INTERVENTION STUDY (CLINICAL TRIALS)

Title:	**Feasibility Study for the Randomized Pragmatic Pediatric Trial of Balanced versus Normal Saline Fluid in Sepsis**
Short Title	**PRoMPT BOLUS - Feasibility**
Drug or Device Name(s):	0.9% Isotonic ("Normal") Saline, Lactated Ringer's
FDA IND	136978
Regulatory Sponsor:	FDA
eIRB Number	17-013936
Protocol Date:	November 6, 2017
Amendment 1 Date:	Amendment 3 Date:
Amendment 2 Date:	Amendment 4 Date:

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ABBREVIATIONS AND DEFINITIONS OF TERMS

°C	Degrees centigrade
95% CI	95% confidence interval
ACCM	American College of Critical Care Medicine
AE	Adverse Event
AKI	Acute Kidney Injury
CHOP	Children's Hospital of Philadelphia
CRF	Case Report Form
DCC	Data Coordinating Center
DKA	Diabetic Ketoacidosis
DSMB	Data Safety and Monitoring Board
ED	Emergency Department
EFIC	Exception from Informed Consent
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ICD-9	International Classification of Diseases, 9th edition
ICH	International Conference on Harmonization
IND	Investigational New Drug
IO	Intraosseus
IRB	Institutional Review Board
IV	Intravenous
kg	Kilogram
LAR	Legally Authorized Representative
LR	Lactated Ringers
ml	Milliliter
NaCl	Sodium Chloride
NS	Normal Saline
NSAID	Non Steroidal Anti Inflammatory Drug
OR	Odds Ratio
PECARN	Pediatric Emergency Care Applied Research Network
PHI	Personal Health Information
PHIS	Pediatric Health Information System
PICU	Pediatric Intensive Care Unit
RCT	Randomized Controlled Trial
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAN	Storage Area Network
SID	Strong Ion Difference
tPA	Tissue Plasminogen Activator

ABSTRACT

Context: Intravenous (IV) crystalloids are the standard resuscitative fluid for pediatric septic shock. Despite proven clinical benefit for both non-buffered 0.9% "normal" saline (NS) and buffered/balanced lactated Ringer's (LR) to restore effective circulation and increasing data supporting relative benefits and improved safety profile for LR over NS, the use of NS overwhelmingly remains the most commonly used crystalloid fluid in pediatric septic shock. A cost-efficient approach to definitively determine the comparative effectiveness and safety of NS and LR is with a large pragmatic randomized trial, though concerns regarding feasibility need to be addressed prior to such a trial.

Objectives: The objective of this study is to assess overall feasibility of this study at CHOP with the following specific aims:

Aim 1: To determine compliance with study fluid administration, throughout the intervention phase, within each randomized arm using a pragmatic study design

Aim 2: To estimate the proportion of eligible pediatric patients with suspected septic shock who may be enrolled into a randomized pragmatic trial of fluid resuscitation

Aim 3: To demonstrate feasibility of patient enrollment into a pragmatic fluid resuscitation trial using Exception from Informed Consent (EFIC)

Study Design: Randomized, controlled, open-label pragmatic pilot trial

Setting/Participants: Eligible patients >6 months and <18 years with clinician concern for septic shock who require at least 20 ml/kg of fluid resuscitation will be enrolled in the Emergency Department of the Children's Hospital of Philadelphia. Patients will be enrolled prior to receipt of >40 mL/kg IV/IO crystalloid fluid. Due to the life-threatening nature of septic shock and the narrow therapeutic window for fluid resuscitation, potential subjects will be enrolled through the federal "exception from informed consent" (EFIC) process, with prospective informed consent obtained as possible in rare circumstances.

Study Interventions and Measures: Seventy subjects will be randomized to receive either open-label NS or LR for all remaining fluid administration (bolus and maintenance) until 11:59pm on the calendar day following randomization such that all patients receive at least 24 hours of study fluid. The primary feasibility outcome for this pilot study will be the proportion of total crystalloids administered as the correct study fluid within each randomized arm (Aim 1). Secondary outcomes will include mean proportion of total crystalloids administered as non-study fluid in each arm (Aim 1), percent enrollment/randomization/treatment of eligible patients (Aim 2), and successful EFIC approval with <10% subject withdrawal. Specified safety outcomes will be monitored as they occur in the course of routine clinical practice but this pilot study will not be powered to assess safety given that both fluids are FDA-approved and have well-described efficacy and safety profiles.

PROTOCOL SYNOPSIS

Study Title	**Feasibility Study for the Randomized Pragmatic Pediatric Trial of Balanced versus Normal Saline Fluid in Sepsis (PRoMPT BOLUS – Feasibility)**
Funder	The Children's Hospital of Philadelphia
Clinical Phase	Pilot/feasibility study
Study Rationale	Intravenous (IV) crystalloids are the standard resuscitative fluid for pediatric septic shock. Despite proven clinical benefit for both non-buffered 0.9% "normal" saline (NS) and buffered/balanced lactated Ringer's (LR) to restore effective circulation and increasing data supporting relative benefits and improved safety profile for LR over NS, the use of NS overwhelmingly remains the most commonly used crystalloid fluid in pediatric septic shock. A cost-efficient approach to definitively determine the comparative effectiveness and safety of NS and LR is with a large pragmatic randomized trial, though concerns regarding feasibility need to be addressed prior to such a trial. The objective of this pilot study is to assess overall feasibility prior to embarking on a larger randomized pragmatic trial comparing the clinical effectiveness of fluid resuscitation with NS versus LR for pediatric patients with suspected septic shock. Necessary feasibility assessments include ensuring appropriate compliance with study fluid in each of the two arms, effectiveness of study enrollment using a pragmatic study design embedded within routine clinical practice, and acceptability of using Exception from Informed Consent (EFIC).
Study Objective(s)	**Primary** • To determine compliance with study fluid administration, throughout the intervention phase, within each randomized arm using a pragmatic study design. **Secondary** • To estimate the proportion of eligible pediatric patients with suspected septic shock who may be enrolled into a randomized pragmatic trial of fluid resuscitation. • To demonstrate feasibility of patient enrollment into a pragmatic fluid resuscitation trial using Exception from Informed Consent (EFIC).
Test Article(s)	• Study arm #1: Fluid resuscitation with lactated Ringer's (LR) • Study arm #2 Fluid resuscitation with 0.9% "normal" saline (NS)

Study Design	Randomized, open-label pragmatic pilot trial to assess feasibility of comparing two different crystalloid fluids for resuscitation of pediatric septic shock.
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** 1. Age >6 months to <18 years 2. Clinician concern for septic shock, operationalized as: a. a "positive" ED sepsis alert confirmed at the physician led "sepsis huddle" OR b. a physician diagnosis of suspected septic shock requiring parenteral antibiotics and fluid resuscitation as per the ED sepsis management pathway Condition 2a above is met by: A. Tachycardia or hypotension for age *AND* B. Fever (home or ED >38 °F), hypothermia, or other signs/symptoms of infection *AND* *At least one of C, D, or E* C. Flash (< 1 second) or delayed (>3 seconds) capillary refill D. Altered mental status E. Existing high-risk condition, including: i. <56 days-old ii. Asplenia iii. Bone marrow or solid organ transplant iv. Central venous catheter v. Malignancy vi. Significant neurological dysfunction or technological dependence at baseline vii. Other immunodeficiency or immunocompromised 3. Administration of at least 20 mL/kg IV/IO fluid resuscitation 4. Receipt of ≤40 mL/kg IV/IO crystalloid fluid prior to randomization 5. Additional fluid deemed likely to be necessary to treat poor perfusion, defined as either hypotension for age or abnormal capillary refill (as determined by clinician's judgment) 6. Parental/guardian permission (informed consent) if time permits; otherwise, EFIC criteria met

Exclusion Criteria:

1. Clinician judgement that patient's condition deems it unsafe to administer either NS or LR (since patients will be equally likely to receive NS or LR at time of study enrollment), including (but not limited to):

a) Clinical suspicion for impending brain herniation based on data available at or before patient meets criteria for study enrollment
b) Known hyperkalemia, defined as non-hemolyzed whole blood or plasma/serum potassium > 6 mEq/L, based on data available at or before patient meets criteria for study enrollment
c) Known hypercalcemia, defined as plasma/serum total calcium >12 mg/dL or whole blood ionized calcium > 1.35 mmol/L, based on data available at or before patient meets criteria for study enrollment
d) Known acute fulminant hepatic failure, defined as plasma/serum ALT >10,000 U/L or total bilirubin >12.0 mg/dL, based on data available at or before patient meets criteria for study enrollment
e) Known history of severe hepatic impairment, defined as diagnosis of cirrhosis, "liver failure", or active listing for liver transplant
f) Known history of severe renal impairment, defined as current dependency on peritoneal dialysis or hemodialysis
g) Known metabolic disorder, inborn error of metabolism, or primary mineralcorticoid deficiency (e.g., mitochondrial disorder, urea cycle disorder, amino acidemia, fatty acid oxidation disorder, glycogen storage disorder, congenital adrenal hypoplasia, Addison's disease) as reported by subject, LAR or accompanying caregiver, or as listed in the medical record

2. Known pregnancy

3. Known prisoner as determined by routine social history disclosed by patient and/or LAR (or other accompanying acquaintance)

4. Known allergy to either normal saline or lactated Ringer's as determined by routine allergy history disclosed by patient and/or LAR (or other accompanying acquaintance) or as indicated in the medical record

	5. Indication of prior declined consent to participate based on presence of a "PRoMPT BOLUS Opt-Out" bracelet with appropriate messaging embossed into the bracelet or opt-out letter that will be provided to the family to be presented to clinical team at time of care
Number Of Subjects	Total Number of Subjects = 80 Total Number at CHOP = 80 Total Number of Sites = 1
Study Duration	Each subject's participation will last up to 90 days, including 1 day for screening, 1-2 days for study intervention, and up to 90 days for follow-up.
Study Phases **Screening** **Study Treatment** **Follow-Up**	(1) Screening: screening for eligibility and obtaining consent/EFIC (2) Intervention phase: use of randomized crystalloid fluid (NS or LR) for resuscitation and maintenance fluid (3) Follow-up: determination of study completion or subject withdrawal, including vital status and clinical outcome assessment at hospital discharge or 90 days following study enrollment, whichever comes first
Efficacy Evaluations	Feasibility will be assessed as part of each aim as follows: • Aim 1: proportion of total crystalloids administered as saline in each arm (primary) and proportion of total crystalloids administered as non-study fluid (i.e., cross-over) in each arm (secondary) • Aim 2: percent enrollment/randomization/treatment of eligible patients • Aim 3: successful EFIC approval with ≤10% subject withdrawal Efficacy outcomes, including mortality, hospital-free days, dialysis, and length of stay, will be collected in preparation for a subsequent multicenter trial, though this pilot feasibility study will not be powered to analyze these endpoints.
Safety Evaluations	For this single-site feasibility study, specified safety outcomes will be monitored as they occur in the course of routine clinical practice but this feasibility study will not be powered to assess safety given that both fluids are FDA-approved and have well-described efficacy and safety profiles.
Statistical And Analytic Plan	The statistical plan will be descriptive for this feasibility study.

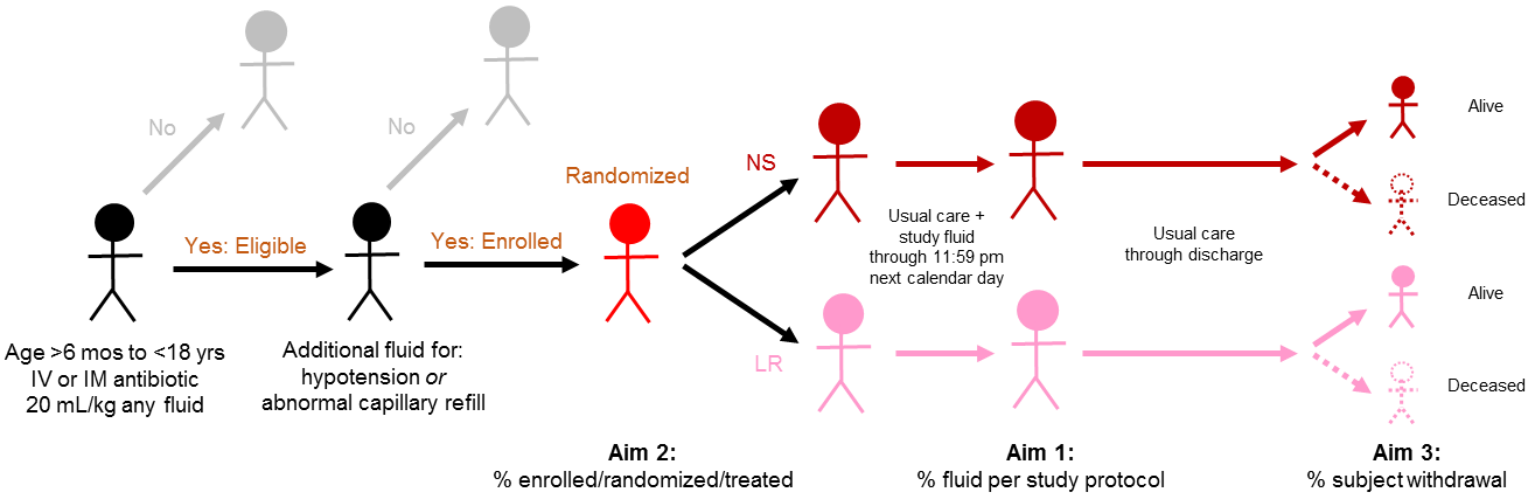
	For Aim 1, feasibility will be defined by either: 1) an absolute difference in the mean use of NS between study arms of at least 65% with a lower 95% CI border of >60%, *or* 2) at least 85% of subjects in the NS arm receiving ≥90% of study fluid as NS during the study window *and* at least 80% of subjects in the LR arm receiving ≥75% of study fluid as LR. The secondary endpoints will be defined as meeting feasibility criteria if: • The proportion of eligible patients treated in the pediatric ED who are enrolled, randomized, and treated with study fluid is >65%. • EFIC is approved by the IRB at CHOP • The proportion of eligible patients who meet criteria for EFIC who are not enrolled or who are enrolled but withdraw prior to completion of the follow-up phase is ≤10%.
Data and Safety Monitoring Plan	Data will be managed and stored by the University of Utah Data Coordinating Center. In addition the PI, an independent Data Safety Monitoring Board (DSMB) will be convened to ensure data quality and patient safety.

