Fluids in Septic Shock (FISSH) Randomized Control Trial

A multicentre concealed-allocation parallel group blinded randomized controlled trial to examine the effect of Ringer's Lactate as compared to 0.9% normal saline on mortality in patients with septic shock

PROTOCOL Version 4.0

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Background

Sepsis, a common problem with a worldwide incidence of approximately 200-300 cases per year per 100,000[1], is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[2]. In patients with septic shock, defined as sepsis with evidence of organ hypoperfusion, hospital mortality rates are estimated at 40%[3].

Intravenous fluids are foundational to sepsis management. In septic shock, pathogen-mediated molecules initiate an inflammatory cascade associated with cytokine release and monocyte, lymphocyte and neutrophil aggregation[4]. This process results in a loss of vascular tone, which in turn leads to systemic hypo-perfusion. Therefore, in addition to antimicrobials and vasopressors, maintaining organ perfusion and oxygen delivery requires resuscitation of the intravascular space. When conducting fluid resuscitation, clinicians may choose from several types of fluid, categorized as either crystalloids or colloids. Each fluid has unique properties, including tonicity, pH, and osmolality, depending on its electrolyte and molecular composition [5]. Colloids are generally not used in the early phase of resuscitation as they are more expensive, and their use is not supported by the evidence [6].

Based on tonicity relative to plasma, crystalloids are classified into hypertonic, isotonic and hypotonic solutions. Isotonic crystalloids are those that primarily function as intravenous volume expanders. Worldwide, the most commonly used isotonic crystalloid is 0.9% normal saline (saline, NS), which contains a supra-physiologic concentration of chloride (154 mM). Other isotonic crystalloid solutions (e.g. Ringer's Lactate [RL]) contain an organic anion (e.g. lactate, maleate, acetate) and therefore have a lower chloride content more closely approximate to human plasma. These solutions that contain more physiologic chloride content are termed 'balanced crystalloids'. Compared to balanced crystalloid solutions, normal saline is associated with hyperchloremic metabolic acidosis, decreased glomerular blood flow, and impaired smooth muscle contractility in animal models [7]. However, it is unclear whether these adverse effects observed in preclinical models result in worse outcomes in critically ill patients.

There is limited evidence examining the impact of high versus low chloride fluid administration in critically ill patients. Fluid administration strategies in patients with sepsis and septic shock, including dose and type, remain controversial. The 2016 Surviving Sepsis Campaign Guidelines recommend that crystalloid solutions be used as first-line intravenous fluid for patients with septic shock, but suggest using either balanced crystalloid or saline [8] until further data are available. Despite evidence of the physiologic benefits associated with balanced solutions, saline remains the most widely used fluid in the world. Given uncertainty about the impact of lower chloride versus higher chloride solutions on mortality, it is unlikely that clinical practice will change without direct randomized controlled trial [RCT] evidence. Editorial commentaries in leading critical care journals have repeatedly called for RCTs to address this highly relevant clinical question [9-15].

In a network meta-analysis (NMA) of all fluid types used for resuscitation in patients with septic shock [16], our group identified 14 relevant RCTs that reported mortality and 10 that reported the use of renal replacement therapy. Results suggested that balanced crystalloids are superior to 0.9% saline in improving survival (NMA OR 0.78; 95% Credible Interval (CrI) 0.58-1.05) and decreasing the use of renal replacement therapy (RRT) (NMA OR 0.85; 95% CrI 0.56-1.30); however, this was based on indirect and low quality of evidence[17 18].

Previously published and ongoing RCTs have important limitations. Since our NMA, the SMART trial - the largest RCT to date (n=15,802) addressing this question, conducted at a single academic centre in the United States – was designed as an open-label cluster-randomized, multiple crossover trial comparing saline with balanced crystalloids in hospitalized patients [19]. Investigators found that balanced crystalloids were associated with an improvement in the composite primary endpoint of death, new RRT or persisting renal dysfunction at 30 days (adjusted OR 0.91, 95% CI 0.84-0.99) without effect on overall mortality. While only a small proportion of study patients had

sepsis (14.8%), this subgroup appeared to benefit more than any other (adjusted odds ratio for 30-day mortality 0.74, 95% CI 0.59-0.93) [20]. Limitations of SMART include a heterogeneous population of all critically ill patients (not just septic shock), an associated low baseline risk of death (11.1%), exposure to only very small amounts of study fluid (mean 1 litre), and more importantly lack of blinding that potentially introduced bias in use of co-interventions and outcome ascertainment (other than mortality). These limitations severely restrict inferences on the basis of the study's results.

