized controlled trial which seeks to determine the optimal approach to fluid resuscitation in paediatric septic shock. SQUEEZE also includes a nested translational study, SQUEEZE-D, investigating the value of plasma cell-free DNA for prediction of clinical outcomes.
Objective: To present a pre-specified statistical analysis plan (SAP) for the SQUEEZE trial prior to finalizing the trial data set and prior to commencing data analysis.
Design: SQUEEZE is a pragmatic, two-arm, open-label, prospective multicentre randomized controlled trial.
Setting: Canadian paediatric tertiary care centres.
Participants: Paediatric patients with suspected sepsis and persistent signs of shock in need of ongoing resuscitation. Sample size target: 400 participants.
Interventions: The trial is designed to compare a fluid-sparing resuscitation strategy to usual care.
Main outcome measures: The primary outcome for the SQUEEZE trial is the time to shock reversal (in hours). The primary outcome analysis will assess the difference in time to shock reversal between the intervention and control groups, reported as point estimate with 95% confidence intervals. The statistical test for the primary analysis will be a two-sided t-test. Secondary outcome measures include clinical outcomes and adverse events including measures of organ dysfunction and mortality outcomes.
Results: The SAP presented here is reflective of and where necessary clarifies in detail the analysis plan as presented in the trial protocol. The SAP includes a mock CONSORT diagram, figures and tables. Data collection methods are summarized, primary and secondary outcomes are defined, and outcome analyses are described.
Conclusions: We have developed a statistical analysis plan for the SQUEEZE Trial for transparency and to align with best practices. Analysis of SQUEEZE Trial data will adhere to the SAP to reduce the risk of bias.

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1. Introduction

Early and aggressive fluid resuscitation has long been a key component of septic shock management, with the initiation of vasoactive agents recommended at the stage of 'fluid refractory shock'.[1,2] However mounting evidence has demonstrated an association between fluid overload and morbidity and mortality in both adults and children.[3–6] The largest and most publicized paediatric trial of fluid resuscitation for suspected septic shock, the Fluid Expansion As Supportive Therapy (FEAST) Trial, demonstrated increased mortality among children treated with aggressive fluid resuscitation in comparison to the conservative fluid resuscitation arm.[7] Given that FEAST was conducted in sub-Saharan Africa in clinical settings where children did not have access to advanced critical care, these findings, while important, are not necessarily generalizable worldwide. Apart from FEAST, there is a paucity of randomized controlled trial evidence to inform fluid resuscitation practices in paediatric septic shock.[8]

The optimal fluid resuscitation strategy and timing of initiation of vasoactive support to achieve therapeutic targets in children with septic shock remains unanswered. While FEAST was able to randomize children to 'no bolus' as this was considered standard of care within the regional context, the same is not true in countries such as Canada. As such, the only way to investigate the signal from FEAST in our context was to investigate a fluid-sparing resuscitation strategy involving early initiation and preferential escalation of vasoactive medication support, while simultaneously restricting fluid bolus therapy. We embarked on the SQUEEZE Trial to determine whether paediatric patients with septic shock would benefit from an early goal-directed fluid-sparing strategy compared to usual care.[9] Here we describe the pre-specified statistical analysis plan (SAP) for the SQUEEZE Trial. The SQUEEZE Trial SAP was finalized prior to locking the final dataset to be used for analysis and commencing data analysis.

2. Methods

2.1. Trial design

SQUEEZE is a pragmatic, two-arm, open-label, prospective multicentre randomized controlled trial designed to compare a fluid-sparing resuscitation strategy to usual care which is fluid-liberal. A superiority hypothesis testing framework will be employed for all between-group comparisons. The definitive phase of SQUEEZE enrolled participants between March 6, 2017 and September 15, 2021. As noted in the protocol, the design included a plan to roll-in SQUEEZE Pilot Trial participants recruited from Jan 6, 2014 to June 3, 2016.[10] The initial pilot trial was designed to examine only feasibility outcomes to allow for potential roll-in of pilot trial participants into the main trial if feasibility criteria were met to proceed.[9] Rolling-in the SQUEEZE pilot trial participants is methodologically acceptable because clinical outcomes were not analysed and the protocol required only minimal changes between the pilot and multicentre trial phases.

2.2. Trial sites

Nine Canadian paediatric tertiary care centres.

2.3. Sample size

The trial protocol prespecified enrolment of 400 participants, including roll-in of pilot trial participants.[10]

2.4. Randomization

The allocation sequence was implemented through a third-party computer-based process accessible on a 24-h basis. Trial site was the only stratification variable. The allocation sequence was computer generated (REDCap) according to parameters input by the Biostatistics Unit of St Joseph's Healthcare Hamilton and this information continues to be kept secret from the investigators. Participants were enrolled into the study by a research assistant or one of the site investigators via REDCap.

2.5. Patient population

Paediatric patients with suspected sepsis and persistent signs of shock. Eligibility criteria are displayed in Table 1.

2.6. Intervention

SQUEEZE Trial participants were randomly allocated to either the Fluid-Sparing (intervention) or Usual Care (control) arm, as previously described.[9] The Fluid-Sparing resuscitation strategy involved avoidance of further fluid bolus therapy and immediate initiation and preferential escalation of vasoactive medication support to treat ongoing signs of shock. The Usual Care resuscitation strategy provided no restrictions on fluid bolus therapy and directed that vasoactive medications not be started until the patient had received a cumulative minimum of 60 mL/kg (3 L for $\geq$50 kg) including fluid bolus therapy received pre-randomization. In both cases, the allocated resuscitation strategy was implemented by the responsible healthcare team who were advised to follow the American College of Critical Care Medicine (ACCM) surviving sepsis guidelines for aspects of care apart from those impacted by the study intervention.[2] The assigned treatment strategy was in effect from allocation until shock was determined to be reversed.

2.7. Primary outcome

2.7.1. SQUEEZE

The primary outcome is the time to shock reversal (in hours). Time zero was defined as the date and time of allocation, while shock was determined to be reversed when all of the following criteria were met in the absence of mechanical circulatory support:

1) Free from all vasoactive medication support
2) Normalization of heart rate (less than 95th percentile for age)
3) Normalization of blood pressure (Systolic Blood Pressure and Mean Blood Pressure greater than the 5th percentile for age)
4) Normalization of capillary refill (<3 s)

These parameters were assessed based on nursing staff documentation in the medical record flowsheet. Where a participant's

Table 1
Eligibility criteria.