TABLE 1: SCHEDULE OF STUDY PROCEDURES

Study Phase	**Screening**	**Intervention**		**Follow-Up[1]**
Study Day	**1**	**1**	**2**	**2 to 90[2]**
Informed Consent/Assent or EFIC	X			
Review Inclusion/Exclusion Criteria	X	X	X	X
Inform patient/LAR of study enrolment (if EFIC)		X	X	X
Demographics/Medical History	X			X
Prior/Concomitant Medications	X	X	X	X
Randomization	X			
Dispense Study Drug		X	X	
Drug Compliance		X	X	
Open-label fluid treatment				X
Data collection		X	X	X
Outcome Assessment: Aim 1			X	
Outcome Assessment: Aim 2	X			
Outcome Assessment: Aim 3				X
Adverse Event Assessment			X	X

[1]Censured at 90 days from study enrollment
[2]Follow-up will cease at 90 days from study enrolment or hospital discharge, whichever comes first

FIGURE 1: PILOT STUDY DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

Approximately 5,000 children die from septic shock each year in the US and thousands more die worldwide.[1,2] Despite widespread implementation of resuscitation protocols, contemporary studies still report 2-6% mortality for children with septic shock treated in the pediatric emergency department (ED).[3-7] In our recent survey of the Pediatric Emergency Care Applied Research Network (PECARN), 45% of physicians had treated a child for septic shock in the ED who subsequently died in the hospital in the past two years (unpublished data).

Fluid resuscitation is the cornerstone of resuscitation for hypovolemia and shock, and intravenous fluids are among the most commonly used therapies worldwide.[8,9] Yet, there remains uncertainty as to the most appropriate fluid type to restore effective blood volume and optimize organ perfusion. In the absence of a clear role for the early use colloids, administration of crystalloid fluids is generally preferred (except in cases of hemorrhage).[10,11] For septic shock, in particular, crystalloid fluids have long been the standard resuscitative fluid.[12] Crystalloid fluids can be categorized as non-buffered (most commonly 0.9% normal saline [NS]) or buffered/balanced (in the US, this is most commonly lactated Ringer's [LR]) solutions. NS and LR are inexpensive, stable at room temperature, and nearly universally available with identical storage volumes and dosing strategies. Notably, both are also of proven clinical benefit in septic shock and have extensive clinical experience for use in fluid resusciation of critically ill patients.[8] However, while NS is currently used in 80-95% of cases of septic shock,[13-15] an increasing body of data now suggest that LR resuscitation may have superior efficacy and safety. Buffered crystalloids, including LR, have demonstrated a 1-4% absolute mortality reduction and up to a 50% lower odds of dialysis compared to NS in observational and non-randomized interventional studies in adult sepsis.[16,17] Nevertheless, because definitive conclusions have not been able to be drawn from existing observational and non-randomized studies, NS overwhelmingly remains the most commonly used fluid based on historical precedent while controversy remains.[18,19]

To definitively test the comparative effectiveness of NS and LR, a well-powered randomized controlled trial (RCT) is necessary. A large pragmatic randomized trial embedded within everyday clinical practice provides a cost-efficient and generalizable approach to inform clinicians about best comparative effectiveness of common therapies.[20] Unlike explanatory RCTs, pragmatic trials need heterogeneity in patients, non-study therapies, and settings.[21] To accomplish this, these trials must be large enough to detect small effects and simple enough to incorporate into routine clinical practice. The characteristics of LR and NS provide the ideal scenario for a large pragmatic trial.[18] An ED-based trial is necessary to enroll patients at initiation of resuscitation.[22,23] While any benefit is expected to be small, even a 1-2% absolute reduction in mortality that is in line with prior adult studies would be a clinically important difference by saving the lives of 50-100 children in the US (and many more worldwide) each year. This overall public health impact is commensurate with changing from NS to LR because such a practice change is a simple, cost-neutral shift from largely using NS to largely using LR.

However, before embarking on a large, pragmatic randomized trial that will determine the comparative effectiveness and safety of NS and LR, several concerns regarding feasibility of such a trial need to be addressed including a) ensuring adequate compliance with study fluid administration within each randomized arm using the proposed pragmatic study design, b) determining that a sufficient proportion of patients can be enrolled using the proposed pragmatic study design that will be embedded within routine clinical practice rather than use of a dedicated study team, and c) demonstrating that the study can feasibly be performed using EFIC when enrolling critically ill infants, children, and adolescents into this clinical trial. If these feasibility criteria can be adequately demonstrated at CHOP as a single site, we will have established the necessary feasibility metrics to indicate a high likelihood of success in a larger, multicenter study that will enroll several thousand patients across the 18 sites comprising Pediatric Emergency Care Applied Research Network (PECARN) to test morbidity and mortality outcomes.

1.2 Name and Description of Investigational Product or Intervention

The study intervention will be the use of lactated Ringer's (LR), a balanced/buffered crystalloid fluid, for initial resuscitation of pediatric patients with suspected septic shock. The comparison group will be use of 0.9% "normal" saline (NS), a non-buffered isotonic crystalloid fluid that is most commonly used to resuscitate patients treated for suspected septic shock in pediatric emergency departments in the United States. For example, in the PECARN registry of three large, academic pediatric EDs, LR was used in only 0.2% of suspected cases of septic shock (personal communication, Elizabeth Alpern). Therefore, although LR is commonly cited in the literature, recommended (along with NS) as an appropriate crystalloid fluid option for pediatric septic shock, and is used in approximately 50% of septic shock cases treated in the CHOP PICU, use of LR as an alternative crystalloid resuscitative fluid to NS in the pediatric ED setting requires a specific interventional study.

The package inserts for NS is included in Appendix 1 and for LR is included in Appendix 2. Table 1 shows the biochemical components of NS and LR.

Table 1: Composition of Human Plasma, Normal Saline, and Lactated Ringer's

Content[1]	Human Plasma	0.9% Normal Saline	Lactated Ringer's
Sodium	140	154	130
Chloride	100	154	109
Potassium	4	0	4
Calcium	5	0	2.7
Magnesium	1.0	0	0
Lactate	1-2	0	28
Bicarbonate	24	0	0
Osmolality (mOsm/L)	290	308	273
Cost (US $ per liter)	--	$1.00 – 2.00	$1.00 - $2.00

[1]Units are mEq/L (unless indicated)

1.3 Findings from Non-Clinical and Clinical Studies

1.3.1 Pre-Clinical Studies

NS contains a supra-physiologic concentration of chloride (1.5X that of plasma) and a strong ion difference (SID) of zero but is isotonic compared to extracellular fluid. LR has less chloride, small amounts of additional electrolytes, and a higher SID due to the presence of lactates as an anion buffer.[8,24] The high chloride content and low SID of NS has been associated with acute kidney injury (AKI), acidemia, hyperkalemia, vascular permeability, inflammation, coagulopathy, fluid overload, and death.[25] For example, infusion of NS reduced renal blood flow and the glomerular filtration rate in a dog model to a greater extent than more balanced fluids.[26] In addition, hyperchloremic metabolic acidosis produces a more profund pro-inflammatory response in a cell model than other forms of acidemia, such as hyperlactatemia.[27] In a rat model of sepsis, fluid resusication with NS resulted in higher blood chloride, lower arterial blood pH, a more severe pattern of acute kidney injury, and higher levels of the pro-inflammatory cytokine interleukin-6.[28]

1.3.2 Clinical Studies

1.3.2.1 Clinical Studies in Adults

In healthy human volunteers, infusion of NS impairs renal blood flow compared to LR and has demonstrated impaired cognition that was not evident with similar volumes of balanced fluids.[29] Moreover, the development of a hyperchloremic metabolic acidosis has been associated with mortality after surgery[30], adult critical illness,[31] and pediatric sepsis (Hector Wong, MD, personal communication, February 14, 2017).

Several studies have compared the effects of infusions of NS and buffered crystalloids on outcomes for adults with sepsis and other critical illnesses. In a sequential period study of critically-ill adults, use of chloride-restrictive fluids reduced AKI by almost 50%.[17] However, the SPLIT crossover trial in 2,278 critically-ill adults found no differences in AKI or mortality for chloride-restrictive versus NS fluid.[32] Similarly, in the CRISTAL open-label randomized trial of adult ICU patients with hypovolemic shock, 31% of 72 patients who received LR died compared to 27% of 1,035 who received NS (p=0.49).[33] In contrast, in a propensity-matched observational study of 6,730 adults with vasopressor-dependent septic shock, resuscitation with at least some crystalloid fluid as LR was associated with a 14% relative reduction in hospital mortality, with a dose-dependent decrease in mortality as proportion of total crystalloid infused as LR increased.[16] In a meta-analysis, adult septic patients who received balanced fluids had a trend towards a lower mortality than those that received NS (OR 0.78, 95% CI 0.58, 1.05) although no trial directly compared NS to balanced fluids.[34] In a randomized trial of 65 adults with trauma, resuscitation with balanced fluids improved acid-base status and decreased hyperchloremia.[35] Finally, in adults undergoing abdominal surgery, use of balanced fluids has been associated with fewer post-operative infections.[36]

Two ongoing trials are currently comparing balanced fluids to NS in adult shock (PLUS study in septic shock, ClinicalTrials.gov NCT02721654 and SaLT-ED study in all shock, ClinicalTrials.gov NCT02614040). However, both trials specifically exclude patients <18 years of age.

1.3.2.2 Clinical Studies in Children

In pediatric sepsis, there are limited data comparing clinical outcomes following LR versus NS resuscitation. While Carcillo et al. demonstrated the importance of early fluid resuscitation in pediatric septic shock, there was no differentiation between use of NS or LR in that landmark study.[37] In a randomized trial of four fluid regimens in children with dengue fever in Vietnam, patients receiving LR required a median of 15 minutes longer to recover from shock compared to NS but this small study was not powered for morbidity or mortality outcomes and dengue shock syndrome has unique circulatory and vasogenic pathophysiology compared to the more typical septic shock syndromes treated in the U.S.[38] In a small randomized study of balanced fluid (sterofundin) versus NS during major surgery in children up to 3 years of age conducted in Germany, subjects randomized to NS had higher blood chloride and more acidemia, but no difference in clinical outcomes. The theme of insufficient power to determine the comparative effectiveness of NS versus LR (or other balanced fluids) is common in the pediatric literature. Unfortunately, the largest prospective study of fluid resuscitation conducted in children with severe infections to date restricted crystalloid fluids only to NS.[39]

To our knowledge, only two observational studies comparing NS and LR have been conducted in pediatric septic shock. The first was a propensity-matched analysis of 2,398 patients in the Pediatric Health Information Systems (PHIS) database who received exclusive NS- or LR-based fluid resuscitation for septic shock and was presented in abstract form at the 2016 Society of Critical Care Medicine Annual Congress. The authors reported a 2% lower mortality for children receiving LR versus NS.[40] The second study, which we recently published in *The Journal of Pediatrics*, was a matched analysis of 4,234 children with septic shock resuscitated with at least some proportion of LR fluid from 382 hospitals in the Premier Healthcare Alliance.[41] Patients were identified using *International Classification of Disease-9-Clinical Modifications* (ICD-9-CM) codes for either severe sepsis/septic shock or a combination of codes indicating infection with organ system dysfunction. Overall, we found no differences in mortality, AKI, or use of renal replacement therapies for patients resuscitated with NS or LR, even when matched by fluid volume and proportion of total fluids given as LR. But for the subset of patients identified using sepsis-specific ICD-9-CM codes (which we and others have previously shown to have more severe illness than patients identified using combination codes), 30-day hospital mortality trended lower in patients who received LR (13.8%) compared to only NS (16.4%; p=0.16), as did the proportion treated with renal replacement therapies (RRT): LR, 1.9% versus NS, 3.9%; p=0.07). However, in our cohort, LR was preferentially used either as first-line fluid in patients with lower illness severity or as an adjunctive fluid in patients who received large amounts of fluid resuscitation, and the matching algorithm was least effective in the most severely ill patients who received the largest total fluid volumes. Consequently, we concluded that the results of our study are best interpreted as establishing the need for and the equipoise to conduct a prospective randomized trial to definitely address the comparative effectiveness of balanced fluids and NS in pediatric sepsis.

Of note, in our recent survey (data unpublished), 95% of PECARN investigators agreed that the existing adult and pediatric data are insufficient to reach consensus on the best crystalloid fluid to use for resuscitation in pediatric septic shock.

1.4 Selection of Drugs and Dosages

Both NS and LR are available with identical storage volumes and dosing strategies.

For this study, standard storage units of NS and LR will be used, including 250, 500, and 1,000 mL units. At the discretion of the care team, dextrose may be added to either NS or LR for resuscitation (uncommon) or maintenance (common) fluid therapy. Commonly used dextrose preparations for pediatric septic shock include NS or LR with 5% or 10% dextrose which are also available in standard volumes of 250, 500, and 1,000 mL units. Potassium or other electrolytes may be added to either NS or LR as clinically indicated.

Volume for fluid resuscitation is typically 10-20 mL/kg per dose administered over 5-20 minutes via the intravenous or intraosseous route, though children with sepsis often receive >100-200 mL/kg total crystalloid volume resuscitation within 24-48 hours. Volume for maintenance fluids is typically determined by patient weight, assessment of intravascular volume status, and need for a specific glucose infusion rate. However, for this study, only the type of base fluid (i.e., NS or LR) will be determined by study protocol, while the actual volume administered (per bolus dose, per hour, and in total), duration of administration, and need for electrolyte additives (i.e., dextrose, potassium, others) will be at the complete discretion of the treating care team.

The costs for NS and LR are equivalent, with both fluids at approximately $1-2.00 per liter. Since the volume of fluid will be determined by the care team and use of both NS and LR are consistent with published guidelines for crystalloid resuscitation of pediatric septic shock, the randomized selection of fluid will not significantly alter health care costs for subjects enrolled in this study.