There are two ongoing international trials (NCT02721654, NCT0287587) and one Canadian trial (NCT02721485) examining a similar research question, however, these trials have important limitations regarding generalizability that FISSH attempts to overcome. The design of these trials differ from the current proposal in that: (i) one is enrolling all hospitalized patients while the other two enrol all critically ill patients – not limited to those with shock. These 3 trials therefore run a high risk of false negative results if, as is likely, benefits of balanced crystalloid are restricted to patients with shock; and/or (ii) these trials evaluate a more expensive, less available, and less studied balanced crystalloid comparator (Plasmalyte) as opposed to FISSH which is using the widely available RL; and/or (iii) enrol patients later in their disease course as compared to FISSH, with greater upfront open label fluid contamination (further increasing the likelihood of a false negative result); and/or (iv) do not include a translational component.

Therefore, FISSH will be the only critical care fluids trial to specifically examine patients with sepsis and those anticipated to receive a large volume of fluid resuscitation (patients with established shock) using a blinded intervention along with employing proven strategies aimed at minimizing non-study fluid resuscitation. Thus, if – as is probable – the benefits of balanced crystalloid are limited to patients with septic shock in whom contamination with other fluid solutions is minimized, the current proposal is the only trial with a high likelihood of demonstrating the benefit.

We have proven feasibility. We successfully completed a 50 patient pilot trial assessing the feasibility of conducting a larger trial [21] and are confident we have the expertise and experience to execute this trial in a cost-efficient and timely manner. Based on these feasibility results, we were funded through the Physician Services Incorporated (PSI) Foundation New Investigator Grant for a further 200 patient provincial trial. Given a similar design between the provincial trial and this protocol, we will include these patients who have already been enrolled in the final analysis.

Research Question

In patients with septic shock, what is the impact of administering 0.9% Normal Saline versus Ringer's Lactate on 30-day mortality and other patient important outcomes including acute kidney injury, need for advanced life support, and ICU/hospital length of stay?

Specific Aims: To examine the effect of NS versus RL on: 1) 30-day mortality; 2) other outcomes important to patients including receipt of advanced life support (renal replacement therapy [RRT], invasive mechanical ventilation, vasopressors), ICU and hospital length of stay and acute kidney injury (AKI).

Hypothesis: In patients with septic shock, administering RL instead of NS will improve survival, reduce the incidence of AKI, reduce the use of life support.

Trial design. This is a multi-centre stratified concealed and blinded RCT with a primary outcome of 30-day mortality. We also include a translational biology sub-study examining serum cell-free DNA levels. We will enrol 1096 patients from 29 hospitals across Canada and Saudi Arabia. We may enrol a few additional patients to account for lost to followup and post-randomization exclusions.

Interventions. Patients randomized to high chloride fluid will receive, for all resuscitation and maintenance fluid infusions, NS (chloride concentration 154 mmol/L); those in the low chloride arm will receive RL (chloride concentration 110 mmol/L). Due to drug-fluid compatibility issues, blood products and fluids used for medication infusions (including a dedicated medication line up to 20 ml/hr) will be exempted. Once a patient is enrolled, study personnel will bring blinded infusion bags of study fluids on pre-prepared carts to the patient's bedside. The timing and amount of fluid infused will remain at the discretion of the treating physician. The ICU clinical team will be blinded to fluid type. This protocol proved feasible in both the pilot and provincial FISSH trials. Study fluids will be administered immediately after randomization and continued until ICU discharge, death, or for 30 days after enrolment, whichever comes first.

Study procedures include minimization of open label fluid use. In rare conditions (e.g., overt hypoglycemia, hypernatremia or profound metabolic acidosis), at the request of the treating physician, the study fluid infusions may be held and open label fluids (e.g., glucose or bicarbonate containing fluid) administered. Blinded study fluid will be resumed as soon as it is deemed safe by the treating physician. Research co-ordinators will document all open-label fluid use for the indications mentioned above and will document reasons for non-adherence. All other aspects of patient care will be left to the discretion of the treating physician. In the FISSH pilot study, 7 of 50 patients received open label fluid; however the volume of non-study fluid administered was small (mean 437 ml/patient). On average, 94% of fluid that patients received was study fluid.