Inclusion Criteria	Exclusion Criteria
Age 29 days to <18 years	Patient admitted to the Neonatal Intensive Care Unit (NICU)
Persistent signs of shock defined as one or more of: i) Vasoactive medication dependence[a] ii) Hypotension (systolic and/or mean blood pressure <5th percentile for age)[b] iii) Abnormal Perfusion[c]	Full active resuscitative treatment not within the goals of care
Suspected or confirmed septic shock	Shock secondary to causes other than sepsis (i.e. obvious signs of cardiogenic shock, anaphylactic shock, hemorrhagic shock, spinal shock)
Fluid Resuscitation threshold met. Patient has received within the previous 6 h a minimum of: i) 40 mL/kg of isotonic crystalloid[d] and/or colloid[e] as IV fluid bolus therapy for participants <50 kg OR ii) 2 L of isotonic crystalloid[d] and/or colloid[e] as IV fluid bolus therapy for participants ≥50 kg	Patients requiring resuscitation in the Operating Room or Post Anaesthetic Care Unit
	Previous enrolment in this trial, where known by the research team

[a] Vasoactive medications needed for hemodynamic support, including any of: Dopamine, Dobutamine, Epinephrine, Norepinephrine, Milrinone, Phenylephrine, Vasopressin.
[b] Guidance for hypotension based on Pediatric Advanced Life Support parameters for 5th percentile for age.
[c] Abnormal perfusion requires the presence of two or more of: abnormal capillary refill (CR < 1 s (flash) or CR ≥ 3 s (delayed), tachycardia (heart rate >95th percentile for age), decreased level of consciousness, or decreased urine output.
[d] Isotonic crystalloid [0.9% Saline or Ringer's Lactate].
[e] Isotonic colloid [5% albumin].

baseline vital sign(s) deviated from normal age-expected values then return to baseline value(s) was the endpoint for determining shock-reversal. Where applicable, this was adjudicated by the local principal investigator with input from the trial principal investigator as needed. Where a participant died or was placed on mechanical circulatory support e.g., extracorporeal membrane oxygenation (ECMO) during the intervention period, shock was ascertained as never reversed. Final determination of the date and time of shock-reversal required shock resolution criteria to be met for 24-h prior to discontinuation of the intervention. Illustrations of SQUEEZE trial participant flow through the protocol and ascertainment of the date and time of shock-reversal in various clinical scenarios are accessible via the following citation links.[11,12]

2.7.2. SQUEEZE-D

For the embedded translational biology study, the primary analysis is to evaluate the value of cell-free DNA (cfDNA) to predict time to shock-reversal (in hours).

2.8. Secondary outcomes

2.8.1. SQUEEZE

Secondary outcomes are specified in Table 2. Ascertainment of Ventilator-Free Days (VFDs) in the 28 days following randomization is based on daily scoring as defined in the SQUEEZE Data Dictionary.[13,14] Where death has occurred within 28 days of randomization, days prior to the date of death will be scored as either ventilator-free[1] or not ventilator-free (0) while days from the date of death onward will be scored as not ventilator-free (0). PELOD-2 score will be calculated as previously reported for days 1, 2, 5, 8, 12, 16, 18, following randomization and censored at hospital discharge where applicable.[15] The peak PELOD-2 score for each participant is the highest score recorded, while the change in PELOD-2 score is the difference between the peak score and the score for Day 1.

For trial purposes, we will determine the presence and stage of acute kidney injury (AKI) based on multiples of creatinine and where applicable, initiation of renal replacement therapy.[16] The AKI trial outcome will be positive where participants have new or worsening AKI of at least stage two according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[16] This outcome will be ascertained based on serum creatinine at enrolment and peak creatinine within 7 days following randomization as described in Supplemental File 3. Creatinine values are obtained from the medical record based on clinical laboratory results as ordered by the clinical care team.

2.8.1.1. Adverse events possibly related to fluid overload or third spacing of fluid. Intraabdominal hypertension is defined in paediatrics as intraabdominal pressure above 10 mm Hg.[17] This outcome will be positive for participants with one or more bladder pressure reading(s) exceeding this threshold. Abdominal compartment syndrome is ascertained in accordance with consensus definitions.[14,17]

Soft tissue oedema rank score (0–4) is obtained from the medical record as recorded by nursing staff as part of routine clinical care.[18] Pulmonary oedema is ascertained based on chest X-ray formal report. Total furosemide exposure (mg/kg) is ascertained by tabulating the drug administered each shift from enrolment to 7 days following shock-reversal. Maximum daily furosemide exposure (mg/kg) is ascertained for the 24-h period with peak drug administration. Exposure to other diuretics is obtained from the medical record.

2.8.1.2. Adverse events possibly related to inotrope/vasopressor use. Clinical signs of digital soft tissue ischemia during the intervention period, and digital ischemia requiring amputation (censored at 90 days) are determined from the medical record. The outcome of clinical signs of compromised bowel perfusion is based on documentation by the paediatric surgical consultation service.

2.8.1.3. Descriptive information regarding clinical course and procedures. Outcomes related to clinical course and procedural interventions are of interest because these may be impacted by the intervention.

2.8.1.4. Health services outcomes. Admission to the Paediatric Intensive Care Unit is an important health services outcome which may be impacted by the intervention.

2.8.2. SQUEEZE-D secondary analyses

Value of cfDNA to predict 28-day mortality.

Table 2
Overview of SQUEEZE outcome measure analysis plan and hypotheses.