Both NS and LR are FDA-approved crystalloid fluid solutions recommend for use[10,12] and clinically used for resuscitation of patients with shock.[13-15] NS was first approved for medical use by the FDA in 1970, and LR was first approved for medical use by the FDA in 1971. Both NS and LR are listed for use in pediatrics based on "clinical practice" and reference in the "medical literature". In the pediatric ED population, however, NS is overwhelmingly the more common fluid used for resuscitation of pediatric septic shock.[15] Therefore, we will consider NS to be the control fluid (since >98% of patients not enrolled in this study would initially receive NS) and LR, the less commonly utilized fluid, the intervention fluid in this study. Specific cautions for use of LR in the pediatric and critically ill population are shown in Table 2:

Table 2: FDA Contraindications and Warnings to LR Administration to the Pediatric and Critically Ill Population

Concern	Type of Caution	Relevance to Proposed Study
***Pediatric Population*:**		
LR and ceftriaxone must not be simultaneously	Contraindication	Not relevant, inclusion criteria are age >6 months to <18 years (see page 11, section 3.4.1)

administered (age ≤ 28 days)		
LR and ceftriaxone must not be simultaneously administered *through the same infusion line* (age >28 days)	Contraindication	If both LR and ceftriaxone prescribed, usual, routine clinical practice will be followed (see page 10, section 3.1.2)
Lactate-containing solutions should be administrated with caution to infants <6 months	Warning	Not relevant, inclusion criteria are age >6 months to <18 years (see page 11, section 3.4.1)
***Critically Ill Population*:**		
LR should not be simultaneously administered with citrate anticoagulated blood through same administration set	Warning	If both LR and blood products are administered, usual, routine clinical practice will be followed (see page 10, section 3.1.2)
LR infusion must be stopped if suspected hypersensitivity develop	Warning	Usual, routine clinical practice will be followed (see page 10, section 3.1.2)
Depending on volume and rate of infusion, infusion of LR can cause fluid overload and/or electrolyte abnormalities	Warning	Not relevant, volume and rate of infusion of both LR (and NS) are at the discretion of the clinical team and both fluid and electrolytes will be monitored as indicated as part of usual, routine clinical practice (see page 10-11, section 3.2.1)
Cautious administration of LR to patients with hyperkalemia or cardiac disease	Warning	Eligibility criteria require treating clinician to determine it is safe to administer both NS and LR (see page 11, section 3.4.1), with known hyperkalemia a specified exclusion criteria. In addition, study fluid may be stopped at clinician's discretion if new data changes this determination during intervention phase (page 11, section 3.1.2)
Cautious administration of LR to patients with metabolic alkalosis	Warning	Not relevant, metabolic alkalosis rare during resuscitation in septic shock and study fluid may be stopped at clinician's discretion (page 11, section 3.1.2)
Cautious administration of LR to patients with inability to metabolize lactate (e.g., fulminant hepatic failure)	Precaution	Although fulminant hepatic failure or complete inability to metabolize lactate is rare in septic shock, eligibility criteria require treating clinician to determine it is safe to administer both NS and LR with known fulminant hepatic failure a specified exclusion criteria (see page 11, section 3.4.1). In addition, study

		fluid may be stopped at clinician's discretion if new data changes this determination during intervention phase (page 11, section 3.1.2)
Cautious administration of LR to patients with hypercalcemia	Precaution	Although severe hypercalcemia is rare in pediatric septic shock, eligibility criteria require treating clinician to determine it is safe to administer both NS and LR (see page 11, section 3.4.1) with known hypercalcemia a specified exclusion criteria. In addition, study fluid may be stopped at clinician's discretion if new data changes this determination during intervention phase (page 11, section 3.1.2)

1.5 Relevant Literature and Data

Infusion of saline to restore circulating blood volume was first attempted during the cholera outbreak of the 1830's. In a letter to the *Lancet* published on June 2, 1832, Thomas Latta noted with intravenous saline "*improvement in the pulse and countenance is almost simultaneous, the cadaverous expression gradually gives place to appearances of returning animation, the livid hue disappears, the warmth of the body returns.*"[42] Fluids of various composition were subsequently described, with the first reference to a solution similar to that of NS in the 1880's. Hartog Joakob Hamburger recognized that erythrocytes did not lyse when placed in NS and concluded that "the blood of man was isotonic with a NaCl solution of 0.9%".[43] Although these observations conceivably led to the "normal" moniker for 0.9% NS (nobody knows for sure), human plasma is actually closer to 0.6% NaCl. Subsequent events leading to the widespread adoption of NS into clinical practice remain unclear. LR was also born in the 1880's when Sydney Ringer added calcium and potassium to saline after observing that inorganic constituents of pipe water better preserved frog heart muscle *ex vivo* than just salt dissolved in distilled water.[44] In 1932, the pediatrician Alexis Hartmann modified Ringer's original formula in order to reduce the acidosis observed in infants with diarrhea.[43]

Although commonly used, an increasing body of literature now links the high chloride content and low SID of NS to acute kidney injury (AKI), acidemia, hyperkalemia, vascular permeability, inflammation, coagulopathy, fluid overload, and death.[25] In particular, when infused in large volumes—as is common in septic shock—NS induces a hyperchloremic metabolic acidosis due to the dilution of plasma bicarbonate within a constant carbon dioxide environment in the absence of an alternative buffer.[45] In blood with normal protein levels, the SID (abbreviated Na + K – Cl) is approximately +40 mEq/L. Infusion of NS with a SID of 0 (154 Na + 0 K – 154 Cl) produces an acidemia.[46] Such a hyperchloremic metabolic acidosis is pro-inflammatory in cell culture experiments[27] and has been associated with mortality following non-cardiac surgery.[30] Moreover, since acidemia is often attributed to tissue hypoperfusion in shock, a low blood pH following NS resuscitation may propagate

a feed-forward cycle of excessive fluid administration and volume overload, which itself has been associated with adverse clinical outcomes in multiple adult and pediatric studies.

However, despite suggestive relative efficacy and safety for balanced fluids like LR over NS for resuscitation of pediatric septic shock, whether there is a benefit for either NS or a more balanced fluid strategy remains unproven, particularly for pediatric septic shock. Because crystalloid fluids are so commonly used, even a small relative benefit of one fluid resuscitation strategy could provide a substantial public health impact. Unfortunately, because of unique pathophysiology and epidemiology for pediatric versus adult septic shock, results from ongoing adult fluid trials are unlikely to be generalizable to pediatric patients. Given both types of fluids are inexpensive, stable at room temperature, commonly used, have identical storage and dosing volumes, and are of proven clinical benefit, crystalloids fluids provide the ideal scenario for a large pragmatic comparative effectiveness trial. The proposed pilot study will address the specific feasibility concerns necessary to next perform a larger trial that will definitively determine the comparative effectiveness of NS versus LR in pediatric septic shock.

Enrollment of patients as close to the initiation of fluid resuscitation is critical, and the lack of early enrollment has been a major criticism of previous fluid resuscitation trials in adult studies.[22,23] In the United States, the majority of children begin fluid resuscitation in the emergency department in which the therapeutic goal is generally to achieve hemodynamic stability prior to transfer to an inpatient setting, including the intensive care unit. Consequently, fluid resuscitation with volumes up to (and exceeding) 80 mL/kg commonly occur in the pediatric ED. Delaying enrollment of patients until after admission to an intensive care unit, thus, risks substantial volume of pre-study fluid resuscitation that may dilute the main effect of a specified fluid intervention. Such contamination with pre-study fluid resuscitation has been a primary criticism of previous sepsis studies focusing on adults admitted to an ICU, in which receipt of a mean fluid volume of 2000 mL prior to study enrollment has been reported in several studies.[22,23] Therefore, enrollment of children with suspected septic shock in the ED setting as close to initiation of fluid resuscitation as possible is necessary to maximize the potential differential effect of NS versus LR fluid.

1.6 Compliance Statement

This study will be conducted in full accordance with all applicable Children's Hospital of Philadelphia Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, 21 CFR Parts 50, 54, 56, 312, and 314. . We will also follow the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization (ICH) except for a limited scope and timeframe for monitoring clinical adverse events (AEs) given the comparative effectiveness nature of the proposed study involving two interventions with routine clinical use in pediatric sepsis and well-documented efficacy and safety profiles of both NS and LR.

The investigators will perform the study in accordance with this protocol, will obtain consent when possible, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be

accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

The purpose of the proposed pilot study is to determine the feasibility of performing a large, pragmatic, randomized, open-label trial comparing the clinical effectiveness and safety of fluid resuscitation with NS versus LR for pediatric septic shock.

2.1 Primary Objective (or Aim)

The primary objective of this study is to determine compliance with study fluid administration, throughout the intervention phase, within each randomized arm using a pragmatic study design.

Specifically, we will determine if the proposed study design is feasible to provide a clinically important difference in crystalloid fluid type between the two study arms by measuring the proportion of intravenous crystalloid fluid administered as 0.9% saline for pediatric patients with suspected septic shock randomized to fluid resuscitation with either saline or lactated Ringer's.

2.2 Secondary Objectives (or Aim)

The secondary objectives are to:

- Estimate the proportion of eligible pediatric patients with suspected septic shock who may be enrolled into a large randomized pragmatic trial of fluid resuscitation with saline versus lactated Ringer's.
- Demonstrate feasibility of patient enrollment into a pragmatic fluid resuscitation trial using Exception from Informed Consent (EFIC).

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

The overall design for this pilot study is a randomized, open-label pragmatic clinical trial of two different crystalloid fluids to resuscitate pediatric septic shock. The two arms include 0.9% "normal" saline (NS; control arm) and lactated Ringer's (LR, intervention arm). See Figure 1 for an overview of the study design and outcome assessment.

3.1.1 Screening Phase

Potential subjects will be referred by the treating team in the ED, but a member of the study team will perform final screening for eligibility based upon the protocol inclusion and exclusion criteria prior to enrollment of the subject. Triggers for potential enrollment to be considered by the treating team will include initial fluid resuscitation with at least 20 mL/kg intravenous (IV)/intraosseous (IO) crystalloid fluid for clinical concern for septic shock. To ensure rapid and appropriate eligibility and enrollment, ED staff (including ED attendings and fellows) will be included as study co-investigators and be trained regarding study enrollment criteria and procedures.

When time permits, parental/guardian permission (informed consent) will be obtained prior to any study related procedures being performed. However, under most circumstances, the life-threatening nature of septic shock and the narrow therapeutic window for fluid resuscitation (on the order of minutes after presentation and shock recognition) will preclude sufficient time for an appropriate discussion of the study to properly seek informed consent and assent. In these cases, enrollment will proceed under the conditions of "exception from informed consent" (EFIC) with notification of the subject's legally authorized representative (LAR) as described in Section 9.6.3.

3.1.2 Intervention Phase

The intervention to be tested is fluid resuscitation with LR compared to the "usual practice" control fluid of NS. Other than prescribing which crystalloid fluid to use, the intervention will be purposely implemented without intense efforts to standardize timing and volume of fluid resuscitation or other components of clinical care.

The proposed interventional plan is that, prior to receipt of >40 mL/kg of crystalloid bolus fluid, eligible patients will be randomized to receive either NS or LR for all remaining fluid administration (bolus and maintenance) for up to 48 hours. The study period will end at 11:59pm on the calendar day following randomization such that all patients receive at least 24 hours of study fluid, which is the time-window from presentation in which most fluid resuscitation is completed for septic shock.[27] This time point for terminating the intervention phase was selected because it provided a pragmatic endpoint that can be used by clinicians to signal the point at which to cease study fluid administration. Selective fluid administration has been previously shown to result in widely different amounts of saline use,[47] though application of these findings in adults using a different allocation strategy to the one proposed for our study is not clear. Study fluids will not be blinded due to costs and interventions that are not in keeping with a simple, pragmatic trial and based on results from the previously published SPLIT fluid trial in which two-thirds of clinicians correctly

identified the randomized crystalloid patients received (despite blinding) as electrolyte differences following NS or LR provide clear indication of fluid selection.[35] The volume and need for additional fluid, as well as all other aspects of care, will be at the discretion of the treating team which will be educated to follow the CHOP ED and/or PICU Sepsis Clinical Pathways both as part of routine care and for specific use in the proposed study (see Appendix 5). All other care will be at the discretion of the clinical team. As study fluids will not be blinded, patient-level randomization will minimize selection bias due to awareness of group assignment. Study fluids can be stopped for clinician concerns noted during routine care (e.g., hyponatremia, hyperkalemia, hypercalcemia, cerebral edema). Adherence to the study intervention will be monitored through random chart audits of both eligible subject enrollment and the volume of study arm crossover. Study arm cross-over is defined as a subject randomized to NS who subsequently receives LR during the intervention period or a subject randomized to NS who subsequently receives NS during the intervention period.

NOTE: Because calcium-containing solutions, including LR, can precipitate when administered simultaneously with ceftriaxone through the same infusion line, teams will be educated to follow usual, routine clinical practice for administration of LR with ceftriaxone. This includes use of either different infusion lines or, if the same infusion in used for sequential administration, then the line must be thoroughly flushed between infusions with a compatible fluid as per usual, routine clinical practice. These practices are consistent with usual, routine care that would otherwise be performed for patients prescribed LR outside of this study. An example of existing safety mechanisms within usual, routine clinical practice is that the following warning is issued within the electronic order entry system to advise caution when ceftriaxone is prescribed and administered:

> "Ceftriaxone and calcium-containing solutions may be administered sequentially of one another for use in patients greater than28 days if infusion lines are thoroughly flushed (with a compatible fluid) between infusions."

In addition, clinical staff will also be targeted for education about safe administration of LR with other medications, such as ceftriaxone, prior to and throughout the study.

NOTE: Because LR should not be administered simultaneously with citrate anticoagulated blood through the same administration set, teams will be educated to follow usual, routine clinical practice for administration of LR with blood products. Clinical staff will be targeted for education about safe administration of LR with blood products prior to and throughout the study.

NOTE: Both NS and LR pose risk of a hypersensitivity reaction during IV/IO infusion. Teams will be educated to following usual, routine clinical practice for discontinuation of administration of study fluid if signs and/or symptoms of hypersensitivity reaction develops.

3.1.3 Follow-up Phase

After 11:59 pm on the calendar day following randomization, no further study fluid will be administered solely for research purposes and all care, including any subsequent crystalloid

fluid administration, will be at the discretion of the clinical team. The follow-up phase will continue for the duration of the hospitalization or up through 90 days following study enrollment, whichever comes first. Final determination of subject study completion versus withdrawal, as well as assessment of vital status and clinical outcomes will occur at hospital discharge or 90 days following study enrollment, whichever comes first.

