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Harmonizing international trials of early goal-directed resuscitation for severe sepsis and septic shock: methodology of ProCESS, ARISE, and ProMISe

The ProCESS/ARISE/ProMISe Methodology Writing Committee

Abstract

Purpose—To describe and compare the design of three independent but collaborating multicenter trials of early goal-directed resuscitation for severe sepsis and septic shock.

Methods—We reviewed the three current trials, one each in the USA (ProCESS: protocolized care for early septic shock), Australasia (ARISE: Australasian resuscitation in sepsis evaluation), and the UK (ProMISe: protocolised management in sepsis). We used the 2010 CONSORT (consolidated standards of reporting trials) statement and the 2008 CONSORT extension for trials assessing non-pharmacologic treatments to describe and compare the underlying rationale, commonalities, and differences.

Results—All three trials conform to CONSORT guidelines, address the same fundamental questions, and share key design elements. Each trial is a patient-level, equal-randomized, parallel-group superiority trial that seeks to enroll emergency department patients with inclusion criteria that are consistent with the original early goal-directed therapy (EGDT) trial (suspected or confirmed infection, two or more systemic inflammatory response syndrome criteria, and refractory hypotension or elevated lactate), is powered to detect a 6–8 % absolute mortality reduction (hospital or 90-day), and uses trained teams to deliver EGDT. Design differences appear to primarily be driven by between-country variation in health care context. The main difference between the trials is the inclusion of a third, alternative resuscitation strategy arm in ProCESS.

Conclusions—Harmonization of study design and methods between severe sepsis trials is feasible and may facilitate pooling of data on completion of the trials.

Keywords

Septic shock; Clinical trial; Severe sepsis; Early goal-directed therapy; Study design; Methodology

Introduction

Severe sepsis is a common and deadly syndrome characterized by acute organ dysfunction secondary to infection [1]. Septic shock is severe sepsis with hypotension and/or

c/o David T. Huang, Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA huangdt@upmc.edu

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hypoperfusion [2]. In 2001, Rivers et al. [3] reported that a specific, protocolized resuscitation approach termed early goal-directed therapy (EGDT) reduced hospital mortality in patients presenting to the emergency department (ED) with severe sepsis and septic shock from 46.5 to 30.5 %. Despite incorporation into the Surviving Sepsis Campaign guidelines [4] and non-randomized, historical control studies indicating benefit [5, 6], adoption of EGDT is not widespread [7-9]. Reasons for limited implementation include concerns over the generalizability of the Rivers' trial findings [10,11], resuscitation protocol complexity, high control arm mortality, potential risks associated with elements of the protocol [12], and financial and infrastructure implications [13].

To address these concerns, three independent, government-funded, multicenter, randomized trials of EGDT are underway in the USA (ProCESS: protocolized care for early septic shock; first enrollment March 2008), Australasia (ARISE: Australasian resuscitation in sepsis evaluation; first enrollment October 2008), and the UK (ProMISe: protocolised management in sepsis; first enrollment February 2011). Perceived between-region variation in health care practice necessitated three separate trials, each designed to inform locally. Leaders of each trial decided, prior to enrollment, to collaborate and to harmonize key design elements and operational logistics to facilitate data pooling on completion of all three trials.

We describe, compare, and explain the three trial designs using the consolidated standards of reporting trials (CONSORT) framework [14]. Our goal is to highlight the issues in performing such efforts in different countries and to provide background for interpreting the eventual trial outcomes.

Materials and methods

We extracted methodological detail from the study protocols and supporting documents for each trial, following the methods sections of the 2010 CONSORT statement and the 2008 CONSORT extension for trials assessing non-pharmacologic treatments [15, 16]. We sought, first, to summarize the commonalities between the trials and second, to note differences, and the rationale for these. The coordinating centers for each trial were collectively responsible for describing both the commonalities and the unique features of their trial.

Results

A summary of trial methods is provided in Tables 1, 2, 3,4, 5, 6. The following CONSORT sections provide additional detail, explanation, and context.

Trial design

Each trial is a patient-level, equal-randomized, parallel-group superiority trial. ProCESS is a three-arm trial; ARISE and ProMISe are two-arm trials.

Participants (subjects)

Inclusion criteria—Each trial (Table 1) seeks to enroll adult ED patients with a primary diagnosis of suspected or confirmed infection, two or more systemic inflammatory response syndrome (SIRS) criteria, and either refractory hypotension (hypotension unresponsive to fluid challenge) or hyperlactatemia (blood lactate ≥4 mmol/L), following the criteria used by Rivers et al. [3].

Refractory hypotension—There is no consensus on the minimum amount and rapidity of fluid needed to identify "refractory hypotension" [17]. Prior severe sepsis trials used various criteria—a set amount, no specific amount (e.g., "adequate"), or a body mass-based amount. Rivers et al. described using a fluid challenge of 20–30 ml/kg over 30 min. However, observational data from Australia and New Zealand suggest this is not routine practice, with a median initial bolus of 1 L [18]. Further, clinicians tend to order fluid in set increments based on available unit sizes rather than by body mass. Even if targeting the latter, the bedside estimation of body mass is imprecise [19]. For each trial we chose to use a fixed 1 L initial fluid bolus (including during transport to the ED) to identify eligible subjects using the refractory hypotension criterion, within 30 min (ProCESS) or 60 min (ARISE, ProMISe). ProCESS initially used a 20-ml/kg bolus before amending the protocol in April 2010 to simplify screening and to be consistent with ARISE and ProMISe.