Outcome Measures	Scale	Type	Method of analysis	Hypothesis
Primary[a,b]				
Time to shock reversal (hours)	Ratio	Continuous	T-test	Lower in control arm
Secondary Outcomes				
1. Clinical Outcomes				
Acute Kidney Injury	Nominal	Binary	Chi-squared test	Lower in intervention arm
Ventilator-Free Days	Ratio	Continuous	T-test	Lower in intervention arm
Highest PELOD-2 score	Ratio	Continuous	T-test	Lower in intervention arm
Change in PELOD-2 score	Ratio	Continuous	T-test	Lower in intervention arm
Length of Pediatric Intensive Care Unit (PICU) stay (days)	Ratio	Continuous	T-test	Lower in intervention arm
Length of Hospital stay (days)	Ratio	Continuous	T-test	Lower in intervention arm
Mortality (28-day)	Nominal	Binary	Chi-squared test	Lower in intervention arm
Mortality (90-day)	Nominal	Binary	Chi-squared test	Lower in intervention arm
Mortality (Hospital Mortality)	Nominal	Binary	Chi-squared test	Lower in intervention arm
2. Adverse Events				
a) Potentially Related to fluid overload/third spacing				
Highest Sodium (mmol/L)	Ratio	Continuous	T-test	Lower in intervention arm
Highest Chloride (mmol/L)	Ratio	Continuous	T-test	Lower in intervention arm
Pleural effusion requiring drainage	Nominal	Binary	Chi-squared test	Lower in intervention arm
Intraabdominal Hypertension	Nominal	Binary	Chi-squared test	Lower in intervention arm
Highest Bladder Pressure recorded	Ratio	Continuous	T-test	Lower in intervention arm
Abdominal Compartment Syndrome	Nominal	Binary	Chi-squared test	Lower in intervention arm
Soft Tissue Edema	Ratio	Continuous	Mann–Whitney test	Lower in intervention arm
Pulmonary Edema	Nominal	Binary	Chi-squared test	Lower in intervention arm
Received Furosemide	Nominal	Binary	Chi-squared test	Lower in intervention arm
Total Furosemide Exposure (mg/kg)	Ratio	Continuous	T-test	Lower in intervention arm
Maximum Daily Furosemide exposure (mg/kg)	Ratio	Continuous	T-test	Lower in intervention arm
Other diuretics used	Nominal	Binary	Chi-squared test	Lower in intervention arm
Spironolactone	Nominal	Binary	Chi-squared test	Lower in intervention arm
Hydrochlorothiazide	Nominal	Binary	Chi-squared test	Lower in intervention arm
Metalozone	Nominal	Binary	Chi-squared test	Lower in intervention arm
b) Potentially related to inotrope/vasopressor use				
Clinical signs of digital soft tissue ischemia	Nominal	Binary	Chi-squared test	Lower in control arm
Digital (or soft tissue) ischemia requiring amputation	Nominal	Binary	Chi-squared test	Lower in control arm
Clinical signs of compromised bowel perfusion	Nominal	Binary	Chi-squared test	Lower in control arm
c) Descriptive information regarding clinical course and procedures during the intervention period				
Invasive Mechanical Ventilation	Nominal	Binary	Chi-squared test	Lower in intervention arm
Renal Replacement Therapy	Nominal	Binary	Chi-squared test	Lower in intervention arm
Arterial Line Placement	Nominal	Binary	Chi-squared test	Lower in control arm
Central Line Placement	Nominal	Binary	Chi-squared test	Lower in control arm
Chest Tube Placement	Nominal	Binary	Chi-squared test	Lower in intervention arm
Peritoneal Drain Placement	Nominal	Binary	Chi-squared test	Lower in intervention arm
Mechanical circulatory support e.g. ECMO to treat refractory shock	Nominal	Binary	Chi-squared test	Lower in intervention arm
d) Health Services Outcomes				
Pediatric Intensive Care Unit (PICU) Admission Rate	Nominal	Binary	Chi-squared test	Lower in control arm

[a] Exploratory subgroup analyses will be conducted for the primary outcome based on participant location (emergency department vs other location) and interpreted using the p-value for interaction.
[b] Exploratory analyses of the primary outcome will be conducted to assess for association between volume of isotonic fluid bolus therapy (crystalloid and/or colloid) received in the 24 h prior to randomization and study outcomes and interpreted using the p-value for interaction.: i) volume of isotonic fluid bolus therapy received prior to randomization (≤60 mL/kg vs > 60 mL/kg), and ii) volume of isotonic fluid bolus therapy received prior to randomization (≤80 mL/kg vs > 80 mL/kg).

Value of cfDNA to predict hospital mortality.
Correlation of cfDNA with PELOD-2 score.
Value of cfDNA when combined with Protein C level, platelet count, and organ dysfunction scores (PELOD-2) to predict clinical outcomes of interest including time to shock-reversal, 28-day mortality and hospital mortality.

2.9. Harms

We planned to report any serious adverse events (SAEs) to the REB and the Data Safety and Monitoring Board (DSMB) as required. To be categorized as an SAE, an event must be serious, as well as unexpected and related to trial participation.[19] In academic critical care research, trial outcomes should not be categorized as SAEs when they are expected.[20]

2.10. Sample size

The SQUEEZE Trial sample size calculation was performed by an independent statistician using SQUEEZE Pilot Trial data. It was determined that a total of 400 participants (200 per arm) were required for the multicentre trial to detect an estimated 30% difference in the time to shock reversal based on a two-sided t-test of the null hypothesis that there is no difference between groups, type one error (α) at 0.05, and power (β) at 80%. (Supplemental File 4) We used the selected estimated difference, corresponding to approximately one nursing shift, as we considered this minimally clinically meaningful.

2.11. Data collection and data management

The trial protocol includes a schedule of enrolment, interventions, and assessments.[10] Participant demographic data and SQUEEZE outcome data are collected from the hospital medical record by a Research Assistant (RA) or one of the investigators. Clinical assessment data (e.g. vital signs, all sources of fluid intake and fluid loss), were measured by bedside nursing staff and routinely recorded in the medical record flowsheet. Laboratory data were measured and reported by the hospital laboratory as requested by the clinical care team for clinical purposes. SQUEEZE

uses the REDCap data management program for all data entry.[21] Data can be entered by designated users from any computer with an internet connection. Data is stored on a secure, firewall-protected server.

SQUEEZE-D data consists of participant cfDNA and Protein C levels determined from analysis of blood samples obtained at two time points following randomization.[9,10,22] Sample A was drawn within 6 h of randomization while Sample B was collected 24–48 h post-randomization. These formal results will be entered into the SQUEEZE RedCap database to support planned translational analyses. Access to all data is limited to those directly involved in the conduct of the study.

