Role of Active Deresuscitation After Resuscitation-2 (RADAR-2) - a pilot randomised controlled trial of conservative fluid administration and deresuscitation in critical illness: study protocol

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Date published: 20/09/2018

Background: Intravenous fluid administration is a common intervention in critically ill patients. However, this frequently contributes to a positive fluid balance, which is consistently associated with adverse outcomes including mortality. A conservative or deresuscitative (use of diuretics or renal replacement therapies to remove accumulated fluid) approach to fluid management in critical illness may be beneficial but evidence is limited.

Methods/Design: Role of Active Deresuscitation After Resuscitation-2 (RADAR-2) is an open-label pilot randomised controlled trial of conservative fluid administration and deresuscitation compared with usual care. Mechanically ventilated patients in an adult intensive care unit expected to need critical care beyond the next calendar day and who do not meet any exclusion criteria will be randomised between 24 and 48 hours from intensive care admission. The intervention comprises discontinuation of maintenance intravenous fluids, concentration of intravenous drugs, and a titrated regimen of furosemide, indapamide and spironolactone commenced if fluid balance is greater than 2 litres positive from intensive care admission or there is clinical evidence of oedema in more than one anatomical site. The primary feasibility outcome is fluid balance between groups over the 24 hour period of study day 2. Secondary outcomes are categorised as feasibility (e.g. cumulative fluid balance, incidence of protocol violations); safety (incidence of adverse events); and clinical efficacy (e.g. change in sequential organ failure assessment scores, mortality). Exploratory mechanistic studies will evaluate cardiac function, cerebral and muscle oximetry and biomarkers of endothelial injury and systemic inflammation.

Discussion: RADAR-2 is a pilot randomised controlled trial comparing a multimodal conservative fluid strategy with usual care in a broad cohort of critically ill patients and will inform future large-scale multicentre comparative effectiveness studies.

Trial Registration: Clinicaltrials.gov NCT03512392

Keywords: Fluid therapy; Water-electrolyte balance; Furosemide; Diuretics; Critical illness; Clinical trial; Deresuscitation; Renal replacement therapy; Spironolactone; Indapamide; Fluid restriction

Funding: The study is funded by The Health & Social Care Research & Development Division of the Public Health Agency, Northern Ireland; National Institute of Academic Anaesthesia Earnest Leach Research Fund; and a British Journal of Anaesthesia/Royal College of Anaesthetists Project Grant.

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Background information

Although intravenous fluid administration is an almost universally applied therapy in critical care, much is unknown about how to maximise benefits and minimise harms. The majority of critically ill patients exhibit alterations in cardiovascular homeostasis, characterised by an exaggerated release of pro-inflammatory cytokines, endothelial injury and capillary leak [1]. Initial fluid resuscitation to improve cardiac output, and thus to optimise oxygen delivery to tissues, is standard care in the management of haemodynamically unstable critically ill patients [2]. Fluid intake is also derived from 'maintenance' fluids, drug diluents, and nutritional intake. In critical illness, excretion of fluid is often impaired as a result of endocrine and renal factors, leading to a positive sodium and water balance over time. There has been increasing recognition of the potential harms of excess extravascular fluid and therefore of the need to balance potential benefits and harms when administering intravenous fluid [3].

There is a strong and consistent association between fluid accumulation in critical illness and poor outcomes, particularly mortality, in observational cohort studies of critically ill patients. This association has now been demonstrated in both adults and children with acute respiratory distress syndrome (ARDS) [4, 5], sepsis [6, 7], acute kidney injury (AKI) [8–10] and other sub-populations [11]. The major limitation with all of these studies, however, is the potential for residual confounding, with more severely ill patients receiving more fluid.