Lactate—Each trial enrolls subjects with a blood lactate ≥4 mmol/L, the threshold used in the Rivers et al. trial. Mortality increases as lactate rises above 2 mmol/L [20, 21]. By restricting to ≥4 mmol/L, each trial seeks to enroll a more severely ill cohort and remain consistent with the original trial. Although arterial lactate is the traditional measure, elevated venous lactate is also associated with mortality and is comparable with arterial measurement [6, 22, 23]. Consequently, for pragmatic reasons, all three trials allow arterial or venous lactate enrollment at the same threshold value. We do not specify the lactate measurement technique, also allowing capillary and point-of-care lactates when those are used to guide routine clinical care at a center.

Time window—Enrollment into each trial must occur within 2 h of meeting the inclusion criteria. This balances the need to study early severe sepsis care versus the time requirements for informed consent and randomization. Subjects must also meet all inclusion criteria within the ED, in either 12 h (ProCESS) or 6 h (ARISE, ProMISe) from ED presentation. This approach allows enrollment of patients that meet inclusion criteria at ED presentation, as well as those who deteriorate in the ED. Pre-trial data on Australasian practice indicated a median time of 1.6 h from ED presentation to meeting ARISE inclusion criteria [18].

Antimicrobial therapy—Each study leaves the choice of antimicrobials to treating physician discretion. ProCESS encourages centers to administer antimicrobial therapy as soon as possible. ARISE and ProMISe mandate that antimicrobial therapy commence before randomization to prevent the possibility that EGDT subjects may receive more rapid antimicrobial administration than those in the usual care arm, and to help ensure that only septic patients are enrolled.

Exclusion criteria—Each trial excludes patients when either severe sepsis is not the primary diagnosis or resuscitation protocol delivery is not possible (e.g., contraindication to central venous catheterization). Each uses the exclusion criterion "treating physician deems aggressive care unsuitable" to capture the intent of the imminent mortality exclusion criterion of many acute care trials (e.g., "patient not expected to survive 28 days" [24]), without requiring time-specific prognostication. Each also excludes hemodynamic instability secondary to active bleeding (e.g., from trauma or gastrointestinal hemorrhage) due to the requirement for blood independent of the EGDT protocol.

Consent—Each trial first seeks subject consent or, if the subject is incapacitated, surrogate consent from a legally authorized representative. Research consent regulations differ between countries and the three trials approach consent differently. ProCESS explored a waiver of consent but did not adopt this mechanism owing to a lack of clear consensus at

centers and among investigators that this mechanism would facilitate recruitment, and because of the increased logistical challenges it would create [25].

ARISE and ProMISe allow delayed consent when a surrogate cannot be contacted, as per the 2007 Australian National Health and Medical Research Council national statement on the ethical conduct of research in humans and section 32(9) and the 2005 UK mental capacity act. In all three trials, consent may be withdrawn at any time by the subject or their legally authorized representative.

Participants (centers and intervention performers)

Centers—Each trial is multicenter and geographically widespread (Table 2, electronic supplement). Center selection was based on a minimum expected ED severe sepsis volume, absence of routine protocolized ED sepsis care, ability to implement study protocols and resuscitation protocols, collaboration between ED and ICU personnel, and prior collaboration with the coordinating centers and/or clinical trials groups of each trial. ProCESS centers are predominantly urban tertiary care academic centers with established departments or divisions of emergency medicine and critical care medicine. ARISE and ProMISe include a mixture of academic and regional centers. These differences are primarily due to differences in enrollment capabilities of centers in each country. In the USA, centers able to execute complex research protocols are generally large academic centers. In Australasia and the UK, past multicenter trials conducted by the coordinating centers have established relationships with regional hospitals that allow study protocol execution. ProCESS, unlike ARISE and ProMISe, also requires centers to collect, process, and ship multiple body fluid samples at serial time points, including during the 6-h resuscitation period. Academic centers' familiarity with research may enhance study protocol execution, whereas enrollment in a broader set of hospitals may increase study generalizability.

Intervention performers—Each trial mandates that a trial protocol-trained center investigator, or authorized and trained designees, oversee care by the clinical team (Table 2). ProCESS uses a specific team dedicated to resuscitation protocol execution for both intervention arms, modeling the "team approach" used in trauma care, where training and availability are constant, although composition can vary. Thus, the exact implementation and staffing of intervention delivery varies between, and within, the trials, depending on resources at each center, and reflecting how the resuscitation algorithms would be introduced in routine practice. Centers can use an ED-based, ICU-based, or hybrid implementation model, for both providers and clinical areas. The trials deem that the team delivering the intervention, and not the clinical area, is paramount to successful intervention execution delivery. For example, if EGDT commences in the ED and an ICU bed becomes available, the subject may be moved to ICU and the intervention completed there. ARISE requires each center formulate a center-specific plan to deliver EGDT, with minimum requirements of 1:1 nursing care for 6 h, supervision by medical staff trained to deliver EGDT, and delivery of EGDT in a monitored environment, generally the ED or ICU. The ARISE coordinating center reviews and approves each plan prior to patient enrollment by the center.

All center investigators are emergency and/or critical care physicians familiar with the interventions, central line placement, and sepsis care. Generally, study physicians are from the same ED or ICU group as those physicians caring for usual care arm subjects. Graduate medical trainees (e.g., residents, junior medical officers) may participate under the supervision of a study physician. Bedside nurses and/or study coordinators carry out study physician orders for fluids, transfusion, and other intervention components. As detailed

below under “Standardization”, each trial standardized training and provided sites around-the-clock access to their respective coordinating center for intervention and other trial-related questions.

ProCESS requires each study physician to pass a certification exam designed to test knowledge of the study interventions. ProCESS mandates that the study coordinator be present, provides the intervention flowcharts with timed instructions and supporting resources (e.g., study checklist, central line cart), and facilitates adherence. ARISE and ProMISe study coordinators are similarly available for EGDT delivery to centers in person and, as necessary, via telephone, to provide guidance and assistance.