Protocol adherence was one of the main reasons for piloting this protocol before moving forward with a full RCT. Anticipating this potential challenge within the study protocol, we attempted to make use of study fluid as easy as possible through provision of a study cart placed directly at the patient's bedside. Although our feasibility goal for the pilot was a protocol adherence of 75%, we achieved a protocol adherence of 94%; meaning on average 94% of total intravenous fluid that each patient received during the study period was study fluid. We were able to achieve this compliance using strategies such as pre-study education sessions for research and clinical staff and routine clinical reminders (including posters, bedside clinical cards and brightly-coloured indicators for patient's charts). We have applied these same tactics in the provincial trial and plan to use the same strategies in the full RCT.

Allocation. A trained ICU research co-ordinator at each institution will screen all patients for eligibility at the time of ICU admission. We have also empowered physician champions (at least 2-3 per study site) in order to facilitate early enrolment. These physician champions are educated on FISSH enrolment criteria, randomization processes, and location of the fluid carts. If a potential study patient is referred either via the emergency department or ward, it is often the physician that is aware first. Our physician champions can either enrol directly into the trial without research co-ordinator support or alert the research co-ordinator in a timely manner in order to facilitate early randomization. The Methods Center, usually the NPA (Dr. Rochwerg), regularly reaches out to the physician champions at each site to assess barriers and facilitators to early randomization. On weekends or after-hours, ICU clinical staff will, when available, perform screening, again greatly facilitated by the local physician champions. For both the 2-centre pilot study [21] and the provincial trial, centres have been successful in operationalizing after-hours remote (off-site) screening and enrolment. In total, 32% of patients from the pilot were enrolled outside traditional working hours. This process was facilitated through close collaboration with the on-call ICU physician, the research co-ordinator and the research pharmacy. We will apply this model and lessons learned from the pilot and provincial trials to this larger FISSH RCT. The research co-ordinator will maintain a screening log at each study centre documenting all patients reviewed and reasons for exclusion.

Research co-ordinators will log into the centralized data centre (www.randomize.net) where computerized prompts will request preliminary identifying data. If eligibility criteria are confirmed,

the patient will be randomly allocated in a 1:1 schedule to either the NS or RL using undisclosed and variable block sizes. Randomization will be stratified by study centre. To expedite study fluid delivery to the bedside, and learning from the pilot study, we will provide the unblinded hospital research pharmacies with a randomization table prepared by the randomization service. The prepared fluid will be placed on a cart that is positioned close to the clinical setting so that it is available when the next eligible patient is identified. Fluids are not prepared specifically for study purposes but rather commercial fluids that are already stocked in hospital and 'masked' for study purposes. The foregoing steps were successfully operationalized early in the pilot and in the provincial trial and helped to avoid up-front contamination with open label fluids.

Eligibility Criteria.

Inclusion: We will include patients ≥16 years of age who meet all of the following: 1) require fluid resuscitation for refractory hypotension (systolic blood pressure <90 mmHg or mean arterial blood pressure <65 mmHg after 1 Litre bolus of any fluid over 1 hour or less) or organ hypoperfusion (serum lactate >4 mmol/L), 2) clinical suspicion of infection; 3) within 6 hours of emergency triage or critical care response team or ICU consultation, and 4) are anticipated to require ICU admission.
Exclusion: Patients will be excluded if they have 1) new intracranial bleed or intracranial hypertension at the time of screening; 2) >10% of body surface area acute burn injury; 3) co-existing hemorrhagic shock; 4) an imminent plan to transition to palliation; 5) previously been enrolled in FISSH or a confounding trial (e.g. a trial examining the effect of other intravenous fluids in septic shock patients); 6) transferred from another hospital or facility >6 hours since presentation to the first hospital; 7) chronic or acute dialysis already in place (whether intermittent or continuous); or 8) admission to ICU directly from the operating room or post anaesthetic care unit.

Justification for Inclusion/Exclusion Criteria: Distributive shock, as seen in sepsis, differs fundamentally from other shock syndromes (e.g. cardiogenic, hypovolemic) as the vascular endothelium becomes porous in response to inflammatory cytokines, resulting in shift of fluid from the intravascular to the interstitial space. This unique and clinically challenging pathophysiologic mechanism necessitates a specific treatment plan that differs from other shock etiologies. Consistent with this hypothesis, exploratory subgroup analysis from the SMART RCT suggested that benefit of balanced crystalloids may have been restricted to patients with sepsis[19]. The volume of study fluid administration in many of the previous fluid studies, including SMART and those included in our NMA, was approximately 1-2 Litres; this low fluid dose will also limit the power of ongoing fluid trials (NCT02721654, NCT0287587, NCT02721485). To overcome this limitation, and ensure that study patients receive an adequate volume of study fluid to demonstrate a difference in outcomes, we will only enrol patients with shock or evidence of organ hypoperfusion. This approach was successfully employed in our pilot, in which patients received an average of 6.6L of study fluid. Finally, we picked a strict 6-hour time window from time of presentation to study enrolment to avoid upfront fluid contamination. This has been a significant limitation of previous trials where patients receive large volumes (3-4L) of open-label fluid prior to randomization versus only approximately 2L in our FISSH pilot. Despite a strict time window, we have been able to meet our monthly recruitment targets.