We recently undertook a systematic review and meta-analysis of randomised trials in which a conservative approach to fluid administration or active deresuscitation was compared to either a liberal approach or standard care [11]. In the 11 randomised trials (2051 patients) included in this meta-analysis, there was a non-significant reduction in mortality with conservative or deresuscitative fluid strategies compared to liberal strategies or usual care (relative risk (RR) 0.92, 95% Confidence Interval (CI) 0.82 to 1.02). There was a significant reduction in intensive care unit (ICU) length of stay (mean difference (MD)-1.88 days, 95% CI -0.12 to -3.64) and an increase in ventilator free days (MD 1.82 days, 95% CI 0.53 to 3.10) with conservative or deresuscitative strategies compared to a liberal strategy or standard care.

The major safety considerations relate to the potential for hypovolaemia, leading to haemodynamic instability and/or worsened perfusion of kidneys and other end organs, and to the metabolic side effect profile of diuretic drugs. In studies of conservative or deresuscitative fluid strategies, haemodynamic stability was similar between intervention and control arms [12–15], and in our systematic review, we found no difference in the incidence of acute kidney injury between conservative or deresuscitative strategies and usual care. Side effects of diuretics include electrolyte abnormalities and metabolic alkalosis. In the largest trial of conservative fluid management to date, a conservative fluid management strategy which utilised loop diuretics resulted in higher rates of hypernatraemia, hypokalaemia, and metabolic alkalosis [14] than a liberal fluid strategy.

In a post-hoc secondary analysis of a small cohort of 122 survivors from the Fluids And Catheter Treatment Trial which compared conservative and liberal fluid strategies in patients with ARDS, Mikkelsen and colleagues [16] identified conservative fluid management as an independent risk factor for long-term cognitive impairment. In a randomised trial of patients with ARDS in which extravascular lung water index was used to guide a conservative fluid strategy compared with usual care, however, Wang *et al* [17] found more favourable cognitive function scores with conservative fluid. The impact of fluid strategy on cognitive outcomes, therefore, remains uncertain.

Current practice regarding fluid strategy in the post-resuscitation phase of critical illness is highly variable. In a 400-patient observational study of fluid management in 10 ICUs in the United Kingdom and Canada, we found considerable inter-site variation in fluid administration, diuretic use, and fluid balance [18]. Similarly, in a survey of over 500 intensive care clinicians in the UK and Europe, we found wide variation in reported practice regarding fluid strategy in a range of clinical scenarios. (unpublished data). The results of our systematic review, observational study, and survey of practice indicate there is uncertainty regarding the optimal fluid strategy for critically ill patients.

We hypothesise that in critically ill patients, following the initial resuscitation period, a fluid strategy comprising conservative fluid administration and active deresuscitation reduces net fluid balance, is safe and improves clinical outcomes.

Design

Study aims

The aims of the study are (1) to determine the feasibility, safety and clinical outcomes of conservative fluid administration and deresuscitation compared with usual care in critically ill patients following initial resuscitation; and (2) to explore the biological effects of conservative fluid administration and deresuscitation.

Study design

This will be a randomised, open-label, allocation concealed, pilot trial of conservative fluid administration and deresuscitation compared with usual care in adult patients who are critically ill following initial resuscitation. The study design conforms to SPIRIT guidelines for the reporting of clinical trial protocols (http://www.spirit-statement.org/), and the Spirit 2013 checklist for this protocol can be found at http://www.criticalcarehorizons.com/radar-2-protocol/.

Study setting

Participants will be recruited from adult general ICUs.

Study participants

Participants in the trial will be eligible if receiving invasive mechanical ventilation, are between 24 and 48 hours of ICU admission at the time of randomisation, and the treating intensive care doctor expects treatment in an ICU to be required beyond the next calendar day. Exclusion criteria are as follows:

- age < 16 years;
- weight < 40 kg;
- known pregnancy;
- expectation of death within 72 hours;
- refusal of consent;
- inability to measure fluid balance;
- inability of the personal consultee to understand written or verbal information where no interpreter is available (a personal consultee is someone who knows the patient in