Interventions

Study arms—Each trial focuses solely on resuscitation. The experimental arms of each trial use a dedicated team and a specific protocol, analogous to the original trial. Ancillary treatments are entirely at the treating physician’s discretion. Each trial leaves the choice of resuscitation fluid, vasoactive agent, and antimicrobials to the site investigators and clinicians, and tracks timing, type, and dose.

Usual care—All care is provided by routine clinical providers. To help minimize drift and other potential biases from exposure of routine clinical providers to the intervention, the ProCESS resuscitation team used to guide care in the intervention arms has no role in the provision of usual care. Study personnel collect data and have no clinical role (Table 3). Usual care varies considerably between countries and provider specialties [26]. Each trial uses an unstructured “wild type” usual care arm [27]. Each trial chose leading academic centers and regional centers committed to following ‘best evidence’ regarding current sepsis care, thereby maximizing the likelihood that the usual care arm represents best current practice.

EGDT—The 6-h EGDT team-delivered protocol consists of placement of a continuous $ScvO_2$ (central venous oxygen saturation) measurement capable, central line and administration of fluid, vasoactive agents, and packed red blood cell (PRBC) transfusion to goals of central venous pressure, mean arterial pressure, and $ScvO_2$ [3]. Only ARISE mandates arterial lines.

Protocolized standard care—ProCESS also includes a third arm—protocolized standard care (PSC). PSC is designed as a simpler alternative to EGDT that could also serve as a structured control arm. Given the higher sample size requirement, a three-armed trial was not chosen by ARISE investigators. ProMISe investigators determined that a protocolized third arm, like PSC, was too similar to usual care in the UK.

Like EGDT, PSC calls for 6 h of team-based, protocolized resuscitation. However, PSC does not mandate central lines, inotropes, or blood. ProCESS investigators designed PSC on the basis of literature review, two independent surveys of emergency physician and intensivist practice worldwide [26, 28], and consensus feedback from center investigators. The PSC components consist of ensuring adequate peripheral venous access (central line placement only if peripheral access is insufficient), and administration of fluid and vasoactive agents to goals of shock index (heart rate/systolic blood pressure), systolic blood pressure, and hourly clinical assessment of fluid status and hypoperfusion (electronic supplement). The PSC protocol requests default fluid administration unless the investigator assesses the subject as fluid replete or overloaded. Compared to EGDT, clinical assessment of fluid status replaces central venous pressure, systolic replaces mean arterial pressure, and assessment of hypoperfusion replaces $ScvO_2$. The PSC protocol encourages but does not

mandate PRBC transfusion for a hemoglobin of 7.5 g/dl [29], and measuring lactate and hemoglobin once during the 6-h resuscitation period to assess lactate clearance [30] and hemodilution from fluid resuscitation [31].

Standardization—To standardize resuscitation protocol intervention delivery, each trial provides standardized training and materials plus continuous coordinating center support to centers. Each trial conducted group investigator training meetings and individual sessions at study launch, and for subsequently added centers. Each trial uses a "train the trainer" approach where coordinating center investigators train each center's principal investigators and coordinators in the rationale and steps of the interventions, who then train their co-investigators and other personnel. Training materials are available on the websites for each trial. Regular site visits, newsletters, around-the-clock access to coordinating centers, center monitoring, adherence reports, and feedback provide additional opportunities for standardization.

Adherence—Adherence to the resuscitation protocol interventions is promoted by regular and frequent monitoring of intervention delivery conduct and center feedback. Each trial regularly examines resuscitation protocol goal achievement, treatments provided, and reasons for non-adherence. Each trial provides feedback to center principal investigators and identifies solutions for rectifying non-adherence.

Thirteen patients assigned to the EGDT arm in the original Rivers et al. trial did not complete the study protocol owing to need for immediate surgery or interventional procedures, discontinuation of aggressive treatment, or refusal to continue participation. We anticipate a similar rate of such events and collect data on protocol completion.

Objectives

Each trial has a primary objective to compare the effect of alternative resuscitation strategies on mortality (Table 4). As ProCESS has three arms and two primary hypotheses, it is designed using sequential hypothesis testing. First, the trial will test if protocolized resuscitation (EGDT and PSC combined) is superior to usual care. If the corresponding null hypothesis is rejected, ProCESS will then determine if EGDT is superior to PSC. ARISE and ProMISe will determine whether EGDT is superior to usual care resuscitation.

Outcomes

Primary—In ProCESS, the primary outcome is hospital mortality, truncated at 60 days to minimize data lags and collection and to parallel the approach adopted by the National Heart, Lung and Blood Institute Acute Respiratory Distress Network (Table 4) [32]. ProCESS will also conduct post-hospital mortality follow-up via National Death Index query, phone calls, and in-person visits. For ARISE and ProMISe, the primary outcome is 90-day mortality, which takes into account mortality attributable to sepsis months after the acute septic event [33, 34]. Each trial will also report the other trial primary outcomes as a secondary outcome.

Secondary

Each trial assesses clinically relevant secondary outcomes including mortality at other time points (e.g., 28 days, ICU), non-mortal and intermediate outcomes such as length of stay and organ dysfunction, and economic outcomes. ProCESS will also examine the biologic effects (inflammation, coagulation, oxidative stress, and tissue hypoxia) of the three resuscitation strategies in a subset of enrolled subjects.

Data quality methods—Each trial has data quality monitoring with safeguards including Web-based data collection, automated queries, and center monitoring visits. Each trial provides structured data collection training to centers prior to study initiation. For the intervention arms, each trial mandates (ProCESS, ARISE) or strongly encourages (ProMISe) contemporaneous data collection during the initial 6-h period. The key data variables across trials are harmonized and defined the same, and the trials have shared data collection instruments, data dictionaries, and variable definitions to achieve common operationalization of data methods.