3.2 Allocation to Treatment Groups and Blinding

Randomization will be performed using 1:1 permuted blocks. Randomization sequence will be generated prior to the start of the study and will be filed using a series of numbered, opaque envelopes. Envelopes with study arm assignment will be stored in close proximity to crystalloid fluids in the CHOP ED. Treatment allocation will be revealed to the clinical care team after eligibility for enrollment has been determined to be appropriate by asking a member of the care team to open the next sequentially numbered envelope. The number of the envelope and study arm assignment will be recorded in a log after opening the envelope. The clinical team will then be directed to use the assigned study fluid for all subsequent crystalloid fluid administration within the remainder of the study window. Compliance with study fluid administration will be the primary feasibility assessment in this study (Aim 1).

Fluid administration will be open-label and neither the subject nor the care team will be blinded to the allocated treatment assignment. Blinding study fluid is not pragmatic and unlikely to even be possible. In the SPLIT fluid trial, two-thirds of clinicians correctly identified the randomized crystalloid patients received as electrolyte differences following NS or LR provide clear indication of fluid selection.[35] However, randomization following study enrollment will help to minimize selection bias that might occur due to pre-enrollment awareness of study group assignment.

3.3 Study Duration, Enrollment and Number of Sites

3.3.1 Duration of Study Participation

The study duration per subject will be up to 90 days, with up to 1 day for screening, up to 2 days for Phase 1 (Intervention Phase), and up to 89 subsequent days (or until hospital discharge, whichever comes first) for follow-up.

3.3.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at one investigative site in the United States (the Children's Hospital of Philadelphia). The University of Utah will act as the Data Coordinating Center (DCC) for this study, but they will not be engaged in human subjects research. Their role is limited to the receipt of a limited dataset from the CHOP investigators.

Recruitment will stop when 70 subjects are enrolled and randomized. It is expected that approximately 80 eligible subjects will be enrolled to produce 70 evaluable subjects.

3.4 Study Population

Eligibility criteria are designed to enroll a broad, heterogeneous cohort of pediatric patients with suspected septic shock who are easily recognizable within routine clinical practice and

are representative of the broader population of pediatric patients treated for suspected septic shock.

3.4.1 Inclusion Criteria

1) Males or females age >6 months to <18 years

2) Clinician concern for septic shock, operationalized as:

   a) a "positive" ED sepsis alert confirmed at the physician led "sepsis huddle" OR

   b) a physician diagnosis of suspected septic shock requiring parenteral antibiotics and fluid resuscitation as per the ED sepsis management pathway

NOTE: Condition 2a above is met by:

A. Tachycardia or hypotension for age *AND*
B. Fever (home or ED >38 °F), hypothermia, or other signs/symptoms of infection *AND*

   At least one of C, D, or E

C. Flash (< 1 second) or delayed (>3 seconds) capillary refill
D. Altered mental status
E. Existing high-risk condition, including:
   i. <56 days-old
   ii. Asplenia
   iii. Bone marrow or solid organ transplant
   iv. Central venous catheter
   v. Malignancy
   vi. Significant neurological dysfunction or technological dependence at baseline
   vii. Other immunodeficiency or immunocompromised

As per the existing CHOP ED Sepsis Alert, the presence of A *and* B *and* either C, D, or E will be determined by the triage nurse (and then continuously by the ED treating nurse if criteria are not initially met). If these criteria are met, then a "sepsis huddle" will be called with immediate physician bedside patient evaluation for possible septic shock. Patients who are considered to have suspected septic shock will be treated on the CHOP ED sepsis management protocol (Appendix 5) and will be considered for study eligibility

NOTE: Condition 2b above is met by any patient who does not meet criteria for a "sepsis huddle" but is diagnosed by the treating ED physician with suspected septic shock requiring parenteral antibiotics and fluid resuscitation.

Combining both the nurse-driven electronic sepsis alert with physician judgement to identify suspected septic shock in the CHOP emergency department, we have documented a 99.4% sensitivity and 99.1% specificity to identify patients who met international consensus criteria for severe sepsis/septic shock while only 5.5% of ED patients who developed severe

sepsis/septic within 24 hours of ED presentation were missed.[48] However, because the positive predictive value of this combined approach was 25.4%, we have required the additional inclusion criterion of administration of at least 20 mL/kg IV/IO fluid resuscitation with additional fluid deemed likely to be necessary to treat poor perfusion, defined as either hypotension or abnormal (either "flash" or >3 second) capillary refill (as determined by clinician's judgment).

3) Administration of at least 20 mL/kg IV/IO fluid resuscitation

4) Receipt of ≤40 mL/kg IV/IO crystalloid fluid prior to randomization

5) Additional fluid deemed likely to be necessary to treat poor perfusion, defined as either hypotension or abnormal (either "flash" or >2 second) capillary refill (as determined by clinician's judgment)[10]

NOTE: Due to the pragmatic nature of this study that is designed to reflect usual clinical practice, we will not define specific thresholds for either hypotension or abnormal capillary refill but rather defer to the treating clinician's discretion to determine hypotension and abnormal capillary refill.

6) Parental/guardian permission (informed consent) if time permits; otherwise, EFIC criteria met

NOTE: For patients who may be transferred to the CHOP ED from an outside facility, many will have started fluid resuscitation prior to arrival in the CHOP ED. If volume of crystalloid fluid administration cannot be easily determined such that receipt of ≤40 mL/kg IV/IO crystalloid volume cannot be easily verified, these patients will be operationalized as not meeting the ≤40 mL/kg inclusion criterion.

NOTE: Patients who are randomized to a study arm at ≤40 mL/kg crystalloid fluid resuscitation *but for whom study fluid is not initiated until after >40 mL/kg* will still be included and should commence with administration of study fluid for the duration of the remaining intervention phase.

3.4.2 Exclusion Criteria

Reflecting the pragmatic design of the proposed study, exclusion criteria are purposely limited to ensure maximal external validity. FDA listed "contraindications" to LR are reflected as absolute exclusions (e.g., age < 6 months), while FDA listed "warnings" and "precautions" to LR administration are incorporated into the below listed exclusion criteria (see Table 2 in Section 1.4 for summary of FDA recommendations for use of LR in the pediatric and critically ill population). In addition, exclusion criteria are operationalized to reflect the common clinical practice (and guideline recommendations) to begin administration of either NS or LR to resuscitate septic shock without delays imposed by waiting for laboratory diagnostic tests.

1) Clinician judgement that patient's condition deems it unsafe to administer either NS or LR (since patients will be equally likely to receive NS or LR at time of study enrollment), including (but not limited to):

   a) Clinical suspicion for impending brain herniation based on data available at or before patient meets criteria for study enrollment
   b) Known hyperkalemia, defined as non-hemolyzed whole blood or plasma/serum potassium > 6 mEq/L, based on data available at or before patient meets criteria for study enrollment
   c) Known hypercalcemia, defined as plasma/serum total calcium >12 mg/dL or whole blood ionized calcium > 1.35 mmol/L, based on data available at or before patient meets criteria for study enrollment
   d) Known acute fulminant hepatic failure, defined as plasma/serum ALT >10,000 U/L or total bilirubin >12.0 mg/dL, based on data available at or before patient meets criteria for study enrollment
   e) Known history of severe hepatic impairment, defined as diagnosis of cirrhosis, "liver failure", or active listing for liver transplant
   f) Known history of severe renal impairment, defined as current dependency on peritoneal dialysis or hemodialysis
   g) Known metabolic disorder, inborn error of metabolism, or primary mineralcorticoid deficiency (e.g., mitochondrial disorder, urea cycle disorder, amino acidemia, fatty acid oxidation disorder, glycogen storage disorder, congenital adrenal hypoplasia, Addison's disease) as reported by subject, LAR or accompanying caregiver, or as listed in the medical record

NOTE: Due to the short therapeutic time window available for fluid resuscitation—and therefore study enrollment (see Section 3.1.1.)—in pediatric septic shock, it is not feasible to wait for diagnostic tests to identify medical conditions. Therefore, exclusion will be based on medical conditions that are known (or, in the case of impending brain herniation, suspected) at or before the time a patient otherwise meets criteria for study enrollment. If such data are not available and the treating clinician does not otherwise, in his/her best judgement, deem it unsafe to administer either NS or LR, then the patient will be eligible for study enrollment if they meet all other inclusion and exclusion criteria. Given the dynamic nature of sepsis, should an enrolled subject be noted to have a condition for which further administration of either NS or LR is deemed to be unsafe, the subject will be withdrawn from further study fluid administration. Because potassium, calcium, and liver function tests are already measured in all patients with suspected septic shock as part of routine care, there is no specific mandate to measure these values for the sole purposes of this study.

2) Known pregnancy determined by routine clinical history disclosed by patient and/or LAR (or other accompanying acquaintance)

NOTE: The exclusion of pregnant women is indicated under the provisions for "exception from informed consent" rather than a specific need to exclude pregnancy women from the interventions to be test in this study. Given the absence of data or plausible adverse biological effect for either NS or LR in pregnancy (see FDA inserts for NS and LR in Appendix 1 and Appendix 2, respectively), the recommended use of crystalloid fluid for resuscitation of pregnant women with septic shock,[12] and the absence of data supporting a

relative difference in efficacy or safety for use of NS versus LR on the developing fetus during any trimester,[49] there is no specific need to exclude pregnant women from the interventions to be tested in this study beyond the requirements for enrollment under "exception from informed consent". In addition, since 2012, none of the 1,420 patients treated for sepsis in the CHOP ED has had a positive pregnancy test. Therefore, because waiting for biochemical testing for pregnancy (e.g., urine β-HCG) would either cause most post-pubertal female patients become ineligible for enrollment (due to receipt of >40 mL/kg of fluid) or delay fluid resuscitation (putting potential subjects at risk of harm) *and* given the extremely low risk for diagnosing pregnancy in this patient population *and* given the safe use of both NS and LR in pregnancy, there will not be a requirement to delay study enrollment while awaiting results of a pregnancy test. Any subject enrolled in the study who is subsequently determined to be pregnant as part of routine clinical care, which at CHOP includes testing for pregnancy in all female patients of child-bearing age, will be immediately withdrawn from this study.

3) Known prisoner as determined by routine social history disclosed by patient and/or LAR (or other accompanying acquaintance)

4) Known allergy to either normal saline or lactated Ringer's as determined by routine allergy history disclosed by patient and/or LAR (or other accompanying acquaintance) or as indicated in the medical record

5) Indication of prior declined consent to participate based on presence of a "PRoMPT BOLUS Opt-Out" bracelet with appropriate messaging embossed into the bracelet (see IRB study 17-013950) or the presence of the patient's name on an opt-out list that will be kept up-to-date and checked prior to randomization.

Concurrent participation in another interventional trial will not be considered an exclusion criteria because such co-enrollment is not expected to impact the feasibility aims and outcomes for this study.

Subjects that do not meet all of the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

4 STUDY PROCEDURES

4.1 Screening Visit

Patients will be screened at arrival to the ED (i.e., at ED triage) and continuously throughout the ED course for presence of eligibility criteria. Referrals for potential subject enrollment will be made by the ED care team if there is clinician concern for septic shock and need for crystalloid fluid resuscitation assessed by the care team. Although all members of the ED care team may participate in subject referral, a member of the study team will review and concur with the treatment team's eligibility assessment prior to enrollment of the subject. To ensure rapid and appropriate eligibility and enrollment, ED staff (including ED attendings and fellows) will be included as study co-investigators and be trained regarding study enrollment criteria and procedures Once patients are determined to be eligible, the following study procedures will occur:

- Informed Consent (if time permits) or determination of EFIC
- Randomization

In addition, review of the daily ED triage logs and use of the ED sepsis pathway order set will be performed by study staff to determine potentially eligible patients who were not enrolled. The reason for non-enrollment for all eligible patients will be determined by querying the attending physician of record and/or relevant members of the clinical care team.

4.2 Intervention Phase

The intervention phase will start immediately following the patient's first 20 mL/kg and randomization has been determined, and will end at 11:59 pm on the calendar day following randomization. During this period, the follow study procedures will occur:

- Dispense study fluid
- Monitor study fluid adherence
- If enrollment after EFIC, review inclusion/exclusion criteria
- If enrollment after EFIC, inform subject and LAR of study enrollment (as soon as feasibly possible)
- Medical record review
- Adverse event reporting

4.3 Follow-up Phase

The follow-up phase will start after 11:59 pm on the calendar day following randomization and will end at hospital discharge or 90 days following randomization, whichever comes first. During this period, the following study procedures will occur:

- Open-label fluid treatment
- If enrollment after EFIC and not accomplished during intervention phase, inform subject and LAR of study enrollment (as soon as possible)
- Medical record review
- Adverse event reporting
- Outcome assessment

4.4 Concomitant Medication

All prior and concomitant use of antibiotics, acyclovir, corticosteroids, bicarbonate, parental calcium, blood products, crystalloid and colloid fluids (including hypertonic saline), mannitol, intravenous immunoglobulin, diuretics, non-steroidal anti-inflammatory medications (NSAIDS), unfractionated or low-molecular weight heparin, vasoactive infusions (i.e., dopamine, dobutamine, epinephrine, norepinephrine, phenylephrine, milrinone, vasopressin) within one day prior to the screening visit and through the end of the study will be recorded. The dates of administration, dosage, and reason for use will be included.

4.5 Rescue Medication Administration

Open-label use of hypertonic saline, mannitol, unfractionated or low-molecular weight heparin, systemic or local tissue plasminogen activator (tPA), or other "blood thinner", parenteral calcium, and parenteral bicarbonate will be recorded, including dates of administration, dosage, and reason for use.

4.6 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care, including following notification of study enrollment under EFIC. Subjects may also be discontinued from the study at the discretion of the Investigator (at any point) for lack of adherence to study treatment or at the discretion of the attending physician of record (during the intervention phase only) if his/her clinical judgment deems it no longer safe to continue to administer either NS or LR. The Investigator may also withdraw subjects to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. If the Investigator becomes aware of any serious, related adverse events after the subject completes or withdraws from the study, they will be recorded in the source documents and on the CRF.

4.6.1 Early Termination Point

Subjects who withdraw from the study will have all procedures enumerated for the follow-up phase in Section 4.3 performed at the early termination point (rather than at hospital discharge or study day 90).