Consent.

Given the time-sensitivity of the intervention, the fact that most patients will not be capable to consent at the time of study entry, and that both the experimental and control study fluids are currently considered the standard of care, we will employ a mixed (*a priori* and deferred) consent model. This model worked well for both the pilot and provincial study centres, ensuring timely enrolment and minimizing contamination with non-study fluids. Patients will be enrolled in the study and consent will either be obtained immediately (*a priori* if possible) or study procedures will be initiated and consent will subsequently be obtained from the patient, the substitute decision-maker (SDM), or both, ideally

within 72 hours. A precedent for using a deferred consent model in studies examining the use of emergency intravenous fluids in Canadian centres exists [22], and Clinical Trials Ontario (CTO) has approved use of this mixed consent model for the FISSH trial as have local REBs for the 10 provincial sites (see Appendix II for approval letter). In the FISSH pilot, 68% of patients were enrolled using deferred consent, while 32% were enrolled using an *a priori* consent model. Using the deferred consent model, none of the patients or SDMs refused ongoing study participation.

Outcomes.

The primary outcome is 30-day mortality. We expect that if a difference in survival is demonstrated that this will be evident within 30 days. In fluid trials that examined a 90-day endpoint, similar results were observed between the 90-day and the shorter time horizon of a 28- or 30-day endpoint [14-16], supporting our hypothesis that the predominant effect of the FISSH fluid intervention would most likely be identified early in the patient's trajectory.

Secondary outcomes include:

- Acute kidney injury – development of stage 2 or worse acute kidney injury (AKI) according to KDIGO guidelines[17] based strictly on serum creatinine criteria. Stage 2 AKI is defined as serum creatinine 2.0-2.9 times baseline. For the purposes of analysis, baseline creatinine will be an outpatient reading within 365 days of the current admission date. If multiple pre-hospitalization values are available, the value closest to the date of hospital admission will be used. If an outpatient pre-hospitalization value is not available, the lowest creatinine value obtained during the current hospitalization will be considered baseline [18].
- Hospital and ICU mortality
- Hospital and ICU length of stay
- Ventilator-free days - defined as cumulative number of days alive without receiving greater than or equal to 2 hours of mechanical ventilation, censored at 30 days; patients who die prior to 30 days will be assigned -1
- Vasopressor-free days - defined as the cumulative number of days alive without requiring greater than or equal to 2 hours of intravenous vasopressor support, censored at 30 days; patients who die prior to 30 days will be assigned -1
- Change in organ failure score - calculated using the SOFA score, defined as the net change in SOFA from day 1 until ICU discharge or death
- Biochemical abnormalities during study period (any serum blood test results showing hyperchloremia, hyperkalemia, hypernatremia, or acidosis)
- Serious adverse events related to study fluid[19] – critically ill patients are admitted to the ICU for life-sustaining therapies and medical complications are likely to occur in this population consistent with severity of illness. Due to these unique morbidity and mortality expectations, we don't collect generic adverse events but instead focus on study-related SAEs that the attending physician believes related to the study fluid with plausible time sequence and biological plausability

Data collection. All outcome data will be collected prospectively at the ICU bedside. The study CRFs were pre-tested (via the FISSH pilot work) and edited for clarity and ease-of-use prior to the original study initiation. Trained research staff at each study centre will record the data onto paper case report forms (CRFs), which they will transcribe into web-based e-CRFs (REDCap – http://www.project-redcap.org) that are encrypted and password-protected. The online database fully complies with FDA and Health Canada rules for electronic data management. Baseline data will include eligibility criteria,