2.12. Statistical analysis

We will adopt the CONSORT guidelines for reporting of RCT results and an intention-to-treat principle to analyse all outcomes.[23,24] The process of participant selection and flow through the study will be summarized using a flow diagram. Baseline characteristics will be reported as mean (standard deviation) or median (interquartile range) for continuous variables, and count (percent) for categorical variables. Continuous and dichotomous outcomes will be analysed using two group t-tests or logistic regression respectively. The statistical significance will be set at $\alpha < 0.05$.

The DSMB for the SQUEEZE Trial performed two blinded interim analyses for safety at the following recruitment milestones: n = 200, ~50% accrual; and n = 300, ~75% accrual. Given the trial size and anticipated small event numbers, there were no prespecified stopping rules. Since the prespecified interim safety assessment did not require interim analysis of the primary outcome, we did not plan adjustments for multiple testing.

SQUEEZE is powered for the primary outcome analysis of the clinical trial. Secondary outcome analyses are exploratory only. The primary and secondary analyses for the nested translational study, SQUEEZE-D are exploratory only. Multiple imputation will be used to handle missing data as described in Section 3.3.[25] All outcomes analysed will be reported as effect estimates with 95% confidence intervals. Statistical analyses will be conducted by a statistician using SAS (Cary, NC, USA).

The SAP and main SQUEEZE Trial manuscript will include all primary and secondary analyses for the clinical trial, and the primary analysis for SQUEEZE-D. Secondary analyses for SQUEEZE-D, while included in the SAP, will be reported in a separate manuscript. SQUEEZE-D analyses are exploratory only. Additional/tertiary exploratory analyses specified in the study protocol will be reported in a separate manuscript. Given that data collected on fluid administration and vasoactive medication use post-randomization is directly impacted by the intervention, reporting of these parameters will be for descriptive purposes only.

2.13. Analysed dataset

The final trial dataset will include all prespecified data fields for the clinical trial as well as for SQUEEZE-D. Since SQUEEZE exclusively utilizes an exception to consent (deferred consent) model, the population of participants to be analysed is as summarized below in alignment with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.[26]

2.14. Participant status for analysis

The population of participants eligible for analysis is outlined in Table 3 and will be analysed according to intention-to-treat principles. Participants will be analysed in the group to which they were randomized.

2.15. Trial profile

A CONSORT Flow Diagram will illustrate the flow of potential participants into the SQUEEZE Trial.[23,24] This will include the number of potential participants who were screened, excluded (with reasons), and those who were randomized. Participants were exclusively enrolled using an exception to consent (deferred consent) process. The flow diagram will include post-randomization exclusions for reasons such as consent decline. A mock CONSORT diagram for the trial is presented as Fig. 1.

2.16. Patient characteristics and baseline comparisons

Participant baseline characteristics for each study arm will be presented in Table 1 of the primary manuscript as shown in Table 4. The full/extended version of Table 1 will be provided as an appendix to the main manuscript (Supplementary File 5). Baseline data will include demographic data, baseline clinical and laboratory data, and data on baseline clinical status including previously diagnosed medical co-morbidities, Pediatric Risk of Mortality (PRISM) IV score, and Acute Kidney Injury (AKI) at enrolment.[16,27] Data presented in Table 1 is for descriptive purposes only and no p-values will be presented.

2.17. Analysis of adherence for initiation of and compliance with the intervention

We will report the time from when a participant was deemed eligible until randomization. We will also report the time elapsed from randomization to communication of the allocation to the healthcare provider team. Some centres participated in the collection of a fluid-sparing bolus record for participants enrolled into the fluid-sparing arm. For this subset of participants, we will describe provider rationale/indications for prescribing any fluid bolus therapy during the intervention period.

2.18. Protocol deviations

Protocol deviations will be summarized by type as recorded in the Protocol Deviation Tracking Log. Protocol deviation codes include deviations related to: consent procedures, eligibility criteria, randomization procedures/allocation, study procedures,

Table 3
Participant status for analysis.

Category	To be Included for Analysis	To be Excluded from Analysis
Deferred Consent Obtained	Include	
Waiver of Consent Approved	Include	
Deferred Consent Declined – Data retention authorized	Include	
Deferred Consent Declined – No data/Data retention not authorized		Exclude
Deferred Consent Not Obtained – No data/Data retention not authorized		Exclude
Randomization Errors		Exclude