In addition, subjects randomized to LR in this unblinded study for whom routine, clinician-directed physical and/or laboratory assessment reveals the following criteria within the up-

to-48 hour time window of the intervention phase will not be required to receive additional study fluid as part of this protocol and will be transitioned to an appropriate fluid as determined by the discretion of the treating clinical team. Recognizing that hepatic and renal injury are a) common in septic shock, b) often improved by fluid resuscitation, and c) vary along a spectrum of mild dysfunction (common) to severe failure (uncommon), stopping criteria are defined when either an immediate unsafe condition is noted or when persistent or worsening organ injury indicates that continued LR administration may be cumulatively unsafe (e.g., potassium administration despite worsening oliguria or lactate administration despite worsening hepatic function).

- Hyperkalemia defined as blood potassium >6 mEq/L confirmed on immediate repeat testing
- Hypercalcemia defined as blood total calcium >12 mg/dL or ionized calcium >0.35 mmol/L confirmed on immediate repeat testing
- Severe hepatic impairment defined as rise in blood ALT to >10,000 U/L or total bilirubin >12.0 mg/dL
- Severe renal impairment defined as initiation of renal replacement therapy (continuous or intermittent hemodialysis or peritoneal dialysis) or urine output <0.5 ml/kg/hr for 16 hours

NOTE: Hepatic impairment was defined as a fulminant rise in ALT or total bilirubin because other markers of liver function are not commonly recommended for use in pediatric septic shock. For example, an acute elevation in INR is more commonly indicative of hematologic dysfunction than hepatic impairment in pediatric septic shock.[50]

NOTE: Urine output <0.5 ml/kg/hr for 16 hours indicates renal injury ("I") in the pRIFLE scoring system and stage II kidney injury in the KDIGO scoring system.[51] Creatinine and creatinine clearance will not be used as stopping criteria in the absence of oliguria or initiation of renal replacement therapy because intermittent lab testing may limit the utility of these measurements compared to continuous urine output monitoring and blood creatinine is a poor proxy for a patient's handling of potassium in that most acute kidney injury in sepsis is caused by acute tubular necrosis, which promotes electrolyte wasting despite a rise in blood creatinine. As an example, in a prior randomized trial of NS versus LR following kidney transplant (as a model of severe acute kidney injury), 19% of patients in the NS developed hyperkalemia >6 mEq/L compared to 0% in the LR group.[52] Consequently, urine output is the most useful clinical indicator of potential electrolyte retention.

The laboratory values noted above, including potassium, total calcium, ionized calcium, ALT, and bilirubin, will be ordered as determined to be clinically indicated by the treating clinical team rather than prescribed by this study protocol. Because patients with septic shock have wide variability in illness severity and clinical course, including large differences in the amount and timing of fluid administration, pre-specifying which laboratory values to obtain and when to obtain them could result in additional unnecessary phlebotomy and/or access of indwelling lines both of which would impose additional harm (e.g., pain) and risk (e.g., central-line associated bloodstream infection risk increases with additional line accesses) that may not have been experienced outside of the study. Therefore, rather than pre-specifying in the study protocol the laboratory values to obtain

and the time points or timeframe at which to obtain them, the study protocol will utilize the institution's existing laboratory recommendations within the clinical sepsis pathway, which includes potassium and total calcium at least every 12 hours, ionized calcium every 2 hours (as part of blood gas analysis), and ALT and bilirubin every 24 hours for patients with active septic shock admitted to the pediatric intensive care unit (with more frequent laboratory assessments in the subset of patients with more severe illness undergoing ongoing fluid [and other] resuscitation). At CHOP, there are no hospital guidelines for ongoing management of patients treated for septic shock in the ED who are subsequently admitted to the floor following resolution of shock. It is anticipated that ongoing fluid resuscitation outside of the ED setting will be almost exclusively limited to patients who require admission to the PICU, such that the existing clinical sepsis pathway will prompt clinicians to ascertain laboratory values appropriately in those patients at risk for fluid-related abnormalities for whom study fluids will no longer be recommended. The timeframes included within the clinical sepsis pathway provide adequate windows to re-assess safety of ongoing study fluid administration because these potential adverse laboratory effects are related to cumulative fluid administration rather than any one particular fluid bolus.

For subjects randomized to either NS or LR in whom routine, clinician-directed physical and/or laboratory assessment reveals clinical concern for hypersensitivity to the study fluid to which they were randomized, will not be required to receive additional study fluid as part of this protocol within the up-to-48 hour time window of the intervention phase.

Any subjects who meet the above "stopping criteria" will remain in the study for data collection and outcome assessment. Clinician-prescribed fluid administered within the intervention phase will continue to be recorded, including any potential continued use of LR and/or alternative fluid.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

The following variables will be abstracted from the medical chart (paper or electronic).

- Name
- Medical record number
- CSN number
- Date/time ED arrival and triage
- Date/time of transfer/discharge from the ED
- Date/time of hospital admission
- Date/time of PICU admission
- Date of birth
- Race
- Ethnicity
- Comorbid medical/surgical conditions
- Pre-hospital medications
- Date, time, and volume of all study fluid administration
- Date, time, and volume of all non-study parenteral fluid administration, including all crystalloids, colloids, blood productions, medications, continuous infusions, and flushes
- Total daily recorded volume administered (all “in’s”) and excreted/removed (all “out’s”)
- Date/time of medications/pharmaceuticals administrated during ED and hospitalization
- Laboratory tests (including date/time and results)
- Microbiology tests
- Radiological tests

- Date/time of PICU transfer/discharge
- Date/time of hospital discharge
- Vital status at hospital discharge, study withdrawal, or 90 days following randomization, whichever comes first

5.1.2 Laboratory Evaluations

No routine laboratory evaluations will be required to be performed as part of this study. However, blood levels of lactate, potassium, calcium, sodium, and chloride are routinely measured at presentation and serially over time in pediatric patients with suspected or confirmed septic shock. Any such laboratory evaluations that are performed during the course of routine clinical care in the ED or during the hospitalization may be abstracted from the medical chart.

No laboratory testing will be required in this study beyond that which is performed as part of routine clinical practice. Because both NS and LR are already FDA-approved with demonstrable efficacy and safety for reversing shock and there exists a long history of clinical experience in using both NS and LR in pediatric patients with septic shock, there does not exist sufficient equipoise to justify a clinical trial to investigate either the individual efficacy or safety profile of NS or LR. Rather, this feasibility study is the first step towards a larger, multicenter comparative effectiveness study which will determine the *relative* efficacy and safety of NS versus LR. The relative benefit one fluid over the other was not been proven or even sufficiently tested in large prospective studies and there is, therefore, equipoise for the question of comparative effectiveness. The goal of the comparative effectiveness study will be to determine if there are clinically overt and significant benefits of either NS or LR, relative to each other. We therefore will seek to measure clinically overt and significant efficacy and safety outcomes which would be identified as part of routine clinical practice rather than specifying biochemical laboratory tests that may identify values outside the range of normal but would not otherwise be considered "clinically overt and significant". For example, there is no compelling reason to shift clinical practice from predominant NS resuscitation to predominant LR resuscitation solely because of hyperchloremia *if* this biochemical abnormality does not translate into a "clinically overt and significant" patient outcome. For these reasons, no laboratory testing will be required beyond that which is performed as part of routine clinical practice. However, as described in Section 6.3.4, for the purposes of this feasibility study, we will track laboratory testing performed as part of routine clinical practice in order to determine the frequency that laboratory results are available for the specified safety outcome measures listed in Section 5.4. In addition, if the designated "stopping criteria" listed in Section 4.6.1 are identified during the course of routine, clinician-directed physical and/or laboratory assessment, no further study fluid will be recommended.

5.1.3 Radiographic Evaluations

No routine radiographic evaluations will be required as part of this study. However, radiographic studies that are performed during the course of routine clinical care will be

abstracted from the medical chart as needed to determine site of infection, diagnosis of venothromboembolism, and diagnosis of cerebral edema/intracranial hypertension.

5.2 Feasibility Evaluations

5.2.1 Aim 1

The primary outcome for Aim 1 will be the proportion of total crystalloids administered as saline in each arm, and the secondary outcome will be the proportion of total crystalloids administered as non-study fluid (i.e., cross-over) in each arm.

The primary outcome will be measured in each subject by dividing the total volume (in mL) of NS administered as fluid boluses or continuous IV/IO fluids (numerator) by the total volume (in mL) of all crystalloids (NS, LR, and Plasma-lyte [with or without dextrose and/or other electrolyte additives]) administered as fluid boluses or continuous IV/IO fluids during the intervention phase (denominator). NS or LR (or other crystalloid) administered to "flush" a medication or check line patency, as a "carrier" fluid designed to maintain IV/IO patency or assist delivery of another medication, or used solely as a diluent for another medication will be excluded from both the numerator and denominator.

The secondary outcome will be measured in each subject by dividing the total volume (in mL) of non-study fluid given as either NS (for patients randomized to the LR arm) or LR (for patients randomized to the NS arm), including pre-study enrollment crystalloid fluids (numerator), by the total volume (in mL) of NS plus LR [with or without dextrose and/or other electrolyte additives]) administered as fluid boluses or continuous IV/IO fluids during the intervention phase (denominator). NS or LR (or other crystalloid) administered to "flush" a medication or check line patency, as a "carrier" fluid designed to maintain IV/IO patency or assist delivery of another medication, or used solely as a diluent for another medication will be excluded from both the numerator and denominator.

5.2.2 Aim 2

The outcome for Aim 2 will be the proportion of eligible patients treated in the CHOP ED who are enrolled, randomized, and treated with study fluid. This outcome will be measured by dividing the number of eligible patients treated in the CHOP ED who are enrolled, randomized, and treated with study fluid (numerator) by the total number of eligible patients treated in the CHOP ED (denominator) over the entire enrollment period of the study.

5.2.3 Aim 3

The outcomes for Aim 3 will be the proportion of eligible patients who meet criteria for EFIC who are not enrolled, randomized, and treated with study fluid or, if enrolled, withdraw prior to completion of the follow-up phase. This outcome will be measured by dividing the number of patients eligible but <u>not</u> enrolled through EFIC and/or withdraw prior to completion of the follow-up phase (numerator) by the number of eligible patients who meet criteria for EFIC (denominator) over the entire enrollment period of the study.

5.3 Efficacy Evaluation

This pilot study will not be powered to determine efficacy. However, the following efficacy outcomes planned for use in a subsequent large pragmatic trial will be measured:

- All-cause hospital mortality (censored at 90 days following randomization), measured as vital status at hospital discharge
- Hospital-free days, measured as the number of calendar days alive and out of the hospital between randomization (day 0) and day 27. Patients who die prior to hospital discharge will be recorded as "zero" hospital-free days. Because follow-up will not proceed after hospital discharge, patients who may have died after hospital discharge but before day 27 will be recorded as having as many hospital-free days up to day 27 as if they had survived to day 27.
- New inpatient dialysis, measured as treatment (or intention to treat if subject does not tolerate treatment) with any renal replacement therapy (including slow continuous ultrafiltration, continuous or intermittent hemodialysis, hemofiltration, or hemodiafiltration, or peritoneal dialysis) that was not a continuation of pre-hospital chronic therapy.
- Hospital length of stay, measured as the number of calendar days between ED arrival and ED or hospital discharge (whichever occurs later).

5.4 Safety Evaluation

This pilot study will not be powered to determine safety. However, the following safety outcomes planned for use in a subsequent large pragmatic trial will be measured if ascertained as part of routine clinical practice:

- Hyperlactatemia, measured as at least one venous or arterial blood lactate measurement >4 mmol/L within four calendar days of randomization
- Hyperkalemia, measured as at least one venous or arterial blood potassium measurement >6 mEq/L (without hemolysis) within four calendar days of randomization
- Hypercalcemia, measured as at least one venous or arterial blood ionized calcium measurement of >1.35 mEq/L or total calcium >12 mEq/L within four calendar days of randomization

- Hypernatremia, measured as at least one venous, arterial, or capillary blood sodium measurement of >155 mEq/L within four calendar days of randomization
- Hyponatremia, measured as at least one venous, arterial, or capillary blood sodium measurement of <128 mEq/L within four calendar days of randomization
- Hyperchloremia, measured as at least one venous, arterial, or capillary blood chloride measurement of >110 mEq/L within four calendar days of randomization
- Clotting of intravenous line in patients who received both ceftriaxone and LR, within four calendar days of randomization
- Therapy for brain herniation, measured as treatment with hyperosmolar therapy (hypertonic saline and/or mannitol) for radiographic and clinical determination of new impending or present brain herniation (but not including a presumptive clinical diagnosis of brain herniation that is disproven by subsequent radiographic studies) within four calendar days of randomization
- Therapy for thromboembolism, measured as radiographic or clinical determination of new venous or arterial thromboembolism requiring initiation of therapeutic anticoagulation for the purposes of treating thromboembolism, within seven calendar days of randomization

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoint will be the proportion of total crystalloids administered as saline in each arm during the intervention phase (Aim 1).

6.2 Secondary Endpoints

Secondary endpoints will include the following:

- The proportion of total crystalloids administered as non-study fluid (i.e., cross-over) in each arm (Aim 1).
- The proportion of eligible patients treated in the pediatric ED who are enrolled, randomized, and treated with study fluid (Aim 2).
- The proportion of eligible patients who meet criteria for EFIC who are enrolled, randomized, and treated with study fluid *and* do not withdraw prior to completion of the follow-up phase.

6.3 Statistical Methods

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g. means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

6.3.2 Feasibility Analysis

The primary analysis will be based on an intention-to-treat approach and will include all subjects randomized whether or not study fluid was administered.

The primary endpoint will be defined as meeting feasibility criteria if <u>either</u> of the following criteria are met:

3) There is an absolute difference in the mean use of NS between arms of at least 65% with a lower 95% CI border of >60%. For example, feasibility criteria would be met if 90% of crystalloid fluid in the NS arm was NS compared to only 25% in the LR arm. The proportion of NS use in each arm will be compared using the chi-squared test with a 95% bootstrap confidence interval with bias correction (assuming skewed distribution of data) around the difference in the proportion of NS use in each arm.
4) At least 85% of subjects in the NS arm receive ≥90% of study fluid as NS during the study window *and* at least 80% of subjects in the LR arm receive ≥75% of study fluid as LR.