baseline demographic data, admitting diagnosis, SOFA score and APACHE II admission prognosis score (see Appendix IV for CRF sample). While patients remain in the ICU, daily data collection will include measures of organ dysfunction, ventilator requirements, hemodynamics, all fluid administered (including study, non-study and blood products), use of renal replacement therapy, and other daily relevant blood test values. Co-interventions will also be captured including but not limited to use of bicarbonate, vasopressors/inotropes, corticosteroids, vitamin C, and diuretics. Vital status will be documented during the 30-day follow-up period (discharge, readmission, death). The web-based CRF allows for real-time consistency checks and frequent audits of entered data to ensure they are complete and accurate. The paper CRFs will be stored as backup, when needed. The centralized data centre will be responsible for managing the database and quality assurance using anomaly searches and logic checks. Immediate data entry will ensure missing data are identified quickly and issues are resolved in a timely manner. Centre staff will initiate inquiries to study centres that are slow to enter data or enter inconsistent data with helpful remediation recommendations offered. Study documents and CRFs will be kept for the duration required by local regulatory bodies. The screening log (maintained by the local research co-ordinator) will be transcribed to the e-CRF on a daily basis to ensure consistency with the information at the centralized data centre. We will use random source data verification to monitor data integrity and ensure data fidelity. We will plan site monitoring visits as necessary and for any site-specific issues.

Sample Size.

The baseline risk of mortality in septic shock based on the existing literature is approximately 35-40% [3]. Our FISSH pilot trial results were consistent with these estimates, with a 30-day mortality rate of 35%. To detect an 8% absolute risk reduction of mortality with the use of RL, as compared with NS, from a baseline rate of 35%, we determined that 548 patients per group (total 1096 patients) would provide a power of 80% with alpha=0.05 and 2-sided testing. This 8% absolute risk reduction in mortality was determined based on other interventional RCTs in patients with septic shock including those examining different intravenous fluids[25 26 34] (range in targeted absolute risk reduction in mortality of 5-10%), the administration of corticosteroids[35] (targeted absolute risk reduction in mortality of 10%), and different blood pressure management strategies[36] (targeted absolute risk reduction in mortality of 10%).

We have increased the sample size by 2% (to achieve a total target sample size of 1118) to account for randomization errors, informed consent withdrawals, and lost to followup.

Trial	Targeted ARR for Mortality
VISEP – Fluid trial [25]	10%
ALBIOS – Fluid trial [26]	7.5%
CRISTAL – Fluid trial [28]	5%
APROCCHS – Steroids in septic shock [35]	10%
SEPSISPAM – Blood pressure targets in septic shock [36]	10%

Data Analysis.

A biostatistician blinded to study group identification will conduct all analyses based on intention-to-treat principle. The baseline characteristics comparing balanced fluid and unbalanced fluid groups will be reported using means (and standard deviations), medians (and inter-quartile ranges) or proportions as indicated. Dichotomous outcomes, such as the primary outcome of mortality, compared between randomized groups will be reported using risk ratio and 95% confidence intervals and calculated using the Mantel-Haenszel approach to account for stratification variables. For non-normally distributed data

such as ICU and hospital length of stay, we will try to log-transform the data and retain a parametric approach or, if this is not possible, use the non-parametric Wilcoxon rank sum test. These continuous variables will be censored at 30 days. An independent t-test will be used to compare the means of the electrolyte values (serum K, Na, pH) between the 2 groups and mean difference with 95% confidence intervals and p-values will be reported. A two-sided $p<0.05$ will be considered statistically significant for all outcomes. Since all data are collected in hospital, we anticipate very little missing data. For dichotomous and continuous outcomes with data missing for more than 5% of patients (eg. SOFA score), we will perform multiple imputation using chained equations and will combine using Rubin's rule [25].

In collaboration with the Data Safety and Monitoring Board (DSMB), we developed a DSMB Charter that included a conservative stopping criteria (e.g. O'Brien-Fleming multiple testing procedure [26]) to avoid inappropriately stopping the trial early[27]. As both the trial intervention and comparator are considered standard of care interventions conferring low risk of harm, we performed a single interim analysis for safety when outcome data were available for 50% of patients. The FISSH Trial team and trial investigators were blinded to the interim analysis results which were only reviewed only by the DSMB.

Five planned subgroups include: patients < 65 years of age versus patients ≥ 65years of age (hypothesizing that older patients will benefit more from low chloride fluid) [28]; patients with a baseline Sequential Organ Failure Assessment (SOFA) score <10 versus ≥ 10 (hypothesizing that those that are sicker will benefit more from low chloride fluid); patients who receive < 2 Litres of fluid pre-randomization versus those that receive ≥ 2 Litres (hypothesizing that those that receive more fluid pre-randomization will show less benefit with low chloride fluids); patients with KDIGO stage 2 AKI or higher at baseline pre-randomization versus those without AKI at baseline (hypothesizing that those with AKI will show more benefit with low chloride fluids); and male versus female patients (no explicit hypothesis). We will perform these subgroup analyses only for the primary outcome. Each analysis will test for an interaction between treatment and subgroup to ascertain whether effects differ significantly. For those that have a statistically significant interaction, we will examine subgroup credibility using the ICEMAN tool[29].