For the usual care arm, data collection differs between trials. ProCESS provides bedside study coordinators during the first 6 h in all three arms. This model allows more complete data and biologic sample collection but could theoretically influence usual care. ProCESS coordinators are instructed to gather data and samples, and then leave the clinical area to avoid influence. ARISE and ProMISe investigators do not provide bedside coordinators in their usual care arm, with data collection carried out post-resuscitation. Data collection completeness for the first 6 h is facilitated by recording data in both trial arms only on the whole hour after randomization. For example, if randomization (time 0) is 10:45, time 1 becomes 12:00, time 2 becomes 1:00, and so on.

Sample size

Determination—The three investigator teams made different decisions about sample size owing to differences in their choice of primary end-point, number of study arms, pre-trial information on usual care event rates, and design assumptions. Nonetheless, all three trials are more conservatively powered than the original study by Rivers et al. (Table 5). All three trials estimated a recruitment rate of 0.25–0.5 patients per site per week.

The ProCESS investigators designed the trial to detect an absolute risk reduction (ARR) of approximately 6–7 % and desired a relative risk reduction (RRR) of 20 % for 60-day hospital mortality for both hypotheses. However, pre-trial usual care mortality estimates ranged from 28.3 % in a ProCESS pilot project to 46.5 % reported by Rivers et al., and there were no estimates for the PSC event rate. Because the uncertainty made sample size calculation for a 20 % RRR impractical (from approximately 1,350 to 5,000 patients across a control event rate of 30–46.5 %), the investigators empirically selected 1,950 subjects (650 per arm), which provided adequate power with adjustment for two interim analyses to find a relatively constant ARR of approximately 6–7 % across a usual care event rate of 30–46.5 %, although with a broader range of RRR (approximately 15–23 %). Prior to the second interim analysis, the blinded overall event rate monitoring was approximately 20 %, lower than initial assumptions although consistent with recent studies, including the multicenter US study of alternative EGDT strategies by Jones et al. [35]. Therefore, with DSMB approval, the investigators performed new blinded sample size simulations. These simulations showed the event rate was too low to find a 20 % RRR without doubling sample size, which was not practical. The 1,950 target sample size was also larger than necessary to find the original ARR. Consequently, the National Institutes of Health (NIH) approved a new sample size of 1,350 subjects (450 per arm) without the second interim analysis, which provides 80 % power to find an ARR of 6.5 % and RRR of 27 % assuming a usual care event rate of 24 % [36].

Both ARISE and ProMISe were designed later than ProCESS, had access to robust national estimates of usual care event rates, and chose 90-day all-cause mortality, regardless of location, as the primary end-point. Neither group is monitoring overall event rate, although the ProMISe DSMB does have the authority to recommend modifications to the sample size. ARISE assumed a usual care hospital mortality of 28 % on the basis of data from the ARISE observational survey [18] and the ANZICS adult patient database for ICU patients

presenting to the ED with severe sepsis or septic shock [37]. A 10 % increase from hospital mortality to 90 days was then assumed with a final 90-day mortality of 38 % [24, 38]. On the basis of these figures, a trial of 1,600 evaluable participants has between 85 and 90 % power with an $\alpha = 0.05$ to exclude a 7.6 % ARR (20 % RRR), allowing for the plausible ranges of loss to follow-up. ProMISe estimated a usual care 90-day mortality of 40 % on the basis of data from the ICNARC case mix programme database for severely septic ICU patients and long-term follow-up studies of severe sepsis patients [39]. With a sample size of 1,260 subjects ProMISe has 80 % power to detect an 8.0 % ARR and 20 % RRR in 90-day mortality, allowing for up to 6 % withdrawal and lost to follow-up.

Interim analyses and stopping rules—Each study submits data to their oversight committees for interim analyses on a predefined schedule and with a priori stopping rules. Before trial completion, only the oversight committees and designated study statisticians see outcome data per arm; the oversight bodies may recommend stopping enrollment for efficacy, harm, or futility. The committees are independent and multidisciplinary, operating without investigator influence. Preestablished statistical plans and oversight committee charters mitigate concerns of spurious early cessation [40]. ProCESS completed an interim analysis after 650 subjects; ARISE conducted an interim analysis at 50 % enrollment; and ProMISe conducted an interim analysis after 500 patients. In all three cases, the oversight committees recommended continuation of the trials without modification.

Randomization

Each trial randomizes at the patient level (Table 6). Randomization at the center level risks enrolling subjects dissimilar at baseline, rendering results difficult to interpret [41]. Each trial stratifies randomization by center, mitigating potential clustering effects. To limit contamination in the usual care arm, each trial provides $ScvO_2$ catheters and monitors only for subjects enrolled to EGDT. Outside the protocolized arms, each trial does not allow access to study materials and discourages $ScvO_2$ central line placement or $ScvO_2$ measurement. ProCESS also prohibits center principal investigators to enroll their own patients when they are staffing the ED. Each trial tracks care across all arms to identify potential contamination.

Sequence generation—Each trial uses patient-level, computer-generated, permuted block randomization with variable block size, and stratification by center. ProCESS also stratifies randomization by race.

Allocation concealment—Each trial ensures concealment of the next randomization assignment by using automated centralized assignment systems. Only after enrollment do the systems assign a trial arm and inform the center investigator. Investigators enroll subjects and administer the intervention protocols but have no knowledge of the sequences or assignments. Each trial also provides continuous coordinating center access for questions and randomization backup.

Implementation—For ProCESS, center investigators enroll and randomize patients via a Web-based data collection system. For ARISE and ProMISe, central randomization occurs through an interactive voice response telephone system.

Blinding or masking

Blinding of study interventions is not possible. The potential for clinician knowledge of randomization assignment to bias treatment is real but modest. Severe sepsis subjects are at high risk of death; we anticipate care decisions will be based on clinical condition not group assignment. Risk of assessment bias is low as trial outcomes are not subjective. Decisions

such as withdrawal of life support could theoretically be postponed in a biased manner past the time of outcome assessment. However, we consider this event unlikely, given late outcome assessment. Where possible, we will examine for differences in the proportion and timing of life support withdrawal across arms. Each trial restricts access to unblinded data to designated study statisticians and to study oversight committees.