The secondary endpoints will be defined as meeting feasibility criteria if:

- The mean proportion of total crystalloids administered as non-study fluid (i.e., cross-over) is ≤ 25% in each arm (for example, ≤25% of total crystalloid is administered as NS for patients randomized to the LR arm).
- The proportion of eligible patients treated in the pediatric ED who are enrolled, randomized, and treated with study fluid is >65%.
- EFIC is approved by the IRB at CHOP
- The proportion of eligible patients who meet criteria for EFIC who are not enrolled or who are enrolled but withdraw prior to completion of the follow-up phase is ≤10%.

6.3.3 Efficacy Analysis

Efficacy endpoints will be tracked between groups as part of this pilot study, but no formal statistical comparisons will be undertaken due to insufficient statistical power. As part of our secondary feasibility analysis, however, we will determine the proportion of patients with complete data available for each efficacy endpoint listed in Section 5.3 to ensure that it is indeed feasible to capture the efficacy outcome measures planned for a subsequent large multicenter trial.

For subjects who may withdraw prior to death and prior to hospital discharge and for whom permission is not granted for continued follow-up of associated clinical efficacy outcomes, the National Death Index will be queried for survival status. According to FDA regulations, when a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status

6.3.4 Safety Analysis

Safety endpoints will be tracked between groups as part of this pilot study, but no formal statistical comparisons will be undertaken due to insufficient statistical power. As part of our secondary feasibility analysis, however, we will determine the proportion of patients with complete data available for each safety endpoint listed in Section 5.5 to ensure that it is indeed feasible to capture the safety outcome measures planned for a subsequent large multicenter trial. Specifically, we will track laboratory testing performed as part of routine clinical practice in order to determine the frequency that laboratory results are available for the specified safety outcome measures listed in Section 5.4. It is notable that routine clinical practice for sepsis includes frequent (i.e., daily or more) measurement of blood lactate, sodium, potassium, chloride, and calcium.

6.4 Sample Size and Power

In a previous PECARN study called the FLUID trial (data not yet published), nearly 1400 pediatric patients presenting to the ED with diabetic ketoacidosis (DKA) were randomized to different fluid volumes and different fluid types (normal saline vs. half-normal saline).

We used FLUID data on adherence to fluid type assignment to simulate adherence in the proposed study, assuming that the LR arm will behave like the half-NS arm (i.e., the study intervention arm) and the NS arm will behave like the NS arm (i.e., the control arm) in the FLUID trial. In the FLUID trial, the mean percentage of correct fluid given was 96% in the NS arm and 91% in the half-NS arm. About 90% of subjects in the NS arm received at least 85% NS, while about 89% of those in the half-NS arm received at least 75% half-NS. Through simulation, by sampling from FLUID data, with 35 patients in each arm, the probability that at least 85% of subjects in the NS arm and 80% in the LR arm will receive the "adequate" amount of correct study fluids (i.e., ≥90% of study fluid as NS in NS arm and ≥75% of study fluid as LR in the LR arm) is approximately 80% (study power for criterion #2 of the Aim 1 feasibility analysis described in Section 6.3.2).

6.5 Interim Analysis

Although a specific interim analysis will not be performed as part of this pilot feasibility study, we will include a potential early stop role for an imbalance in mortality between the two groups if there is a difference of more than six deaths in one group compared to the other after enrollment of at least 36 subjects (approximately 18 per group). An imbalance of at least six deaths will provide statistical significance at the level of 0.05 between the two groups. Hospital deaths will be monitored continuously as they occur throughout the course of the study. If the potential early stop rule is reached, the DCC will provide these data to the DSMB for an interim review and consideration to proceed versus terminate the study based on their review of the study data, cause of death, and/or other possible data deemed necessary by the DSMB.

7 STUDY MEDICATION

7.1 Description

Existing hospital supplies of NS and LR will be utilized for this study without any change to packaging or labeling.

7.1.1 Packaging

Both NS and LR will be supplied in their usual bags and/or syringes that are in current use as part of routine clinical practice.

7.1.2 Labeling

Only FDA-approved hospital-issued fluids will be used for this study. The current supply of fluids used at CHOP to be included in this study is NS manufactured by Baxter Healthcare Corporation and LR manufactured by Baxter Healthcare Corporation. Both NS and LR will be labeled as per their existing labels that are in current use as part of routine clinical practice. NS is labeled as "0.9% Sodium Chloride Injection USP" and LR is labeled as "Lactated Ringer's Injection USP" as part of routine clinical practice. Although an IND will be sought for this study for the purposes of EFIC, since only FDA-approved study fluids that are used as part of routine clinical care for pediatric septic shock (as well as other indications) will be used for this study, no additional labeling will be applied to bags of either NS or LR for the purposes of this study. At CHOP, while NS remains the most common fluid to treat pediatric septic shock in the ED, 50% of the resuscitation fluids used to treat children with septic shock in the pediatric intensive care unit are NS and 50% are LR. Given both NS and LR are commonly used in routine clinical practice and both are FDA-approved, application of study-specific labeling can only contribute to medication errors by altering routine clinical practice. Given the pragmatic nature of the proposed study design that is required to expand this work to the larger PECARN network, enroll several thousand patients, and optimize external validity, it is not practical to employ a dedicated study team to guard against medication errors that may ensue by introducing a non-standardized label on FDA-approved, hospital-issued fluids to be used in this study.

7.1.3 Dosing

Both NS and LR have identical dosing recommendations for use as crystalloid fluid resuscitation in pediatric septic shock, which is 20 mL/kg of body weight administered as rapid IV/IO bolus. Actual doses administered can vary based on clinician preference and/or patient clinical condition. This study will not prescribe a specific dose of either NS or LR to be administered; rather, all dosing decisions will remain at the discretion of the clinical care team with guidance as per existing ED and PICU sepsis pathways (see Appendix 5).

7.1.4 Treatment Compliance and Adherence

Because study fluids can only be given by the clinical care team (rather than self-administered by the patient and/or LAR), there will be no concerns for patient or parent/guardian-related issues with treatment compliance and adherence.

Compliance/adherence with use of study fluid consistent with the randomized arm will be tracked for every patient as part of Aim 1 of this pilot trial. Details of this assessment are described further in Sections 5.2.1 and 5.7.2.

7.1.5 Drug Accountability

The basis of this feasibility study is to establish and test the feasibility of a pragmatic study design that will ultimately be extended to at least 18 sites through the PECARN network and will enroll several thousand patients. Therefore, it is not practical to account for details of fluid administered (including, for example, lot number and residual volume not administered) beyond that which is collected for clinical purposes. Because both NS and LR are already used in common clinical practice at CHOP, are both FDA-approved, and all decisions regarding timing and volume of fluid to be administered will be governed by the treating clinical team (rather than study protocol), no specific study procedures will be established to monitor study fluid accountability. Rather, administration and disposal of residual volumes of both NS and LR will occur as part of routine practice carried out at CHOP. No fluid will be specifically supplied for the purposes of this study since all decisions regarding timing and volume of fluid will be determined by the clinical care team and because there is no meaningful cost differential for the administration of either NS or LR. Thus, because all study patients will receive an efficacious fluid (either NS or LR) to reverse shock without additional fluid-related costs generated by participating in this study, hospital-stocked fluid supplies will be utilized for this study without need for additional accountability beyond routine practice.

8 SAFETY MANAGEMENT

8.1 Clinical Adverse Events

Septic shock is a complex and life-threatening condition for which we expect a wide range of potential adverse events, including organ dysfunction, hospital-acquired infections, and death, to occur as part of the routine clinical course. In addition, because all intravenous/intraosseous medications, including crystalloid fluids such as NS and LR, can result in intravenous and/or intraosseous extravasation with soft tissue infiltrates, we expect that intravenous and/or intraosseous extravasation with soft tissue infiltrates will occur as part of the routine clinical care for some subjects enrolled in this study. Since all decisions to administer fluids for a specified indication, timing, and/or volume remain at the discretion of the clinical care team, we do not consider intravenous and/or intraosseous extravasation with soft tissue infiltrates to be an unexpected event. Finally, because of the strong existing safety profile of both NS and LR, common clinical use of both fluids to treat septic shock, pragmatic study design with limited, targeted data collection, and because there is no biologic plausible reason to anticipate that adverse events related to study fluid administration should occur remote from fluid administration itself, we will not plan to continuously monitor for clinical adverse events (AEs). Instead, we will monitor for AEs by a chart review that will occur at two time points—1) after the end of the intervention phase and 2) at 5-7 days after the intervention phase (or at hospital discharge, whichever comes first) as shown in Appendix 3. We will limit the time period for determination of AEs to 5-7 days following the end of the administration of study fluid because there is no biologically plausible reason to anticipate that either LR or NS should lead to adverse events remote from the immediate intervention period. We selected a time period of 5-7 days following the end of the intervention period in order to ensure that no clinically significant AEs are missed in this pilot feasibility study in order to better inform a subsequent large randomized multicenter trial.

If AEs are identified, the AE will be reported as they arise as described in Section 8.5 and then will be followed through to resolution or hospital discharge, whichever comes first. In addition, we will also monitor for the specific safety endpoints noted in Section 5.4 that we have *a priori* identified as potential events that may be differentially impacted by use of NS or LR. These safety endpoints will be ascertained through intermittent data collection throughout the intervention and follow-up phases and at hospital discharge or 90 days following randomization, whichever comes first.

8.2 Adverse Event Reporting

Unanticipated problems related to the research involving risks to subjects or others that occur during the course of this study (including SAEs) will be reported to the IRB in accordance with CHOP IRB SOP 408: Unanticipated Problems Involving Risks to Subjects. AEs that are not serious but that are notable, unanticipated, and could involve risks to subjects will be summarized in narrative or other format and submitted to the IRB at the time of continuing review.

8.3 Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a subject who has received an intervention (drug, biologic, or other intervention) and is not anticipated to occur as a part of the routine clinical course of septic shock. Because septic shock is a complex and life-threatening condition for which we anticipate a wide range of potential medical events, including organ dysfunction, hospital-acquired infections, and death, to occur as part of the routine clinical course, there are few events that will be unanticipated. However, the occurrence of an AE does not necessarily have to have a causal relationship with the treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product, that was not anticipated to occur as part of the routine clinical course of septic shock.

All unanticipated AEs (including serious AEs) will be noted in the study records and on the case report form with a full description including the nature, date and time of onset, determination of non-serious versus serious, intensity (mild, moderate, severe), duration, causality, and outcome of the event. AEs that occur within the timeframe noted in Section 8.1 will be followed until either resolution or hospital discharge, whichever occurs first.

Intensity of AEs will be defined as follows:

- Mild: mild event of its type that does not interfere with routine activities
- Moderate: moderate event of its type that interferes with routine activities
- Severe: severe event of its type that makes it impossible to perform routine activities

8.4 Definition of a Serious Adverse Event (SAE)

As noted above, septic shock is a complex and life-threatening condition that commonly causes organ dysfunction, need for invasive medical and surgical therapies (including, but not limited to, mechanical ventilation, renal replacement therapy, plasma exchange, extracorporeal membrane oxygenation, and cardiopulmonary resuscitation), subsequent hospital-acquired infections, and even death. Consequently, the development of new or progressive organ dysfunction, need for invasive medical and surgical therapies (including, but not limited to, mechanical ventilation, renal replacement therapy, plasma exchange, extracorporeal membrane oxygenation, and cardiopulmonary resuscitation), identification of a hospital-acquired infection, and death are all anticipated to occur as part of routine clinical practice for subjects enrolled in this study (see Table 3 below for list of expected and possible unexpected adverse events).

An SAE will be defined as any unanticipated adverse drug experience that results in any of the following outcomes:

- an unanticipated life-threatening event (at risk of death at the time of the event), or
- requires prolongation of existing hospitalization, or
- a persistent or significant disability/incapacity.

Other important unanticipated medical events that may not be life-threatening or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A distinction should be drawn between serious and severe AEs. A severe AE is a major event of its type. A severe AE does not necessarily need to be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but would not be an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

8.4.1 Relationship of SAE to study drug or other intervention

The relationship of each SAE to the study intervention will be characterized using one of the following terms in accordance with CHOP IRB Guidelines: definitely, probably, possibly, unlikely or unrelated.

8.5 IRB/IEC Notification of SAEs and Other Unanticipated Problems

The Investigator will promptly notify the IRB of all on-site unanticipated, serious Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the eIRB system and in accordance with the timeline below. External SAEs that are both unexpected and related to the study intervention will be reported promptly after the investigator receives the report.

Type of Unanticipated Problem	Initial Notification (Phone, Email, Fax)	Written Report
Internal (on-site) SAEs that are Life Threatening	24 hours	Within 2 calendar days
Internal (on-site) SAEs All other SAEs	7 days	Within 7 business days
Unanticipated Problems Related to Research	7 days	Within 7 business days
All other AEs	N/A	Brief Summary of important AEs may be reported at time of continuing review

8.5.1 Reporting procedures

AEs will only be reported if judged by the investigators to be related to administration of study fluid. SAEs will be reported regardless of whether these are judged to be related to administration of study fluid. See “Adverse Event Reporting” in Appendix 3 for a flow diagram outlining the need for and timing of reporting of AEs and SAEs.

AEs and SAEs to be collected for subjects enrolled in this study are listed in Table 3, along with classification as either expected within the study population of pediatric patients with septic shock or unexpected. All of the events lists in Table 3 could potentially be related to the study fluid intervention, though this determination will be made on a case-by-case basis. Other unexpected events not listed in Table 3 will not be collected unless the clinical care team and/or the study investigators determine that the event may be related to the study fluid intervention.