Knowledge Translation and Exchange. We will publish study findings in a high-impact journal and present them at national (Canada Critical Care Forum) and international (Society of Critical Care Medicine Congress [SCCM]) conferences. Drs. Rochwerg, Lamontagne and Alhazzani are heavily involved as methodologists supporting societal clinical practice guidelines, including the Surviving Sepsis Campaign[6] and BMJ Rapid Recommendations[40], and will ensure the results of the FISSH trial are appropriately incorporated into future guidelines and healthcare policy. We will use avenues such as Twitter (www.twitter.com), online medical education blogs and the CCCTG network of dissemination (www.ccctg.ca) to increase awareness of trial results.

Trial Management.

CLARITY at McMaster University (Clinical advances through research and information translation) will act as the coordinating Methods Centre (http://www.clarityresearch.ca/). Dr. Rochwerg is one of the CLARITY faculty members. CLARITY, under Dr. Rochwerg's direction, will be responsible for data management, data queries, data analysis, and for providing progress and data reports to the Steering Committee. Dr. Rochwerg, Peggy Austin (trial co-ordinator), and Lisa Buckingham (trial data manager) will oversee day-to-day management for the study and report back regularly (at least monthly) to the Steering Committee.

Steering Committee

Dr. Bram Rochwerg is the principal investigator. Dr. Rochwerg has published over 225 peer-reviewed manuscripts. He has co-authored 7 textbook chapters. He has acquired over $1.8 million in grant support as principal investigator and over $25 million dollars as a collaborator. Dr. Rochwerg holds leadership positions as the Grants and Manuscript chair for the CCCTG and the Director of Knowledge Translation for the Canadian Critical Care Society. He routinely supervises Health Research Methodology (HRM) Master's students, and clinical residents and fellows in their research projects. Dr. Rochwerg will lead the Steering Committee that includes senior and experienced ICU trialists, a trial manager (Peggy Austin), an experienced biostatistician (Diane Heels-Ansdell), a data manager (Lisa Buckingham), and other local and international experts in ICU research methodology and fluid resuscitation. Current members of the Steering Committee include Drs. Deborah Cook, Maureen Meade, Gordon Guyatt, Michelle Zeller, Sangeeta Mehta, Frederick D'Aragon, and Francois Lamontagne. Drs. Cook, Meade and Mehta are internationally recognized ICU trialists who have led a number of large multinational CIHR funded studies [41-44]. Dr. Cook has also provided mentorship for 2 other trials of fluid resuscitation [22 45]. Dr. Gordon Guyatt is an internationally acclaimed methodologist with extensive RCT expertise. Dr. Francois Lamontagne is a mid-career clinician-investigator with experience running RCTs in the area of resuscitative medicine [46].

Quarterly meetings of the Steering Committee will occur either in person or via teleconference. In addition to Steering Committee meetings, Dr. Rochwerg meets with Drs. Cook, Meade and Guyatt at least monthly for research-related discussion. This ensures ongoing opportunities for training and mentorship in order to maintain Dr. Rochwerg's continued development and success as a Clinician-Scientist. The Steering Committee will be responsible for monitoring study recruitment and targets, monitoring issues with data collection and missing data, and making decisions on new centre recruitment. Dr. Rochwerg meets with the trial manager weekly, and will be responsible for overall start-up and study management. Site principal investigators (PIs) have been identified at each centre and they will be responsible for all local procedures in conjunction with Dr. Rochwerg. This includes local REB approval, hospital approval, enlisting pharmacy cooperation and ensuring all parties are not only properly trained, but have suitable ongoing research oversight. The Steering Committee and central Methods Center staff will closely support local PIs. At the time of centre initiation all relevant paperwork and standard operating procedures (SOPs) will be supplied to the local PI. Dr. Rochwerg and the trial manager will provide on-site training sessions for the local PIs and research co-ordinators on the study protocol and data collection procedures. Research meetings with all research staff from all centres will take place at least twice a year with relevant study updates, recruitment numbers and motivational messages. Dr. Rochwerg, or a Steering Committee member, will be available 24 hours a day, 7 days a week if problems or questions arise. The FISSH Trial has been registered on clinicaltrials.gov (NCT03677102).

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