Statistical methods

For each trial, independent statisticians blinded to treatment allocation will conduct the primary intention-to-treat analysis using a pre-established and pre-published statistical plan. Each trial will use standard statistical tests to compare groups for their primary mortality outcomes and reject the null hypothesis when $p < 0.05$. We will report results in accordance with the CONSORT statements.

Discussion

Despite between country differences in health care context, the three trials conform to CONSORT guidelines, address the same fundamental questions, and share key design elements. Although each trial follows the EGDT protocol, there were many key decisions to make on how to operationalize the Rivers protocol in a multicenter environment. For example, trial leaders discussed the challenge of defining refractory hypotension, resulting in a decision to harmonize the trials by each using the same operational definition. Another key decision was to allow the 6-h EGDT protocol to be completed outside the ED; the original trial mandated that the entire protocol be conducted in the ED.

Two design differences merit note—informed consent and number of arms. Only the US trial does not use telephone or delayed consent. Obtaining informed consent can lead to selection bias and non-representativeness of enrolled subjects [42]. ProCESS may enroll a different study population than ARISE and ProMISe. ProCESS also is the only trial that uses a third arm (PSC), which increased trial complexity, but may allow greater insight into the effect of protocolization itself and the use of a dedicated team versus the specific resuscitation protocol deployed. The PSC arm also addresses NIH trial design controversies regarding control arms. A 2005 NIH conference, “considering usual medical care in clinical trial design: scientific and ethical issues,” concluded there was no universal solution to the quandary of “What is best control—wild type (individualized by both patient and provider) or structured but generally accepted care?” [43]. ProCESS decided to do both, with PSC serving both as a simplified alternative approach and a structured control arm.

Despite these differences, common standards, design elements, and data collection variables will allow the three trials to collaboratively conduct a prospective individual patient data meta-analysis, using the raw data from each trial [44, 45]. Many past trials of critically ill patients have failed to show a mortality benefit because of insufficient power [46]. Each of the three trials is powered to detect modest, but not small, risk reductions. However, with over 4,000 subjects combined, our pre-planned individual patient-level meta-analysis will provide considerable power to find far smaller effects and to better explore subgroups [44]. A priori subgroup analyses include sex, hyperlactatemia-only enrollment, type of infection, and center characteristics.

Conducting independent trials in parallel has different trade-offs versus conducting a single combined trial. National funding agencies often have restrictions on spending monies and sharing data outside the home country. Thus, separate national trials can be easier to fund than one multinational trial. With multiple national trials, however, the sharing of data monitoring becomes complex [47]. For our trials, the three DSMB chairs regularly discussed trial progress. Research review board requirements and decisions also vary between

countries. We also carefully considered the type of control arm necessary. A placebo control arm for a worldwide sepsis drug trial is standard, whereas the usual care control arm for a sepsis resuscitation trial will vary between sites and countries. Our three trials each obtained independent federal funding and have harmonized study design and methods to optimize joint analyses.

Conclusions

Prospective collaboration and harmonization of study design and methods between severe sepsis trials are feasible and may facilitate pooling of data on completion of the trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Coordinator center staff for each trial (in alphabetical order): ProCESS: T. Eaton, E. Gimbel, K. Wofford. ARISE: A. Jovanovska, G. Syres, D. Rajbhandari. ProMISe: R. Jahan, H. Muskett, S. Power, J. Tan. This study was supported by (ProCESS) National Institute of Health P50GM076659 and GM076659-S1, (ARISE) National Health and Medical Research Council Project Grant 491075, (ProMISe) National Institute for Health Research Health Technology Assessment programme HTA 07/37/47.

Appendix: members of ProCESS/ARISE/ProMISe methodology writing committee

ProCESS (after Chair, authors are listed alphabetically): David T. Huang, MD, MPH (Chair)[1,2,3], Derek C. Angus, MD, MPH[1,2], Amber Barnato, MD[1,4], MPH, Scott R. Gunn, MD[2,3], John A. Kellum, MD[1,2], Diana K. Staple-ton, RN, BS[1,2], Lisa A. Weissfeld, PhD[1,5], MS, Donald M. Yealy, MD[3].

ARISE (after first two, authors are listed alphabetically): Sandra L. Peake, BM BS, BSc (Hons) PhD, FCICM[11,17,18], Anthony Delaney MBBS MSc FCICM, FACEM[12,13], Rinaldo Bellomo MBBS, MD, FRACP, FJFICM[6,7,8,9], Peter Cameron MBBS, MD, FACEM[10,11], Alisa Higgins MPH, BPhysio (Hons)[14], Anna Holdgate, MBBS (Hons), MMed, FACEM[15,16], Belinda Howe RN, CCCert, BAppSc (Nursing)[14], Steven A. Webb MBBS, PhD, FRACP, FCICM, MPH[14,19,20], Patricia Williams RGN, BN Int. Care[17,18].

ProMISe: Tiffany M. Osborn, MD, MPH[21], Paul R. Mouncey MSc[21], David A. Harrison PhD[21], Sheila E. Harvey PhD[21], Kathryn M. Rowan, PhD[21].

1. The CRISMA (Clinical Research, Investigation, and Systems Modeling of Acute Illness) Center.

2. Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA.

3. Department of Emergency Medicine, University of Pittsburgh, Pittsburgh, PA.

4. Department of Internal Medicine, Division of General Internal Medicine, Center for Research on Health Care.

5. Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.