	STUDY DAY(S)							
	0	1	2	3	4	5	6-28	180
ENROLMENT								
Eligibility assessment	X							
Informed consent	X							
Randomisation		X						
INTERVENTION								
Hold maintenance fluids (I)		X	X	X	X	X		
Minimise drug diluent volume (I)		X	X	X	X	X		
Per-protocol diuretics/ultrafiltration (I)			X	X	X	X		
ASSESSMENT								
Echocardiogram (selected sites)		X	**once at 48-96 hours after randomisation**					
NIRS (selected sites)		X	X	X				
Blood and urine sampling		X		X		X		
Adverse event reporting		X	X	X	X	X		
Data collection		X	X	X	X	X	X	X
Telephone interview								X

Table 1. Study schedule: (I) = intervention group only

a personal capacity, and is able to advise the researcher about that patient's likely wishes and feelings in relation to the project and whether they should participate in the study);

- active treatment for diabetic ketoacidosis, hyperosmolar hyperglycaemic state, non-traumatic subarachnoid haemorrhage, acute cardiac failure, cardiogenic shock, end-stage renal failure, or active diabetes insipidus.

Inclusion and exclusion criteria are designed to include a broad population of critically ill patients, while excluding those for whom a specific fluid strategy is a standard of care, or those at increased risk of adverse events.

Study procedures (Table 1)

Patients will be prospectively screened daily. All patients meeting inclusion criteria will be entered into a screening log, and reasons for non-recruitment recorded.

It is anticipated that the incapacitating nature of the condition will almost invariably preclude obtaining prospective informed consent from participants. In this situation, advice will be sought from a personal consultee as to their views on the wishes and feelings of the patient if they had capacity. Patients will be informed of their participation in the trial once they regain capacity and asked for consent to continue to participate in the trial.

Subjects will be randomised in a 1:1 ratio using blocks of variable size and randomisation will be stratified by study site. Online randomisation software (www.sealedenvelope.com) will be used.

Blinding of participants, caregivers and investigators will not be undertaken for short-term outcomes in the 28-day study period. Investigators undertaking assessment of long-term follow up of cognitive function and biomarker assays will be blinded to group assignment.

Intervention

On study day 1 (from randomisation until 07:00 the following day), maintenance intravenous fluids will be discontinued and all prescribed medications will be given in minimum volumes according to standard guidelines. The clinical team responsible for the patient will be asked to administer intravenous fluids only where there is suspected blood or other overt fluid loss, to treat electrolyte abnormalities, or where alternative therapies for cardiovascular instability are deemed to have failed or to be contraindicated.

On study days 2-4, fluid restriction will be continued as above and there will be an assessment of eligibility for deresuscitation each day.

Criteria for deresuscitation are (a) the presence of oedema in > 1 site i.e. arms, legs, flanks, abdominal wall, lungs (PaO_2/FiO_2 ratio $\leq$ 40 kPa (300 mm Hg) and chest radiograph consistent with pulmonary oedema), or (b) cumulative fluid balance from ICU admission > 2000 ml.

Contra-indications to deresuscitation are (a) noradrenaline (or adrenaline) dose > 0.2 mcg/kg/min, (b) more than 1 vasopressor agent in use, (c) uncorrected hypokalaemia (< 3.0 mmol/L), (d) uncorrected hyponatraemia (< 130 mmol/L), or (e) uncorrected hypernatraemia (> 150 mmol/L).

If deresuscitation criteria are met, the intervention will comprise administration of indapamide 5 mg enterally 24-hourly, spironolactone 100 mg enterally 24-hourly, 0.5 mg/kg furosemide (rounded to nearest 10 mg, maximum 40 mg) intravenously as a single dose, and an intravenous infusion of furosemide. The infusion will be titrated within the range 2.5 to 20 mg/hour to target a negative fluid balance of 1000 to 3000 ml/day (42-125 ml/hour) (Figure 1). For patients on renal replacement therapy (RRT), diuretics will not be administered and ultrafiltration will be used to target a daily negative fluid balance of 2000 ml (83 ml/hour).