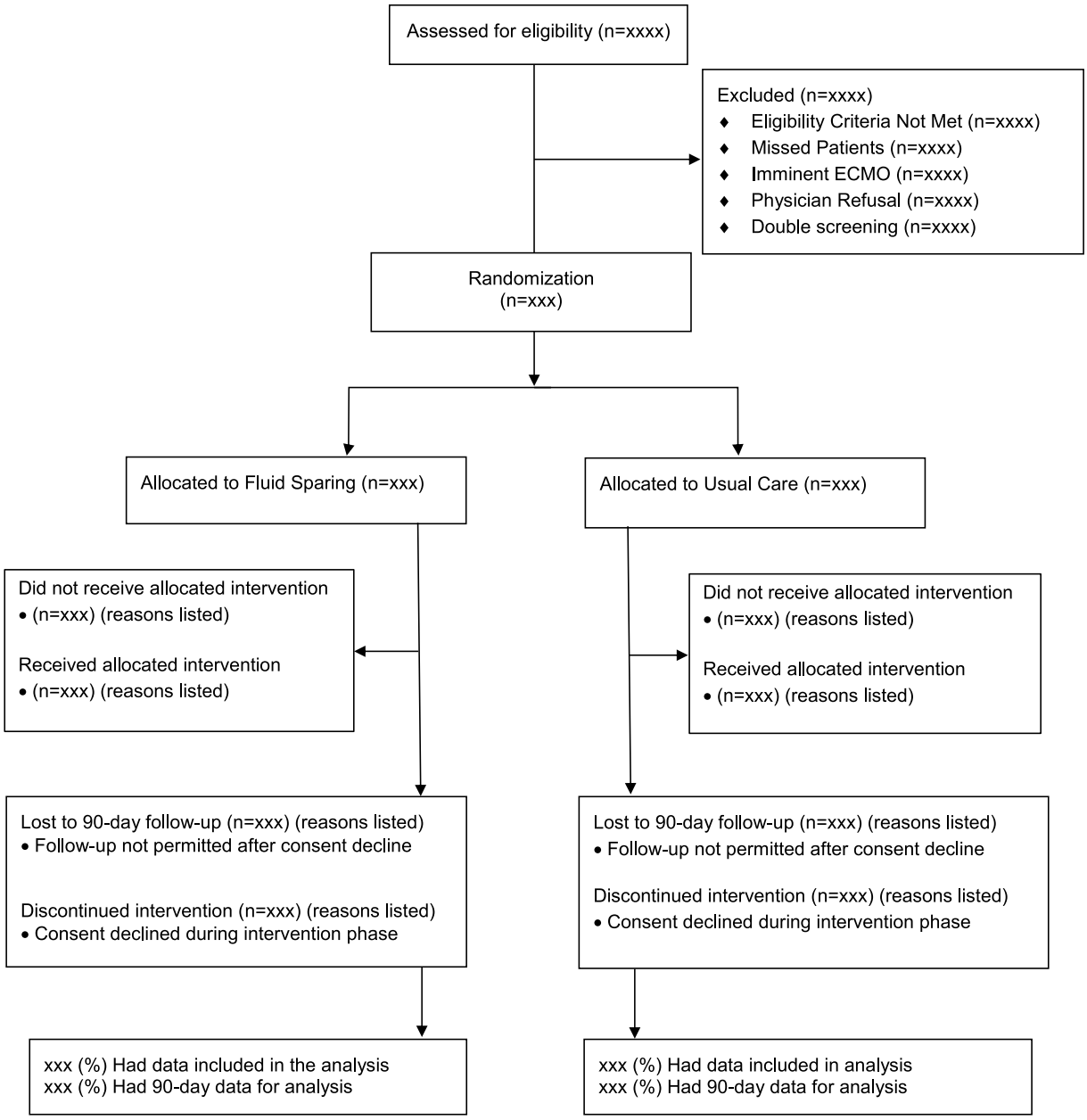

Fig. 1. CONSORT flow diagram.

serious adverse event reporting, biological specimen collection, or 'other'.[10]

3. Analysis of the primary outcome

3.1. Principal analysis

The mean time to shock reversal (in hours) will be reported for each group with 95% confidence intervals. The principal analysis will be a t-test of the geometric means of the treatment groups to assess whether these are significantly different, based on a type one error of 0.05, and power of 80%. The primary effect estimate, i.e., the mean difference will be reported with 95% confidence intervals. There are no pre-specified adjusted analyses.

3.2. Adjusted sensitivity analysis

None prespecified.

3.3. Treatment of missing data

If more than 5% of participants have missing data in the final trial dataset, missing data will be imputed using multiple imputation, a flexible technique for handling missing data.[25] It is important to note that missing data should be distinguished from data

Table 4
Table 1 Main manuscript (abbreviated): Baseline characteristics.

Baseline Variable	Category	Group A N =	Group B N =
Demographic/Descriptive			
Age (months): n, mean[a] (sd)		N, mean (sd)	N, mean (sd)
Gender: n (%)	Female	N (%)	N (%)
	Male	N (%)	N (%)
Body Weight (kg)		N, mean (sd)	N, mean (sd)
Location Patient Deemed Eligible	Study Site Emergency Room	N (%)	N (%)
	Study Site Hospital Ward	N (%)	N (%)
	Study Site PICU	N (%)	N (%)
Arrived to study site within past 48 h	Yes	N (%)	N (%)
	Transferred in from another facility	N (%)	N (%)
	Presented from home	N (%)	N (%)
	No	N (%)	N (%)
Previous Medical Comorbidities	Yes	N (%)	N (%)
	No	N (%)	N (%)
Previous Medical Comorbidities	Neurological	N (%)	N (%)
	Cardiac	N (%)	N (%)
	Pulmonary	N (%)	N (%)
	Hematological	N (%)	N (%)
	Malignancy	N (%)	N (%)
	Gastrointestinal	N (%)	N (%)
	Endocrine	N (%)	N (%)
	Autoimmune disorder	N (%)	N (%)
	Immunodeficiency	N (%)	N (%)
	Genetic/Hereditary disorder	N (%)	N (%)
	Renal	N (%)	N (%)
	Other	N (%)	N (%)
Surgical Associated Sepsis	Yes	N (%)	N (%)
	No	N (%)	N (%)
Admission Diagnosis related to sepsis	Yes	N (%)	N (%)
	No	N (%)	N (%)
Randomization Form Data			
Study Site	1	N (%)	N (%)
	2	N (%)	N (%)
	3	N (%)	N (%)
	4	N (%)	N (%)
	5	N (%)	N (%)
	6	N (%)	N (%)
	7	N (%)	N (%)
	8	N (%)	N (%)
	9	N (%)	N (%)
Randomization Time of Day	Daytime (0800–17:00)	N (%)	N (%)
	After hours (17:01–07:59)	N (%)	N (%)
Time to Communication of Allocation to Medical Team	Time elapsed (min)	N, mean (sd)	N, mean (sd)
Screening Form Clinical Data			
Vasoactive Medication Dependence	Yes	N (%)	N (%)
	No	N (%)	N (%)
Hypotension	Yes	N (%)	N (%)
	No	N (%)	N (%)
Abnormal Perfusion	Abnormal Capillary Refill	N (%)	N (%)
	Tachycardia	N (%)	N (%)
	Decreased Level of Consciousness	N (%)	N (%)
	Decreased Urine Output	N (%)	N (%)
	None of the above	N (%)	N (%)
Baseline Clinical Data			
Heart Rate (bpm)		N, mean (sd)	N, mean (sd)
Systolic Blood Pressure (mm Hg)		N, mean (sd)	N, mean (sd)
Mean Blood Pressure (mm Hg)		N, mean (sd)	N, mean (sd)
Capillary Refill Time (seconds)		N, mean (sd)	N, mean (sd)
Altered Mental Status	Yes	N (%)	N (%)
	No	N (%)	N (%)
Respiratory Rate (bpm)		N, mean (sd)	N, mean (sd)
SpO2 (%)		N, mean (sd)	N, mean (sd)
Temperature (°C)		N, mean (sd)	N, mean (sd)
pH		N, mean (sd)	N, mean (sd)
Lactate (mmol/L)		N, mean (sd)	N, mean (sd)
HC03 (mmol/L)		N, mean (sd)	N, mean (sd)
Glucose (mmol/L)		N, mean (sd)	N, mean (sd)
Potassium (mmol/L)		N, mean (sd)	N, mean (sd)
Sodium (mmol/L)		N, mean (sd)	N, mean (sd)
Chloride (mmol/L)		N, mean (sd)	N, mean (sd)
Positive Malaria status	Yes	N (%)	N (%)
	No	N (%)	N (%)