6. School of Medicine, University of Melbourne, Melbourne, VIC, Australia.

7. School of Medicine, Monash University, Melbourne, VIC, Australia.

8. Howard Florey Institute, Melbourne University, Melbourne, VIC, Australia.

9. Department of Intensive Care Medicine, Austin Hospital, Heidelberg, VIC, Australia.

10. Department of Emergency Medicine, Alfred Hospital, Melbourne, VIC, Australia.

11. Department of Epidemiology and Preventive Medicine, School of Public Health and Preventative Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, VIC, Australia.

12. Intensive Care Unit, Royal North Shore Hospital, Sydney, NSW, Australia.

13. Northern Clinical School, Sydney Medical School, University of Sydney, NSW, Australia.

14. Australian and New Zealand Intensive Care Research Centre, School of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia.

15. South West Clinical School, University of New South Wales, Sydney, NSW, Australia.

16. Department of Emergency Medicine, Liverpool Hospital, Sydney, NSW, Australia.

17. Department of Intensive Care Medicine, The Queen Elizabeth Hospital, School of Medicine, Adelaide, SA, Australia.

18. Discipline of Acute Care Medicine, Faculty of Health Science, University of Adelaide, SA, Australia.

19. Intensive Care Unit, Royal Perth Hospital, Perth, WA, Australia.

20. School of Medicine, Pharmacology and Public Health, University of Western Australia, Perth, WA, Australia.

21. Intensive Care National Audit and Research Centre (ICNARC), Napier House, 24 High Holborn, London, UK.

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Table 1

Participants (subjects)

CONSORT	ProCESS	ARISE	ProMISe	Reference trial [3]
Inclusion criteria	18 years of age Suspected infection ≥Two SIRS criteria Refractory hypotension (systolic blood pressure <90 mmHg despite a 1,000-ml IV fluid challenge over 30 min [including IV fluids administered pre-hospital])[a] or Blood lactate ≥4 mmol/L	18 years of age Suspected infection ≥Two SIRS criteria Refractory hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg despite a 1,000-ml IV fluid challenge over 60 min (including IV fluids administered pre-hospital]) or Blood lactate ≥4 mmol/L First dose of IV antimicrobial therapy commenced prior to randomization	18 years of age Known or presumed Infection ≥Two SIRS criteria Refractory hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg despite a 1,000-ml IV fluid challenge over 60 min (including IV fluids administered pre-hospital]) or Blood lactate ≥4 mmol/L First dose of IV antimicrobial therapy commenced prior to randomization	18 years of age ≥Two SIRS criteria Refractory hypotension (systolic blood pressure no higher than 90 mmHg after a crystalloid-fluid challenge of 20–30 ml/kg over 30 min) or Blood lactate ≥4 mmol/L
Exclusion criteria	Primary diagnosis of acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, major cardiac arrhythmia, active gastrointestinal hemorrhage, seizure, drug overdose, burn, or trauma Do-not-resuscitate status, advanced directives restricting protocol implementation Treating physician deems aggressive care unsuitable Transferred from another in-hospital setting Contradiction to blood transfusion (e.g., Jehovah's Witness) Contraindication to central venous catheterization Participation in another interventional study Requirement for immediate surgery Absolute neutrophil count <500/mm^3 Known CD4 <50/mm^3 Known pregnancy	Hemodynamic instability due to active bleeding A "limitation of therapy" order has been documented restricting implementation of the study protocol or the treating clinician deems aggressive care unsuitable An underlying disease process with a life expectancy of <90 days Death is deemed imminent and inevitable In-patient transfer from another acute health care facility Contraindication to blood products (e.g., Jehovah's Witness) Contraindication to superior vena cava central venous catheter insertion Inability to commence delivery of the EGDT protocol within 1 h of randomization or complete 6 h of EGDT Pregnancy (confirmed or suspected)	Primary diagnosis of acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, major cardiac arrhythmia (as part of primary diagnosis), seizure, drug overdose, injury from burn or trauma; hemodynamic instability due to active GI hemorrhage Do-not-resuscitate status, advanced directives restricting protocol implementation Attending physician deems aggressive care unsuitable Transferred from another in-hospital setting Contradiction to blood transfusion or central venous catheterization Requirement for immediate surgery Not able to initiate protocol delivery within 1 h of randomization or complete within 6 h Known history of AIDS Known pregnancy	Pregnancy Presence of an acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, cardiac dysrhythmias (as a primary diagnosis) Contraindication to central venous catheterization Active gastrointestinal hemorrhage Seizure Drug overdose Burn injury Trauma Requirement for immediate surgery Uncured cancer (during chemotherapy) Immunosuppression (because of organ transplantation or systemic disease) Do-not-resuscitate status, or advanced directives restricting implementation of the protocol

SIRS systemic inflammatory response syndrome, *IV* intravenous, *EGDT* early goal-directed therapy

[a] From March 2008–April 2010, the fluid challenge was ≥20 ml/kg

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Table 2

Participants (centers and intervention performers)

CONSORT	ProCESS	ARISE	ProMISe	Reference trial [3]
Centers	Approximately 26 academic medical centers in the USA	Approximately 45 academic, community, and rural hospitals in Australia, New Zealand, Hong Kong, Finland, and Ireland	Approximately 48 hospitals throughout the UK; may include university-associated tertiary care referral centers to non-academic hospitals. Locations may be metropolitan or rural	One urban, academic, tertiary care hospital in Detroit, Michigan, USA
Eligibility criteria	Absence of routine protocolized ED sepsis care ED severe sepsis volume Identified ED and ICU investigator champions Research capabilities and resources	EGDT not part of routine practice and commitment to not implementing EGDT as standard of care for duration of the trial ED severe sepsis volume Identified ED or ICU medical and/or nursing champions Research capabilities and resources Prior participation in ANZICS CTG-endorsed studies (not essential)	Local ProMISe champion from emergency medicine and critical care medicine required and acute care medicine encouraged when available Research capabilities and resources Must not already be doing early, goal-directed protocolized resuscitation (using continuous $ScvO_2$) as part of routine practice	Not applicable
Intervention performers				
Eligibility criteria	Study certification Able to administer intervention protocol, including central line placement	Center principal investigator or authorized member of center research staff who can deliver and/or oversee delivery of the intervention protocol	Center principal investigator or authorized member of center research staff who can deliver and/or oversee delivery of the intervention protocol	Patients were treated in a 9-bed unit in the ED by an emergency physician, 2 residents, and 3 nurses

