Complete Summary

OVERALL GOALS: The primary goal of our research is to define the optimal approach to intravascular (IV) fluid resuscitation in pediatric septic shock. We will also generate new knowledge on early sepsis biomarkers and experiences with exception to consent (deferred consent) in children.

BACKGROUND: Current pediatric septic shock resuscitation guidelines from the American College of Critical Care Medicine (ACCM) focus on the early and goal directed administration of IV fluid followed by vasoactive medication infusions for persistent and fluid refractory shock. The ACCM guidelines promote aggressive fluid resuscitation, however, accumulating adult and pediatric data suggests that excessive fluid administration is associated with worse patient outcomes including death, and that a restrictive fluid resuscitation strategy may improve outcomes in septic shock.

AIM 1: To determine in pediatric patients with septic shock whether use of a ***Fluid Sparing*** strategy to target ACCM hemodynamic goals results in improved clinical outcomes without an increased risk of adverse events, compared to ***Usual Care***.

METHODS: ***Design****:* pragmatic, 2-arm, parallel group, open label randomized controlled trial (RCT) in 8 Canadian pediatric tertiary care centres. ***Sample size:*** 276 participants. ***Participants:*** Children 1 month to 17 yrs with persistent fluid refractory septic shock requiring ongoing resuscitation despite administration of 40 mL/kg (2 litres for ≥ 50 kg) of isotonic crystalloid or colloid. ***Interventions:*** Eligible children will be randomized to further resuscitation according to 1) Fluid Sparing Strategy OR 2) Usual Care.

PRIMARY OUTCOME: Difference in time to shock reversal between groups (hrs)

SECONDARY OUTCOMES: 1) Patient Important Clinical Outcomes e.g. PICU Length of Stay, Organ dysfunction scores, Ventilator Free Days, Mortality. 2) Complications attributable to fluid overload and vasoactive medications. 3) Clinical course, procedures and resource use. 4) Health system outcomes e.g. PICU admission rate.

AIM 2: To describe early sepsis biomarkers in SQUEEZE participants and associations with clinical outcomes.

METHODS: Plasma will be obtained at baseline and 24 hrs. Early sepsis biomarkers will be measured and associations with clinical outcomes determined.

SQUEEZE-D OUTCOME: Association between cell free DNA levels and PICU length of stay.

AIM 3: To explore the experiences of trial participants and substitute decision makers (SDMs) with the exception to consent process.

METHODS: Trial participants and SDMs will be invited to participate in a nested qualitative study involving individual interviews. Interviews will be transcribed and coded using NVivo.

SQUEEZE-Q OUTCOME: Qualitative evidence characterizing experiences with deferred consent.

EXPERTISE: Our team includes research experts in critical care, pediatric emergency medicine, translational research, biostatistics, and bioethics. We receive support and mentorship from the Canadian Critical Care Trials Group and Pediatric Emergency Research Canada.

SIGNIFICANCE: SQUEEZE will provide high-level evidence to inform future iterations of the ACCM guidelines of the optimal fluid resuscitation strategy in pediatric septic shock. Translational results will identify early sepsis biomarkers with potential clinical value in children worthy of further study. Qualitative findings will support development of evidence-based ethics guidelines and inform conduct of future resuscitation trials in Canada and beyond.