Table 3: Adverse Events To Be Collected

Event	AE or SAE	Expected in Pediatric Sepsis
Death[1]	SAE	Expected
Cardiac arrest requiring CPR	SAE	Expected
Arrhythmia requiring intervention	AE	Not Expected
Vasoactive infusion	SAE	Expected
Extracorporeal membrane oxygenation (ECMO)	SAE	Expected
Invasive mechanical ventilation	SAE	Expected
Non-invasive mechanical ventilation	AE	Expected
Dialysis (not pre-existing) [1]	SAE	Expected
Liver dysfunction	SAE	Expected
Limb necrosis	SAE	Expected
Brain herniation[2]	SAE	Not Expected
Seizure	AE	Not Expected
Pulmonary embolus	SAE	Not Expected
Deep venous thrombosis	AE	Expected
Central venous line clot requiring pharmacologic therapy[2]	AE	Expected
Bleeding (not requiring massive transfusion protocol)	AE	Expected
Bleeding (requiring massive transfusion protocol)	SAE	Not Expected

Hospital-acquired infection[3]	AE	Expected
Pressure ulcer	AE	Expected
IV infiltrate (grade 3 or 4)	AE	Expected
Rash	AE	Expected
Hyperlacatatemia > 4 mmol/L[2]	AE	Expected
Hyperkalemia >6 mEq/L[2]	AE	Not Expected
Hypercalcemia (ionized calcium > 1.35 mEq/L or total calcium > 12 mEq/L) [2]	AE	Not Expected
Hypernatremia >155 mEq/L[2]	AE	Not Expected
Hyponatremia <128 mEq/L[2]	AE	Not Expected
Hyperchloremia >110 mEQ/L[2]	AE	Expected

[1]Event also included as pre-specified efficacy outcome

[2]Event also included as pre-specified adverse outcome

[3]Includes central line-associated bloodstream infection, urinary tract infection (both catheter-associated and non-catheter-associated), ventilator-associated pneumonia, ventilator-associated tracheitis, hospital-acquired viral infection, surgical site infection, and *C. difficile* colitis)

8.5.2 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) will be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

8.6 Investigator Reporting of a Serious Adverse Event to Sponsor

Reporting will be consistent with all regulatory and sponsor requirements, including the IND submitted to the FDA. Dr. Scott Weiss, a CHOP co-investigator, will be the sponsor for the IND.

8.7 Medical Emergencies

Medical emergencies that might develop during the course of the study will be diagnosed and treated at the discretion of the clinical team.

9 STUDY ADMINISTRATION

9.1 Treatment Assignment Methods

9.1.1 Randomization

Prior to enrollment of any subjects, a complete randomization scheme will be completed using a 1:1 permuted blocks. The randomization sequence will be filed within a series of sequentially numbered, opaque envelopes. A supply cart with both NS and LR will be available where the randomization envelopes are located and will be immediately available for enrollments, so as not to delay treatment of subjects. While not specifically a goal of this study, we do anticipate that the presence of the supply cart may actually enhance the speed of treatment since the fluid will be immediately available at the bedside.

9.1.2 Blinding

Study fluids will not be blinded due to costs and interventions that are not in keeping with a simple, pragmatic trial. Moreover, it may not even be possible to effectively blind clinicians to study fluid assignment due to common electrolyte differences following NS or LR that will suggest a specific fluid selection. This scenario was borne out in the previously published SPLIT fluid trial in which two-thirds of clinicians correctly identified the randomized crystalloid patients received (despite blinding) based on diverging electrolyte profiles.[32]

9.2 Data Collection and Management

Data will be managed and stored by the University of Utah Data Coordinating Center (DCC), which has an established working relationship with PECARN (the planned research network for the subsequent multicenter pragmatic trial). We will work with the DCC to create the electronic case report form (CRF) for this study. The CRF will be password-protected with the safeguards noted below to maintain confidentiality for all data entered into the CRF. The CRF will be password-protected and entered via CHOP-issued computers. There will be a separate master list linking subject PHI and study data and will be stored separately from the study data and will only be accessible to the CHOP study team. Locally secured, identifiable information and partially identifiable information will be stored locally at CHOP for this pilot study.

The Data Coordinating Center has a state-of-the-art computer infrastructure with a dedicated server room with a fire suppression system, air conditioning, cooling system and separate air filtering. The server facility is locked separately from the remainder of the Data Coordinating Center and access to the building is monitored by security personnel year round. The Data Coordinating Center coordinates its network infrastructure and security with the Health Sciences Campus (HSC) information systems at the University of Utah. This provides the Data Coordinating Center with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University.

Network equipment includes four high-speed switches. User authentication is centralized with two Windows 2008 domain servers. Communication over public networks is encrypted

with virtual point-to-point sessions using SSL or VPN technologies, both of which provide at least 128 bit encryption. REDCap, OpenClinica (Web-based clinical studies data management system), eRoomTM (Web-based collaborative workspace) and other web applications use the SSL protocol to transmit data securely over the Internet. Direct access to Data Coordinating Center machines is only available while physically located inside the Data Coordinating Center offices, or via a VPN client. All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and IT staff are notified of intrusion alerts.

Production servers running mission critical applications are clustered and configured for failover events. Servers are backed up with encryption through a dedicated backup server that connects across an internal 10 gigabit network to a tape drive. Storage area networking (SAN) applications, clusters, and switch-to-switch links are also on a 10 gigabit network. Incremental backups occur hourly during the week. Incremental backups also are performed nightly with full system backups occurring every week. Tapes are stored in a fireproof safe inside the data center facility, and full backups are taken to an off-site commercial storage facility. Security is maintained with Windows 2008 user/group domain-level security.

Users at both CHOP and University of Utah will be required to change their passwords every 90 days, and workstations at University of Utah will time out after 5 minutes of inactivity. All files are protected at group and user levels; database security is handled in a similar manner with group level access to databases, tables, and views in Microsoft SQL Server. All portable computers at University of Utah are whole-disk encrypted.

9.3 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study.

The PI and other research personnel have all completed training and received certification in Human Subjects Research Protection and HIPAA. All project staff hired will also successfully complete this training prior to engaging in any research or treatment with study participants and renew this training as required by their institution.

The investigators and staff of the Data Coordinating Center are fully committed to the security and confidentiality of all data collected for the PRoMPT Bolus-Feasibility study. All Data Coordinating Center personnel at the University of Utah have signed confidentiality agreements concerning all data encountered in the center. Violation of these agreements may result in termination from employment at the University of Utah. In addition, all personnel involved with data coordinating center data systems have received Human Subjects Protection and HIPAA education.

The staff, reviewers and investigators involved with this study will be required to sign agreements from the Data Coordinating Center that relate to maintenance of passwords, information system security, and data confidentiality.

No identifiable data will be used for future study without first obtaining IRB approval. The investigator will obtain a data use agreement between the provider (the PI) of the data and any recipient researchers (including others at CHOP) before sharing a limited dataset (PHI limited to dates and zip codes).

9.4 Regulatory and Ethical Considerations

9.4.1 Data and Safety Monitoring Plan

The principal investigator will be responsible for overseeing data collection and the safety of all study procedures. In addition, a Data Safety Monitoring Board (DSMB) will be convened made up of representatives who are independent of the study investigators.

Before initiation of the clinical study, the sponsor-investigator will arrange a pretrial monitoring visit with the IND & IDE Support Program and the Office of Research Compliance (ORC) to confirm clinical trial readiness. After enrolling and starting administration of the investigational agent to the first subject, the sponsor-investigators will contact ORC to arrange a monitoring visit. Thereafter, ORC will monitor the study at least once during the course of the pilot. Monitoring activities will be guided by ICH E6 section 5.18. Monitoring of subject data will be initiated at 100% verification of the data recorded. This may be amended, and a tapered approach to monitoring may be employed, if conduct and documentation of the study reaches a level of reliability that would permit valid conclusions based upon a sampling of data

9.4.2 Data Safety Monitoring Board (DSMB)

The PRoMPT Bolus – Feasibility study will have a Data Safety Monitoring Board (DSMB) composed of five members from the CHOP/University of Pennsylvania community who have no other involvement in any aspect of the proposed study. Members of the DSMB will be invited by the study investigators in consultation with the DCC. At least one member will be knowledgeable in medical ethics and at least one member will be a patient advocate. The DSMB will have a charter, will approve the protocol prior to implementation, and will meet prior to initiation of subject enrollment, after hospital discharge of the first 36 subjects, and again at the conclusion of the study along with meetings scheduled *ad hoc* as necessary.

The purpose of the DSMB will be to advise the study investigators regarding the continuing safety of study subjects and the continuing validity and scientific merit of the study. The DSMB is responsible for monitoring accrual of study subjects, adherence to the study protocol, assessments of data quality, review of serious adverse events and other subject safety issues, and review of formal statistical analyses. The DCC will send reports relating to these topics to DSMB members ten days prior to each DSMB meeting and will notify the DSMB if the mortality difference exceeds the predetermined stopping rule noted in Section 6.5.

The DCC will remotely staff DSMB meetings and produce minutes of open sessions. Minutes of closed or executive sessions of the DSMB will be produced and retained by the DSMB Chairperson. These closed minutes will not be available outside the DSMB prior to the end of the study.

The DSMB Chairperson will prepare a summary of each DSMB meeting that conveys the public conclusions of the DSMB, with respect to protocol alterations and recommendations concerning continuation of the study. The summary will be provided to the DCC and the DCC will send this summary to all participating investigators for submission to their respective Institutional Review Boards.

The DSMB will meet prior to the start of subject enrollment and then after enrollment of all subjects for this feasibility study. The DSMB, however, will have the discretion to alter meeting timing and frequency, as well as meet ad hoc as necessary throughout the course of the study.

9.4.3 Risk Assessment

Because both NS and LR have both been previously proven as efficacious for fluid resuscitation of pediatric septic shock, both NS and LR are currently used in common clinical practice for this indication, and because patients will only be considered eligible if the clinical care team (usually the attending physician) deems it safe for the patient to receive both NS and LR, the risks presented by this study will be limited. However, because there is a prospect of a relative benefit in efficacy and/or safety for one fluid over the other, subjects may be randomized to an arm with relatively inferior efficacy or relatively worse safety.

Several safeguards have been put in place to minimize risk of randomized (rather than clinician-prescribed) fluid administration, including:

a) Because of the FDA noted caution in using lactate-containing fluids, such as LR, in patients <6 months of age, only patients >6 months-old will be eligible for this study.
b) Any patients for whom clinician judgement deems it unsafe to administer NS or LR will be excluded from enrollment, with specified exclusions noted (but not limited to) clinical suspicion for impending brain herniation, known hyperkalemia, known hypercalcemia, and known fulminant hepatic failure.
c) Exclusion of patients with known pregnancy, known prisoner status, or known allergy to NS or LR.

In addition, post-marketing risks reported with infusion of either NS, LR, or both fluids are listed in Table 4. All of these risks that have been reported with (but not necessarily causally linked to) use of either NS, LR, or both and are all consistent with the risks subjects would experience if they received these fluids as part of clinical care. Therefore, participation in this study is unlikely to expose patients to risks beyond that incurred as part of routine clinical care. However, since it is likely that more patients will receive LR than otherwise would as part of routine clinical care, there may be a slight increase in risk for the study population as a whole than would otherwise be the case as part of routine clinical care.

Table 4: Reported risks associated with infusion of NS and/or LR

Risk	Reported with NS	Reported with LR
Anaphylaxis/anaphylactoid reaction	X	X

Angioedema/Laryngeal edema	X	X
Chest pain/chest discomfort	X	X
Bronchospasm		X
Dyspnea/Respiratory distress	X	X
Cough	X	X
Urticaria or other rash	X	X
Pruritis	X	X
Nausea	X	X
Pyrexia	X	X
Infusion site reaction (erythema, pruritis, numbness, pain, edema, extravasation)	X	X
Bradycardia		X
Tachycardia		X
Hypotension		X
Anxiety	X	X
Headache	X	X
Dysgeusia (metallic taste in mouth)		X
Paresthesias		X
Sneezing		X
Hyperkalemia	X[a]	X
Hypervolemia	X	X
Pulmonary edema	X	X
Acid-base disturbance	X[a]	X
Hyponatremia		X
Hyperlactatemia		X
Hypernatremia	X	

Hyperchloremia	X	
Hypercalcemia		X
Acute kidney injury	X[a]	X
Infection	X[a]	X
Coagulopathy	X	X
Venothromboembolism	X	X[b]
Cerebral edema	X	X[b]

[a]Risk reported in patients receiving both NS and LR but may be more common with NS

[b]Risk reported in patients receiving both NS and LR but may be more common with LR

The other major risk to subjects enrolled in this study is breach of patient confidentiality, which is itself limited by the safeguards noted in Section 8.3.

9.4.4 Potential Benefits of Trial Participation

Because fluid resuscitation with either NS or LR may offer relative superior efficacy and/or safety, there is a prospect of direct benefit to subjects from trial participation.

Additionally, indirect benefits to society are clear because this pilot study will help to inform a larger pragmatic comparative effectiveness study to meet the needs of clinicians making treatment decisions about fluid resuscitation for pediatric patients with suspected septic shock. By informing the most beneficial and safe crystalloid fluid for clinicians to select, society (and future patients) may benefit from a reduction in sepsis-associated morbidity and mortality.

9.4.5 Risk-Benefit Assessment

Because NS and LR are both known to be efficacious for resuscitation of pediatric septic shock and both fluids are currently used in clinical practice, there is a minimal expected impact on the overall risk-benefit balance to patient to participation in this trial beyond that which would be incurred as part of ordinary routine clinical practice. Nonetheless, because subjects enrolled in this study will receive type of fluid determined by randomization rather than clinician-prescribed (as in usual practice) and there is a potential for a relative benefit in efficacy and/or safety for one fluid over the other, the risks incurred by enrollment in this study may be slightly higher than in clinical practice. However, this small potential for risk for subjects randomized to a relatively inferior fluid is balanced by the prospect of direct benefit for subjects randomized to a relatively superior fluid with all subjects having an equal chance of randomization to either arm. The primary benefit of this trial for patients is that each patient has a random chance to be exposed to a potentially more effective fluid resuscitation strategy. Given the lack of definitive data indicating which fluid is more effective and, thus equipoise, it cannot be known before the study which fluid arm may or

may not provide the most benefit. Risks due to breach of confidentiality are another risk, but this will be mitigated by the steps outlined in Section 8.3.

Given the potential of direct patient benefit with only minimal risk greater than routine clinical care, the study is justified to proceed based on the balance between risks and benefits.

9.5 Recruitment Strategy

Subjects will be recruited as part of routine clinical practice within the CHOP pediatric ED. Prospective subjects will be identified by the clinical care team when they meet eligibility criteria. We anticipate that activation of the CHOP ED Sepsis Pathway order set will be a primary trigger to consider eligibility for inclusion of a patient in this study. However, patients do not necessarily have to be treated on the CHOP ED sepsis pathway to be considered for eligibility of enrollment into this study. A member of the study team—including ED attendings and fellows included and trained as study co-investigators—will ensure subjects meet all eligibility criteria prior to study enrollment. After eligibility is confirmed and, in the rare cases were sufficient time is available for prospective informed consent, a member of the study team—including ED attendings and fellows included and trained as study co-investigators—will seek informed consent. For most cases, however, we anticipate that conditions will not permit sufficient time for prospective informed consent and we will proceed with enrollment under Exception From Informed Consent (EFIC, see Section 9.6.3) for which a member of the clinical care team, under the supervision of the attending physician of record or his/her designee, will be responsible for obtaining an "opt-out" from the LAR when possible (see Section 9.6.3 for further details of "opt-out" plan). Study fliers (approved under CHOP IRB study 17-013950) will be posted in the CHOP ED to further inform potential subjects and LARs of this study.