ED emergency department, *ICU* intensive care unit, *CTG* clinical trials group

Table 3

Interventions

CONSORT	ProCESS	ARISE	ProMISe	Reference trial [3]
Study arms				
Usual care	All care provided by existing care providers	All care provided by existing care providers	All care provided by existing care providers	After arterial and central venous catheterization, patients in the standard-therapy group were treated at the clinicians' discretion according to a protocol for hemodynamic support (CVP, MAP, urine output goals), with critical-care consultation, and were admitted for inpatient care as soon as possible
EGDT	As per Rivers et al,, except protocol can be completed outside of ED and arterial line not required	As per Rivers et al., except protocol can be completed outside of ED	As per Rivers et al., except protocol can be completed outside of ED, arterial line recommended but not required, and physiologic goals are minimum values rather than ranges	As described in Rivers et al. [3], Entire 6-h protocol delivered in the ED
PSC	A structured, alternative approach using only common ED monitoring devices and interventions (see Appendix for full protocol)	Not applicable	Not applicable	Not applicable
Standardization	Standardized teaching material used at start-up and refresher meetings, frequently asked questions, access to trial physician 24/7 Investigator start-up meetings, individual site training sessions, study website Regular site visits and news letters Site monitoring Regular adherence reports and feedback to individual sites	Standardized teaching material used at start-up and refresher meetings, frequently asked questions, access to trial physician 24/7 Investigator start-up meetings, individual site training sessions, study website Regular site visits and news letters Site monitoring Regular adherence reports and feedback to individual sites Submission of a center-specific protocol implementation plan	Standardized teaching material used at start-up and refresher meetings, frequently asked questions, access to trial physician 24/7 Investigator start-up meetings, individual site training sessions, study website Regular site visits and newsletters Site monitoring Regular adherence reports and feedback to individual sites	Reference trial was a single-center trial. The lead investigator provided close supervision. Entire 6-h protocol delivered in the ED
Adherence	Computerized audits to ensure resuscitation protocols are being followed, combined with regular center-specific feedback and monitoring, center initiation, standardized operating procedures, 24/7 coordinating center support	Computerized audits to ensure resuscitation protocols are being followed, combined with regular center-specific feedback and monitoring, center initiation, standardized operating procedures, 24/7 coordinating center support	Computerized audits to ensure resuscitation protocols are being followed, combined with regular center-specific feedback and monitoring, center initiation, standardized operating procedures, 24/7 coordinating center support	Reference trial was a single-center trial. The lead investigator provided close supervision. Entire 6-h protocol delivered in the ED

EGDT early goal-directed therapy, *PSC* protocolized standard care, *ICU* intensive care unit, *ED* emergency department, *CVP* central venous pressure, *MAP* mean arterial pressure

Table 4

Objectives and outcomes

CONSORT	ProCESS	ARISE	ProMISe	Reference trial [3]
Objectives	To compare the clinical efficacy of alternative resuscitation strategies (EGDT vs. PSC vs. usual care) for septic shock Hypotheses: Protocolized resuscitation (EGDT + PSC) is superior to usual care EGDT is superior to PSC To better understand the mechanisms by which resuscitation strategies affect clinical outcomes To assess the costs and cost-effectiveness of alternative resuscitation strategies	To determine whether providing EGDT, compared to standard care, reduces 90-day mortality in patients presenting to the ED of hospitals in Australasia with severe sepsis Hypothesis: EGDT, compared to standard Australasian resuscitation practice, reduces 90-day all-cause mortality in patients presenting to the ED with severe sepsis	To determine the effect of early, goal-directed, protocolized resuscitation compared with usual resuscitation on mortality at 90 days and incremental cost-effectiveness at 1 year in the UK Hypothesis: Early, goal-directed, protocolized resuscitation, when compared to usual resuscitation, reduces 90-day all-cause mortality in a cost-effective manner	To examine whether EGDT before admission to the ICU effectively reduces the incidence of multiorgan dysfunction, mortality, and the use of health care resources among patients with severe sepsis or septic shock
Outcomes				
Primary	Hospital mortality (prior to discharge or at 60 day, whichever comes first)	90-day all-cause mortality	90-day all-cause mortality	Hospital mortality
Secondary	Duration of survival Clinical evidence of organ dysfunction Markers of inflammation, oxidative stress, cellular hypoxia, and coagulation/ thrombosis Resource use and costs	Death at 28 days and at ICU and hospital discharge Duration of survival from randomization Duration of ED, ICU, and hospital stay Need for, and duration of, artificial organ support Quality of life	Incremental cost per QALY gained at 1 year, mortality at 1 year Duration of survival Requirement for, and duration of organ support Duration of ED, ICU, and hospital stay Health-related quality of life at 90 days and 1 year Resource use and costs at 90 days and 1 year Lifetime incremental cost-effectiveness	Resuscitation end points, organ dysfunction scores, coagulation-related variables, administered treatments, and the consumption of health care resources
Data quality methods	Standardized data collection and recording Web-based DCF with built-in logic checks, automatic data queries, and streamlined user interface Periodic DCF checks to monitor data irregularities and protocol compliance Detailed center study coordinator DCF training and periodic conference calls Center monitoring visits and independent, random review of source documents	Standardized data collection and recording Web-based DCF with built-in logic checks, automatic data queries, and streamlined user interface Periodic DCF checks to monitor data irregularities and protocol compliance Detailed center study coordinator DCF training and periodic conference calls Center monitoring visits and independent, random review of source documents	Standardized data collection and recording Web-based DCF with built-in logic checks, automatic data queries, and streamlined user interface Periodic DCF checks to monitor data irregularities and protocol compliance Detailed center study coordinator DCF training and periodic conference calls Center monitoring visits and random review of source documents	Not reported