The study treatment regimen will be continued until one of the following criteria is met: (a) beginning of study day 5

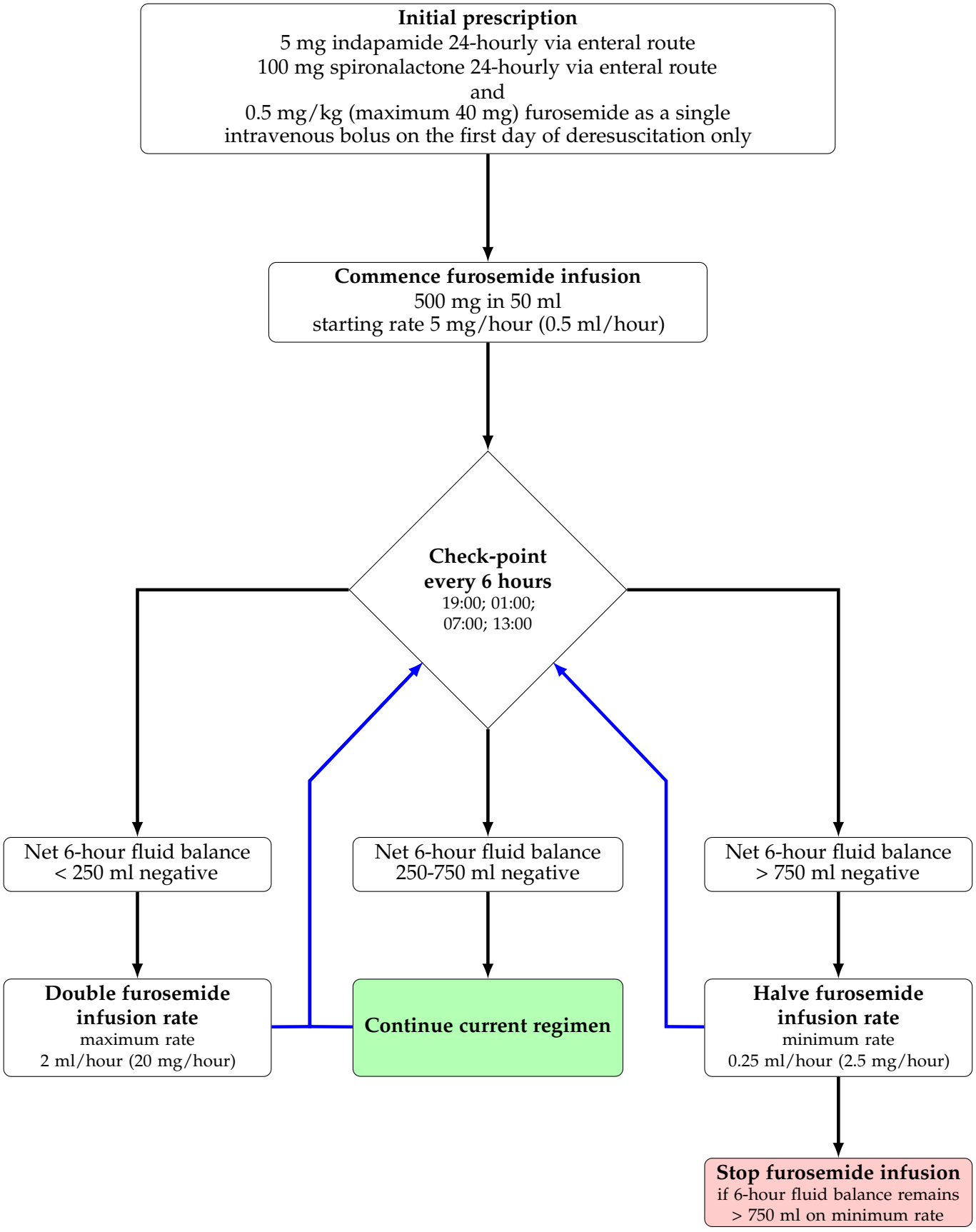

Figure 1. Deresuscitation regimen

OUTCOMES	DETAILS
Feasibility	Cumulative fluid balance (mL) from ICU admission until beginning of study days 3 and 5, and at ICU discharge Rates of recruitment (% of patients screened and % of all patients admitted to ICU (per site)) Incidence of significant protocol violations (total number of patients, per site, and by nature of protocol violation).
Safety	Incidence of serious adverse events
Efficacy	Change in overall and organ SOFA scores from baseline to beginning of day 3 and end of day 5 Mortality (28-day and 180 day) Duration of mechanical ventilation in survivors and non-survivors (number of days or part thereof from initiation of mechanical ventilatory support until unassisted breathing, censored at 28 days) Length of ICU stay (number of days or part thereof from admission to an ICU or being under the care of a critical care team or consultant until ICU discharge, censored at 28 days) Cardiovascular stability (highest and mean dose of vasopressors; highest and mean heart rate and serum lactate) Volume of fluid bolus administration until the beginning of study day 3 and to end of day 5 Incidence of new AKI defined as Kidney Disease: Improving Global Outcomes (KDIGO) Stage 3, before and after correction for fluid balance, up to end of day 5. Cognitive function score at 180 days (assessed using the Montreal Cognitive Assessment (MoCA-blind) instrument) Health-related quality of life (HR-QoL) at 180 days (assessed using absolute values of a telephone-administered EQ-5D questionnaire) Incidence of anxiety and depression, absolute number (defined as Hospital Anxiety and Depression Scale (HADS) score $\geq$ 11) Incidence of post-traumatic stress disorder (defined as Impact of Events Scores-Revised (IES-R) score $\geq$ 33)