Based on internal data from CHOP and published estimates,[53] we anticipate 189-290 eligible patients per 100,000 ED visits. With approximately 20,000 visits over 4 months to the CHOP ED, we anticipate sufficient subjects to achieve the study goals with enrollment over 4 months.

9.6 Informed Consent/Assent and HIPAA Authorization

Subjects will be enrolled using a combination of written informed consent and HIPAA Authorization, if feasible, or Exception From Informed Consent (EFIC) under specified conditions (see below).

We seek a waiver of assent for all subjects (see below).

9.6.1 Informed Consent and HIPAA Authorization

For patients who meet inclusion criteria and in the rare scenario where sufficient time is available to properly and ethically seek prospective informed consent without endangering the patient, the parents or legal guardians (i.e., LARs) will be approached for study enrollment. A trained member of the study team—including ED attendings and fellows included and trained as study co-investigators—will engage them in a discussion regarding reasons for the study, the study procedures, and the risks and benefits and answer all

questions. A study team physician will also be available to explain the medical aspect of the study and answer questions during the consent process. Due to anticipated critical nature of the patients' condition in septic shock, this discussion may take place at the patient's bedside or in an alternative location (e.g., family conference room) at the parent/guardian's option and the consenter's discretion. Regardless of the where this discussion takes place, all reasonable safeguards to ensure patient privacy will be taken. If it is necessary for a study team member to discuss the study with the LAR via phone (e.g., LAR cannot be physically present but time permits for prospective informed consent), then written informed consent will still be obtained by either faxing or emailing the informed consent form to the LAR for a written signature.

For patients who meet inclusion criteria and in the rare scenario where sufficient time is available to properly and ethically seek prospective informed consent without endangering the patient, we will also obtain written permission for HIPAA Authorization on the combined consent-HIPAA authorization form.

We will provide a copy of the combined consent-HIPAA authorization document to the parent/guardian and will write a note in the patient's medical record documenting the informed consent discussion.

If the LAR consents to participate in the study, the LAR will be notified that PHI will be retained indefinitely in a coded fashion with all safeguards in place to maintain confidentiality as described in Section 8.3.

9.6.2 Waiver of Assent

We are seeking a waiver assent for all patients due to the critical nature of the patients' illness in septic shock, often with altered mental status and neurologic dysfunction from a combination of sepsis encephalopathy, shock, hypoxemia, hypercarbia, and/or hyperthermia, which will make them unable to participate in a meaningful way. However, any patients who are capable and willing to participate in the prospective informed consent discussion (in rare scenarios where it is appropriate) will be involved and engaged in this process.

9.6.3 Exception From Informed Consent (EFIC)

Enrollment of subjects under Exception from Informed Consent (EFIC) requires the following conditions to be present:

1) Subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence is necessary to determine the safety and effectiveness of a therapy

2) Obtaining prospective informed consent is not feasible

3) Subjects may benefit from the research

4) Research could not be carried out without an EFIC

The specific elements of our study that meet each of these conditions are:

1) Septic shock is a life-threatening medical emergency requiring immediate therapy, analogous to myocardial infarction, stroke, or trauma [12]. There are currently no data proving the most effective crystalloid fluid to use for initial, immediate resuscitation of children (or adults) with septic shock and existing guidelines are silent as to which crystalloid fluid to use as first-line therapy (with both NS and LR currently considered to be equivalent options). Prior observational studies in adults and pediatric patients have not been able to determine the comparative safety and effectiveness of different available crystalloid fluids to use for resuscitation in septic shock, leading to multiple calls for prospective randomized trials to provide the necessary evidence to determine comparative effectiveness.

2) The current ACCM guidelines to treat hemodynamic shock in pediatric sepsis recommend crystalloid fluid resuscitation within 15 minutes of recognition of septic shock. Thus, in most instances, this exceedingly short time window is too short for a proper discussion of prospective informed consent, including sufficient opportunity to explain study procedures, discuss risks/benefits, and answer all questions, to be feasible. Expanding the therapeutic window beyond 15 minutes would result in either 1) delay of fluid resuscitation which would place patients at risk of life-threatening complications of untreated septic shock, including cardiac arrest and death and/or 2) administration of a large volume of pre-study, non-randomized fluids that will prevent the necessary clinically important separation between study arms to determine comparative effectiveness of NS versus LR resuscitation. Our data from CHOP and two additional published studies demonstrate that 25-55% of deaths due to pediatric septic shock occur within 24 hours of presentation, necessitating rapid screening, enrollment, and randomization if we are to maximize the chances of identifying a benefit for one resuscitation strategy versus another. In addition, because of the pragmatic study design, front-line clinicians will be required to screen and enroll eligible patients. Given the life-threatening nature of septic shock and need for prompt resuscitation, removing a member of the clinical care team to seek prospective informed consent may compromise clinical care and place patients at risk of life-threatening complications of untreated septic shock, including cardiac arrest and death. Finally, our data from a survey conducted in the CHOP ED, supports that parents/guardians would prefer not to be approached for informed consent in the initial critical period of their child's emergency care. Therefore, in most instances, obtaining informed consent will not be feasible.

   In rare circumstances, fluid resuscitation may be necessarily delayed such as with parental or clinician initial preference to avoid or limit fluid resuscitation (e.g., concern for concurrent heart failure for which large-volume, rapid fluid resuscitation may not be in the best interest of the patient) or with delayed IV/IO access. In these rare circumstances when the therapeutic window is extended beyond 15 minutes from recognition of septic shock, there may be an opportunity to seek prospective informed consent.

3) Because fluid resuscitation with either NS or LR may offer relative superior efficacy and/or safety, there is a prospect of direct benefit to subjects from trial participation.

4) Because informed consent is not feasible (as noted above), this study could not be carried out without EFIC. Moreover, alternative study designs, such as observational studies have already proven insufficient to determine comparative effectiveness of NS versus LR. Finally, the study proposed does not meet the human subjects research obligations needed to obtain a waiver of informed consent.

As required by EFIC, if the LAR is immediately and physically present during the 15 minute therapeutic window, a member of the care team will notify the LAR that this study is being conducted in conjunction with routine sepsis care and that details regarding the study will be provided as soon as feasibly possible. The study team will first seek to inform of study enrollment and the option to withdraw from continued participation: (a) the subject, (b) then the subject's legally authorized representative if the subject remains incapacitated, and (c) then the subject's family if the LAR is unavailable, to comply with the EFIC requirements.

Given the short therapeutic time window of 15 minutes following recognition of septic shock, anything more than a brief notification of the intent to randomize to one of two efficacious fluids would constitute a contrived and hollow attempt to adequately inform the LAR of the study details. Still, if the LAR objects to study participation after this notification, then the patient will not be enrolled. As part of this discussion to offer opportunity to opt-out of study enrollment, a member of the ED care team will first seek "opt-out" from the a) potential subject, b) then the subject's LAR if the subject remains incapacitated or age <8 years, and c) then the subject's family if the LAR is not available. The ED staff will be provided with recommended "opt-out" language to ensure a reasonably consistent approach for pre-enrollment study opt-out. Recommended language will include that a) participation is voluntary, b) subjects do not have to agree to participation to continue to receive care at CHOP, and c) that subjects can withdraw without penalty or loss of benefits to which the subject is otherwise entitled. However, if the subject is incapacitated or <8 years and neither the LAR or family member are immediately and physically present, then we will forego pre-enrollment opt-out in order to not delay treatment or study enrollment. As part of this pilot study, we will offer a quantitate debriefing to ED providers following enrollment through EFIC to ascertain concerns about the enrollment and opt-out procedures.

In addition, the LAR for each subject enrolled via EFIC will be approached as soon as feasibly possible to inform of subject study enrollment and provided the opportunity to continue or withdraw from further study participation. To facilitate this discussion, we will provide the LAR with a "Post-Enrollment Opt-Out Information Sheet" which will summarize the details of the study, including that the subject was enrolled and treated without their consent (as there was no time to obtain it), that the IRB has approved an excpetion from informed consent for the study, and what the procedures for continued participation will be required (i.e., possibly additional study fluid and medical record review). In addition, the "Post-Enrollment Opt-Out Information Sheet" will disclose that continued participation is voluntary, not necessary to continue to receive care at CHOP, and that subjects can withdraw without penalty or loss of benefits to which the subject is

otherwise entitled. The LAR will also be provided with the prospective Informed Consent Form as a means of providing complete information about what this study involves, though the LAR will not be asked to sign the Informed Consent document. In order to document this encounter, we will ask the LAR to either sign the Post-Enrollment Opt-Out Information Sheet if physically present or have a study team member sign the form if the discussion occurs over the phone. We acknowledge that the LAR's signature will neither constitute nor substitute for informed consent, as these patients would have been enrolled under EFIC. However, because of concerns raised by potential PECARN sites for a possible future multicenter trial and our own ethical interests, we feel it is important to document that the study indeed discussed the details of the study with the subject/LAR and provided an opportunity to opt-out/withdraw by asking the LAR to sign that this discussion took place. Whether the subject/LAR chooses to continue in the study post-enrollment or not, we will document their decision on the "Post-Enrollment Opt-Out Information Sheet" to acknowledge this discussion.

For subjects enrolled via EFIC, if the subject's LAR or family member could not be informed of the subject's participation prior to the subject's death, they will be informed after the subject's death.

Our full proposal for executing the elements of EFIC, including community consultation, public disclosure, and submission of an investigational new drug application to the Federal Drug Authority (FDA), have been separately described in detail under a separate applicate to the CHOP IRB (IRB # 17-013950). Because of the challenges of EFIC, particularly in a pediatric population, we have ensured that the study team includes individuals with prior experience in this area. Dr. Jill Baren is a recognized expert in human subjects regulations related to clinical trials and has experience with EFIC through a prior pediatric trial in PECARN.[54] In addition, Dr. Nathan Kuppermann, Professor of Pediatrics at the University of California at Davis, is an experienced clinical trialist in pediatric emergency care and will provide support, mentorship, and oversight to Dr. Weiss for his IND application to the FDA for use of EFIC and to Dr. Balamuth as the principal investigator of this EFIC-based study.

All efforts to contact legally authorized representative and/or family members when prospective informed consent cannot be obtained will be documented and this information will be made available to the IRB at the time of continuing review. In addition, all IRB-approved materials used for public disclosure will be submitted to the IND and Public Docket 95S-0158, as required. In addition, we will also submit the materials used to disclose the study results following completion of the clinical investigation.

9.6.4 Non-English Speakers

Non-English speaking families should be afforded the same opportunity to participate in human subjects research as English-speaking families, especially when there is a prospect for direct benefit. For non-English speaking parents/guardians (LARs), an interpreter will assist in the prospective informed consent discussion (if time permits as described above in Section 8.6.1) using the standardized short-form consent form process. Informed consent will be documented using the CHOP standard short-form consent document in the appropriate native language and on a Study Summary Document written in English. When an in-person interpreter is available, the interpreter will be in the same room with the

investigators and may act as witness to sign the witness/interpreter section of the Study Summary Document if the LAR agrees to prospective informed consent.

If a non-English speaking subject meets criteria for enrollment via EFIC an interpreter fluent in both English and the native language of the subject (parent/guardian) will assist in the pre- and post-enrollment opt-out discussion. The pre-enrollment opt-out discussion will take place as soon as it is possible for a member of ED care team to identify an appropriate translator (e.g., in-person or via phone) and proceed with the opt-out discussion, just as it would occur for English speakers. However, just as if an English-speaking subject is incapacitated or <8 years and neither the LAR or family member are immediately and physically present, we will forego pre-enrollment opt-out in order to not delay treatment or study enrollment. Because availability of an interpreter may be a limiting factor, we do acknowledge the potential for non-English speakers to be less likely than English speakers to have the opportunity to opt-out prior to subject enrollment and initiation of study intervention procedures. Nonetheless, this consideration needs to be balanced against equal access to the opportunity to participate—and potentially benefit from enrollment—in this study (as mandated by the requirement for "justice" under the Belmont Report). Given the short therapeutic time window of 15 minutes following recognition of septic shock to administer fluids and enroll subjects into this study, we anticipate that there will rarely be sufficient time to proceed with pre-enrollment opt-procedures regardless of English or non-English language and, thus, we feel that differential potential for pre-enrollment opt-out by language is largely theoretical.

For post-enrollment opt-out discussions, an interpreter fluent in both English and the native language of the subject (parent/guardian) will assist in the post-enrollment opt-out discussion and help to interpret the "Post-Enrollment Opt-Out Form". When an in-person interpreter is available, the interpreter will be in the same room with the investigators and may act as witness to sign the witness/interpreter section of the "Post-Enrollment Opt-Out Form". In the case that an in-person interpreter is not available, a phone interpreter who is fluent in both English and the native language of the patient (parent/guardian) will be utilized and a separate third-party witness to the phone conversation will sign the "Post-Enrollment Opt-Out Form" as the witness.

The interpreter/witness will not be part of the study team or otherwise involved with the study. If a phone interpreter is utilized for prospective informed consent, we will ask that the interpreter email the investigators a statement attesting to the LAR's understanding of the study and consent to participate. if a phone interpreter is used in the post-enrollment opt-out discussion, then a separate third-party witness may sign the "Post-Enrollment Opt-Out Form" to attest that the discussion took place with an appropriate interpreter.

9.7 Payment to Subjects/Families

No payment, reimbursement, gifts, or compensation of any kind will be provided to subjects/families for participation in this study.

10 PUBLICATION

This pilot study is not specifically designed for publication, but rather to assess feasibility for implementation of a subsequent large multicenter pragmatic randomized trial. However, should the decision be made to disseminate the results of our pilot study, we will only present and/or publish de-identified aggregate data following appropriate peer review.

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APPENDIX

Appendix 1: FDA package insert for NS

Appendix 2: FDA package insert for LR

Appendix 3: Timing of adverse event collection

Appendix 4: Decision-tree for adverse event reporting

Appendix 5: Fluid Management Algorithm