EGDT early goal-directed therapy, *PSC* protocolized standard care, *DCF* data collection form, *ICU* intensive care unit, *ED* emergency department, *QALY* quality-adjusted life year

Table 5

Sample size determination and interim analyses

CONSORT	ProCESS	ARISE	ProMISe	Reference trial [3]
Sample size	l,350[a]	1,600	1,260	263
Determination	6.5 % ARR and 27 % RRR of hospital mortality Assumes 24 % usual care hospital mortality HI: protocolized resuscitation (EGDT + PSC) is superior to usual care Sequential hypothesis testing—if null hypothesis of H1 rejected, will test: H2: EGDT is superior to PSC ≥80 % power, 2-sided alpha of 0.05 O'Brien-Fleming rule to adjust for multiple looks [48]	7.6 % ARR and 20 % RRR of 90-day mortality Assumes 38 % 90-day usual care mortality Hypothesis: EGDT, compared to standard practice, reduces 90-day all-cause mortality in patients presenting to the ED with severe sepsis 85–90 % power, 2-sided alpha of 0.05 Assumes 5 % withdrawal and loss to long-term follow-up rate O'Brien-Fleming rule to adjust for a single look	8 % ARR and 20 % RRR of 90-day mortality Assumes 40 % 90-day usual care mortality Hypothesis: Early protocolised resuscitation reduces 90-day all-cause mortality for severe sepsis patients initially presenting to the ED 80 % power, 2-sided alpha of 0.05 Assumes a 6 % refusal, withdraw, loss to follow up rate [49] A single look using Peto-Haybittle at p <0.001	15 % ARR in hospital mortality Assumed rate of refusal or exclusion of 10 % 80 % power, 2-sided alpha of 0.05
Interim analyses and stopping rules	Interim analysis after 650 with 2-sided p value of 0.0005[b] Twin-boundary symmetric O'Brien-Fleming design	One interim analysis at 50 % enrollment with a 2-sided p value of 0.005 Twin-boundary symmetric O'Brien-Fleming design	One interim analysis after 500 patients with a 2-sided p value of 0.001 Further interim analyses will be performed if required by the data monitoring and ethics committee Peto-Haybittle stopping rule	Two interim analyses at 1/3 and 2/3 enrollment Alpha spending function of DeMets and Lan used to determine that a $p \leq 0.04$ would be considered statistically significant

DCF data collection form, *EGDT* early goal-directed therapy, *IV* intravenous, *PSC* protocolized standard care, *ED* emergency department, *ARR* absolute risk reduction, *RRR* relative risk reduction

[a] Modified from 1,950 based on in-trial blinded overall event monitoring (see sample size determination)

[b] Original plan of 1,950 included 2 interim analyses, at 650 and 1,300, with 2-sided p values of 0.0005 and 0.014. Second interim was dropped with resizing

Table 6

Randomization, blinding or masking, and statistical methods

CONSORT	ProCESS	ARISE	ProMISe	Reference trial [3]
Randomization				
Sequence generation	Patient-level, permuted block randomization with variable block sizes Stratified by center and race Randomized equally to each study arm (EGDT, PSC, usual care in a 1:1:1 ratio)	Patient-level, permuted block randomization with variable block sizes Stratified by center Randomized equally to each study arm (EGDT, usual care in a 1:1 ratio)	Patient-level, permuted block randomization with variable block sizes Stratified by center Randomized equally to each study arm (EGDT, usual care in a 1:1 ratio)	Patient-level, computer-generated block randomization of 2–8 Randomized equally to each study arm (EGDT, usual care in a 1:1 ratio)
Allocation concealment	Central Web-based randomization, accessible 24 h/day	Central telephone randomization via an IVRS, accessible 24 h/day	Central telephone randomization via an IVRS, accessible 24 h/day	Study group assignments were placed in sealed, opaque, randomly assorted envelopes
Implementation	Local center investigators enroll patients via Web-based DCF Web-based DCF then assigns patients to trial arm, based on computer generated allocation sequence	Local center investigators enroll patients via IVRS IVRS then assigns patients to trial arm, based on computer generated allocation sequence	Local center investigators enroll patients via IVRS IVRS then assigns patients to trial arm, based on computer generated allocation sequence	Opaque envelopes opened by a hospital staff member who was not one of the study investigators
Blinding or masking	Trial arm assignment can not be blinded Unblinded data restricted to study statisticians and DSMB	Trial arm assignment can not be blinded Unblinded data restricted to study statisticians and DSMB	Trial arm assignment can not be blinded Unblinded data restricted to study statisticians and DSMB	Trial arm assignment could not be blinded in the ED; ICU clinicians were unaware of the patients' study group assignments Study investigators did not influence patient care in the ICU
Statistical methods	Intention-to-treat Primary data analysis, including subgroup analyses, to be carried out according to pre-established analysis plan	Intention-to-treat Primary data analysis, including subgroup analyses, to be carried out according to pre-established analysis plan	Intention-to-treat Primary data analysis, including subgroup analyses, to be carried out according to pre-established analysis plan	Intention-to-treat

ED emergency department, *ICU* intensive care unit, *DCF* data collection form, *DSMB* data safety monitoring board, *EGDT* early goal-directed therapy, *PSC* protocolized standard care, *SIRS* systemic inflammatory response syndrome, *IVRS* interactive voice response system