(*continued on next page*)

Table 4 (*continued*)

Baseline Variable	Category	Group A N =	Group B N =
PRISM IV score		N, mean (sd)	N, mean (sd)
PCO2		N, mean (sd)	N, mean (sd)
Creatinine (umol/L)		N, mean (sd)	N, mean (sd)
BUN (umol/L)		N, mean (sd)	N, mean (sd)
WBC count (x 10^9/L)		N, mean (sd)	N, mean (sd)
PTT (aPTT)		N, mean (sd)	N, mean (sd)
PT (INR)		N, mean (sd)	N, mean (sd)
Platelet count (x 10^9/L)		N, mean (sd)	N, mean (sd)
Acute Kidney Injury at baseline (prevalent AKI)	Yes	N (%)	N (%)
	No	N (%)	N (%)
Positive cultures and Anti-Infective Agents Administered prior to randomization			
Positive Organism(s) on cultures	Yes	N (%)	N (%)
obtained in the 24 h period prior to randomization	No	N (%)	N (%)
Site(s) Culture was obtained from	Blood – Arterial Line	N (%)	N (%)
	Blood – Central Venous Line	N (%)	N (%)
	Blood – Peripheral	N (%)	N (%)
	Urine – Midstream Urine	N (%)	N (%)
	Urine – Catheter	N (%)	N (%)
	Cerebro-spinal Fluid	N (%)	N (%)
	Feces	N (%)	N (%)
	Chest Tube	N (%)	N (%)
	Naso-pharyngeal Swab	N (%)	N (%)
	Tissue sample	N (%)	N (%)
	Peritoneal Drain	N (%)	N (%)
	Other	N (%)	N (%)
Organism Category	Bacterial	N (%)	N (%)
	Viral	N (%)	N (%)
	Fungal	N (%)	N (%)
	Parasitic	N (%)	N (%)
Organism Gram Stain	Gram Positive	N (%)	N (%)
	Gram Negative	N (%)	N (%)
	Neither (bacteria)	N (%)	N (%)
	Not applicable (non-bacterial)	N (%)	N (%)
Anti-infective agents administered in the 24 h period prior to randomization	Yes	N (%)	N (%)
	No	N (%)	N (%)
Fluids and Blood Products Received in the 24 h period prior to randomization			
Total Volume as Fluid Bolus Therapy (include 0.9% Saline (NS), Ringer's Lactate (RL), Plasmalyte, 5% Albumin) (mL)		N, mean (sd)	N, mean (sd)
Total Volume as Fluid Bolus Therapy (include 0.9% Saline (NS), Ringer's Lactate (RL), Plasmalyte, 5% Albumin) (mL/kg)		N, mean (sd)	N, mean (sd)
Total Volume as Blood products (exclude 5% Albumin as fluid bolus) (mL)		N, mean (sd)	N, mean (sd)
Total Volume as Blood products (exclude 5% Albumin as fluid bolus) (mL/kg)		N, mean (sd)	N, mean (sd)
Total Volume Received (mL)		N, mean (sd)	N, mean (sd)
Total Volume Received (mL/kg)		N, mean (sd)	N, mean (sd)

[a] For outcomes planned to be reported as mean, median will instead be reported if data are discovered to be skewed at analysis.

which are not available for reasons that are known such as death. Only data which are truly missing will be considered for multiple imputation.

3.4. Evaluation of heterogeneity in treatment effect

None prespecified.

3.5. Subgroup analyses

While statistical power for subgroup analyses is limited, we will conduct exploratory analysis to assess for association between location of participant eligibility and study outcomes.

a. Emergency Department location vs other hospital location

3.6. Exploratory analyses of the primary outcome

We will conduct exploratory analyses to assess for the association between the volume of isotonic fluid bolus therapy received in the 24 h prior to randomization and study outcomes.

Subgroups of interest include:

a. Participants who received $\leq$60 mL/kg vs > 60 mL/kg as fluid bolus therapy pre-randomization
b. Participants who received $\leq$80 mL/kg vs > 80 mL/kg as fluid bolus therapy pre-randomization

3.7. Additional analyses

Kaplan–Meier analyses will be conducted to compare the time from randomization until shock reversal for the two treatment groups. The results will be displayed graphically as Kaplan–Meier curves and presented as a figure in the primary manuscript.

Table 5
Table 2 Main manuscript: Clinical outcomes and adverse events.