Exploratory	Systemic endothelial function and injury (as measured by plasma levels of angiopoietin I/II (Ang-1 and Ang-2) and Ang-1/Ang-2 ratio, syndecan-1). Systemic inflammatory mediators (as measured by plasma levels of C-reactive protein (CRP), tumour necrosis factor α (TNF-α), interleukin-6 (IL6), interleukin 8 (IL8), soluble TNF receptor 1 (sTNFr1) and other biomarkers). Cardiac function (echocardiographic measures including left ventricular ejection fraction, E/E' ratio (ratio of trans-mitral doppler inflow velocity to tissue doppler early diastolic mitral annular velocity). Renal function and injury (plasma and urine levels of cystatin C and NGAL). Cerebral oximetry (as measured by near-infrared spectroscopy (NIRS) measurement of regional cerebral oxygen saturation) Tissue oxygenation (as measured by NIRS measurement of muscle tissue oxygen saturation).

Table 2. Secondary study outcomes

(maximum treatment period), (b) discharge from critical care, (c) death or discontinuation of active treatment, (d) request for withdrawal from the trial by patient or their personal consultee, (e) decision by the attending clinician on safety grounds, or (f) a treatment-related serious adverse event.

Comparator

Patients in the comparator group will receive usual care with respect to fluid management at the discretion of the responsible clinical team.

Outcome measures

The primary endpoint is the fluid balance (mL) during the 24-hour period up to the beginning of study day 3. Secondary clinical outcomes are shown in Table 2.

Further exploratory work

We will explore the relationship of cerebral oximetry measurements with cognitive outcomes, adjusting for fluid status and group assignment. We will further explore the relationship between vital signs and measurements of cerebral and tissue oximetry.

Ethical considerations

The trial has been approved by the Northern Ireland Research Ethics Committee B (17/NI/0192). The study will be conducted in accordance with the ethical principles which have their

origin in the Declaration of Helsinki. All data will be stored securely in a pseudoanonymised fashion.

Adverse event reporting

We will collect data on adverse events and serious adverse events during follow-up. The occurrence of a treatment-related serious adverse event will trigger withdrawal of the patient from the study.