Outcome Variable	Group A	Group B	Effect Estimate [95% CI]	p-value
Primary Outcome				
Time to shock reversal (in hours)	N, mean (SD)	N, mean (SD)	Mean difference	x.xx
Secondary Outcomes				
1. Clinical Outcomes				
Acute Kidney Injury	N (%)	N (%)	Relative Risk	
Ventilator-Free Days	N, mean (SD)	N, mean (SD)	Mean difference	
Highest PELOD-2 score	N, mean (SD)	N, mean (SD)	Mean difference	
Change in PELOD-2 score	N, mean (SD)	N, mean (SD)	Mean difference	
Length of Pediatric Intensive Care Unit (PICU) stay (days)	N, mean (SD)	N, mean (SD)	Mean difference	
Length of Hospital stay (days)	N, mean (SD)	N, mean (SD)	Mean difference	
Mortality (28-day)	N (%)	N (%)	Relative Risk	
Mortality (90-day)	N (%)	N (%)	Relative Risk	
Mortality (Hospital Mortality)	N (%)	N (%)	Relative Risk	
2. Adverse Events				
a) Potentially Related to fluid overload/third spacing				
Highest Sodium (mmol/L)	N, mean (SD)	N, mean (SD)	Mean difference	
Highest Chloride (mmol/L)	N, mean (SD)	N, mean (SD)	Mean difference	
Pleural effusion requiring drainage	N (%)	N (%)	Relative Risk	
Intraabdominal Hypertension	N (%)	N (%)	Relative Risk	
Highest Bladder Pressure recorded	N, mean (SD)	N, mean (SD)	Mean difference	
Abdominal Compartment Syndrome	N (%)	N (%)	Relative Risk	
Soft Tissue Edema	Median Rank [IQR]	Median Rank [IQR]	Median difference	
Pulmonary Edema	N (%)	N (%)	Relative Risk	
Received Furosemide	N (%)	N (%)	Relative Risk	
Total Furosemide Exposure (mg/kg)	N, mean (sd)	N, mean (sd)	Mean difference	
Maximum Daily Furosemide exposure (mg/kg)	N, mean (sd)	N, mean (sd)	Mean difference	
Other diuretics used	N (%)	N (%)	Relative Risk	
Spironolactone	N (%)	N (%)	Descriptive	
Hydrochlorothiazide	N (%)	N (%)	Descriptive	
Metalozone	N (%)	N (%)	Descriptive	
b) Potentially related to inotrope/vasopressor use				
Clinical signs of digital soft tissue ischemia	N (%)	N(%)	Relative Risk	
Digital (or soft tissue) ischemia requiring amputation	N (%)	N (%)	Relative Risk	
Clinical signs of compromised bowel perfusion	N (%)	N (%)	Relative Risk	
c) Descriptive information regarding clinical course and procedures during the intervention period				
Invasive Mechanical Ventilation	N (%)	N (%)	Relative Risk	
Renal Replacement Therapy	N (%)	N (%)	Relative Risk	
Arterial Line Placement	N (%)	N (%)	Relative Risk	
Central Line Placement	N (%)	N (%)	Relative Risk	
Chest Tube Placement	N (%)	N (%)	Relative Risk	
Peritoneal Drain Placement	N (%)	N (%)	Relative Risk	
Mechanical circulatory support e.g. ECMO to treat refractory shock	N (%)	N (%)	Relative Risk	
d) Health Services Outcomes				
Pediatric Intensive Care Unit (PICU) Admission Rate	N (%)	N (%)	Relative Risk	
e) Other				
Serious Adverse Events	N (%)	N (%)	Relative Risk	

3.8. Analyses of other secondary outcomes

Clinical outcomes and adverse events will be reported in Table 2 of the main manuscript as outlined in Table 5.

3.9. Analyses of adverse events and serious adverse events

Many secondary outcomes in SQUEEZE are characterized as adverse events as is common in critical care research.[20] In addition to those prespecified, we will describe other reported adverse events and events which met the criteria for reporting as a SAE for each treatment group.[19]

3.10. Additional analyses of descriptive data

Descriptive data on vasoactive medication use, fluid balance, and related variables during the intervention period will be presented by group in Table 3 of the main manuscript (Table 6). The highest vasoactive inotropic score (VIS) will be calculated for each participant and the mean highest VIS will be reported by group.[28] The proportion of participants administered parenteral (IV) steroids will be described. For the intervention group only, descriptive data describing justification for any fluid bolus therapy will be reported. Descriptive data on fluid intake, fluid output, and fluid balance during the resuscitation phase, will be displayed by group for the 24-h period following allocation (Day 1) and the 72-h period following allocation (Day 1–3) (Supplementary File 6). Additional tables to be provided as appendices to the main manuscript include: Site of infection and antimicrobial use data (Supplemental File 7), mortality descriptive data (Supplemental File 8), consent process data (Supplemental File 9), SQUEEZE-D (Supplemental File 10), Organisms grown from cultures obtained pre-randomization (Supplemental File 11), Organisms grown from cultures obtained during the intervention period (Supplemental File 12).

3.11. Statistical software

All analyses will be performed using SAS [9.4] (Cary, NC, USA).

4. Funding, registration and ethics approval

Funding to support SQUEEZE Trial conduct was obtained from multiple sources as listed in Supplemental File 13. The pilot trial [NCT 01973907; Registered Oct 27, 2013] and the multicentre phase

Table 6
Table 3 Main Manuscript: Descriptive Data on Vasoactive Medication Use, Fluid Balance, and related Clinical Variables During the Intervention Period.

Variable		Group A	Group B
Vasoactive Medication Used to treat Septic Shock		N (%)	N (%)
First Vasoactive Medication administered	Dopamine	N (%)	N (%)
	Dobutamine	N (%)	N (%)
	Epinephrine	N (%)	N (%)
	Norepinephrine	N (%)	N (%)
	Phenylephrine	N (%)	N (%)
	Milrinone	N (%)	N (%)
	Vasopressin	N (%)	N (%)
Duration of Vasoactive medication use (hours)		N, mean (sd)	N, mean (sd)
Highest Vasoactive medication score		N, mean (sd)	N, mean (sd)
IV Steroid Administration	Yes	N (%)	N (%)
	No	N (%)	N (%)
	Study Drug	N (%)	N (%)
Fluid Intake, output, and fluid balance			
Fluids Administered			
IV Maintenance Fluids (mL)		N, mean (sd)	N, mean (sd)
IV Maintenance Fluids (mL/kg)		N, mean (sd)	N, mean (sd)
IV Parenteral Nutrition (mL)		N, mean (sd)	N, mean (sd)
IV Parenteral Nutrition (mL/kg)		N, mean (sd)	N, mean (sd)
IV Fluid Bolus Therapy (mL)		N, mean (sd)	N, mean (sd)
IV Fluid Bolus Therapy (mL/kg)		N, mean (sd)	N, mean (sd)
Enteral fluid and nutrition (mL)		N, mean (sd)	N, mean (sd)
Enteral fluid and nutrition (mL/kg)		N, mean (sd)	N, mean (sd)
Red Blood Cells (mL)		N, mean (sd)	N, mean (sd)
Red Blood Cells (mL/kg)		N, mean (sd)	N, mean (sd)
Platelets (mL)		N, mean (sd)	N, mean (sd)
Platelets (mL/kg)		N, mean (sd)	N, mean (sd)
5% Albumin not as fluid bolus (mL)		N, mean (sd)	N, mean (sd)
5% Albumin not as fluid bolus (mL/kg)		N, mean (sd)	N, mean (sd)
25% Albumin (mL)		N, mean (sd)	N, mean (sd)
25% Albumin (mL/kg)		N, mean (sd)	N, mean (sd)
Fresh Frozen Plasma (mL)		N, mean (sd)	N, mean (sd)
Fresh Frozen Plasma (mL/kg)		N, mean (sd)	N, mean (sd)
Intravenous immunoglobulin (IVIG) (mL)		N, mean (sd)	N, mean (sd)
Intravenous immunoglobulin (IVIG) (mL/kg)		N, mean (sd)	N, mean (sd)
Cryoprecipitate (mL)		N, mean (sd)	N, mean (sd)
Cryoprecipitate (mL/kg)		N, mean (sd)	N, mean (sd)
IV Replacement Fluid (mL)		N, mean (sd)	N, mean (sd)
IV Replacement Fluid (mL/kg)		N, mean (sd)	N, mean (sd)
IV Medication Administration (mL)		N, mean (sd)	N, mean (sd)
IV Medication Administration (mL/kg)		N, mean (sd)	N, mean (sd)
IV Fluids while in Operating room (mL)		N, mean (sd)	N, mean (sd)
IV Fluids while in Operating Room (mL/kg)		N, mean (sd)	N, mean (sd)
Total Fluids In (mL)		N, mean (sd)	N, mean (sd)
Total Fluids In (mL/kg)		N, mean (sd)	N, mean (sd)
Fluid Losses/Removal			
Urine Output (mL)		N, mean (sd)	N, mean (sd)
Urine Output (mL/kg)		N, mean (sd)	N, mean (sd)
Output from drains (mL)		N, mean (sd)	N, mean (sd)
Output from drains (mL/kg)		N, mean (sd)	N, mean (sd)
Losses as vomit/stool (mL)		N, mean (sd)	N, mean (sd)
Losses as vomit/stool (mL/kg)		N, mean (sd)	N, mean (sd)
Renal Replacement Therapy net fluid removal (mL)		N, mean (sd)	N, mean (sd)
Renal Replacement Therapy net fluid removal (mL/kg)		N, mean (sd)	N, mean (sd)
Total Fluids Out (mL)		N, mean (sd)	N, mean (sd)
Total Fluids Out (mL/kg)		N, mean (sd)	N, mean (sd)
Fluid Balance			
Fluid Balance over the Intervention Period (mL)		N, mean (sd)	N, mean (sd)
Fluid Balance over the Intervention Period (mL/kg)		N, mean (sd)	N, mean (sd)
Clinical Variables			
Highest Central Venous Pressure (CVP)		N, mean (sd)	N, mean (sd)
Highest Mean Airway Pressure		N, mean (sd)	N, mean (sd)
Fluid Bolus Therapy Descriptive Data			
Fluid Bolus Therapy Type received by participant	0.9% Saline (NS)	N (%)	N (%)
	Ringer's Lactate (RL)	N (%)	N (%)
	5% Albumin	N (%)	N (%)
	Plasmalyte	N (%)	N (%)
Number of fluid boluses administered to participant	All Isotonic fluids	N, Median [IQR]	N, Median [IQR]
Fluid Bolus volume of each bolus (mL)	All isotonic fluids	N, mean (sd)	N, mean (sd)
Fluid Bolus volume of each bolus (mL/kg)	All isotonic fluids	N, mean (sd)	N, mean (sd)
Justification for Fluid Bolus (Fluid Sparing only)	Yes	N (%)	N (%)
	No	N (%)	N (%)
Justification Provided for Fluid Bolus (Fluid Sparing only)	Hypotension	N (%)	N (%)
	Hypoperfusion	N (%)	N (%)

Table 6 (*continued*)

Variable		Group A	Group B
	Hypotension & Hypoperfusion	N (%)	N (%)
	Justification not Provided	N (%)	N (%)
How Intravascular hypovolemia was determined by Clinician	Tachycardia	N (%)	N (%)
	Central Venous Pressure (CVP)	N (%)	N (%)
	Hepatojugular Reflex	N (%)	N (%)
	Straight Leg Raise	N (%)	N (%)
	Bedside Ultrasound	N (%)	N (%)
	Formal Echocardiogram (ECHO)	N (%)	N (%)
	Capillary Refill Time/Signs of poor perfusion	N (%)	N (%)
	Increased Lactate/worsening metabolic acidosis	N (%)	N (%)
	Urine quantity	N (%)	N (%)
	Other	N (%)	N (%)
	Justification not provided	N (%)	N (%)

of the trial [NCT03080038; Registered Feb 28, 2017] were prospectively registered on clinical trials.gov. Ethical approval for pilot trial conduct was obtained from the Hamilton Integrated Regional Ethics Board (HIREB Project # 13–295). The multicentre trial phase received ethical approval from HIREB (HIREB Project # 1803) and was transferred subsequently to Clinical Trials Ontario (CTO Project # 0833). Ethical approval was obtained for participation of each trial site prior to commencing enrolment.

5. Discussion

We present here the statistical analysis plan for the SQUEEZE Trial to align with best practices. The SAP should be read in conjunction with the SQUEEZE Trial Protocol which also outlines prespecified analyses.[29] Where necessary, further elaboration has been provided within this SAP. The final participant was enrolled into the SQUEEZE Trial prior to completion of this SAP document. However, the SAP has been completed in advance of the trial dataset being finalized. Beyond assessing trial data for accuracy and completeness, the authors have otherwise not looked at trial data.

Role of the study sponsor and funders

The study sponsor and funders have not been involved in the study design, and will not be involved in the collection, management, analysis, or interpretation of data. The study sponsor and funders have not been involved in the writing of this manuscript, nor will they have input into any manuscript reporting study findings. The study sponsor and funder do not have any input into the decision to submit this or future work for publication. The authority for overseeing study conduct, analysis, interpretation and dissemination of findings rests with the study investigators.

Disclaimer

The views expressed herein do not necessarily represent the views of the Canadian federal government.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2024.02.002.

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