A Data Monitoring Committee (DMC) will be appointed which will be independent of the study team and sponsor, and will comprise an Intensive Care consultant, a clinician with experience in undertaking clinical trials, and a statistician. The DMC will meet 6-monthly for the duration of the trial, and will function primarily as a check for safety, reviewing adverse events. Any issues pertaining to safety will be reported to the Chief Investigator who will be responsible for informing the sponsor.

Sample size

Based on data from our recently completed observational study, we anticipate a fluid balance in the 24 hours up to day 3 of 494 +/- 1512 mL in the usual care group. A sample size of 174 subjects (87 in each group) will have 90% power at a two-tailed significance level of 0.05 to detect a difference in fluid balance of 750 mL over 24 hours. We have allowed for a drop-out rate of 3% and the study will therefore require a total of 180 patients (90 in each group).

Statistical analysis

The study will be analysed on an intention to treat basis. A p value of < 0.05 will be considered as significant. A single final analysis is planned at the end of the trial.

We will undertake subgroup analyses for patients with, and without, ARDS (Berlin criteria) [19]; sepsis [20]; patients with traumatic brain injury; and patients with hypo- and hyper-inflammatory phenotypes [21].

The primary outcome of day 3 fluid balance and other fluid balance variables will be formally compared between groups using an independent samples Student's t-test, since the treatment must affect fluid balance in order to justify a clinical outcomes trial. Other feasibility outcomes assess various aspects related to the feasibility of completing a large-scale clinical outcomes study and will be reported descriptively.

For safety, efficacy and exploratory outcomes, continuous variables will be analysed using independent t-tests or non-parametric alternatives. Categorical variables will be analysed using Chi-square tests (or Fisher's Exact tests). Time to event variables will be analysed using survival analysis technique and the Kaplan-Meier method will be used to estimate median survival time and 95% CI. Equality of survival curves will be tested using log rank tests. A Cox proportional hazard model will be used if proportional hazards assumptions hold. Repeated measures ANOVA will be used to analyse serial measures over time for continuous variables. Scatterplots will be used to assess the relationship between biological markers, physiological and clinical outcomes. If a linear relationship exists, Pearson's correlation coefficient or non-parametric alternative will be used to estimate the strength of the relationship.

A full statistical analysis plan will be made available as a supplementary appendix to this manuscript at a later date prior to database lock.

Trial status

To date, 45 patients have been randomised in 3 sites, in keeping with the planned recruitment rate. We anticipate completion of the trial in Autumn 2019.

Discussion

Although fluid management is an integral aspect of intensive care management of the critically ill, considerable uncertainty remains as to the indications, benefits and harms associated with fluid administration and deresuscitation. Despite the large body of observational evidence demonstrating harm associated with fluid overload, RADAR-2 is the first randomised trial of an integrated conservative fluid administration and active deresuscitation intervention to be performed in a broad cohort of critically ill patients. This study is primarily a feasibility trial, with a view to undertaking a large multicentre randomised trial in the future, but also affords the opportunity to explore physiological and biochemical aspects of fluid management.

Our study has a number of limitations. Caregivers and researchers will not be blinded to group assignment, due to the limited likelihood of successful blinding given diuretics have the signature physiological effect of inducing diuresis, as well as the manufacturing cost of a suitable placebo. The open-label nature of the study also risks the Hawthorne effect, and indeed it is possible that clinical practice is already changing towards a more conservative approach to fluids, given recent attention in the literature to the harms of fluid overload. In addition, protocolising fluid and diuretic therapy is challenging, when the response to both is highly patient-dependent. For these reasons, it is important to test the feasibility of the proposed intervention in the current trial prior to embarking on a large multi-centre randomised trial powered for clinical outcomes.

Declaration of interests

The investigators confirm that they have no competing interests.

Dissemination of results

The results of this trial will be published in a peer-reviewed journal and may be presented at medical conferences. No professional writers will be involved. Criteria for authorship will be those set out by the International Committee of Medical Journal Editors (http://icmje.org/).

Role of funders and sponsor

Neither the funders nor the sponsor have any responsibility for study design, data collection or analysis, interpretation or publication.

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