Radar2

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

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| Statistical Analysis Plan | v1.1 | 5th March 2020 |
| Study protocol | v2.0 | 3rd May 2019 |

Trial Registration: ClinicalTrials.gov NCT03512392

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## Background and rationale

Although fluid administration is an almost universally used therapy in critical care, much is unknown about how to maximise benefits and minimise harms. 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 [1-4]. In a recent meta-analysis of 11 randomised trials (2051 patients), there was a non-significant reduction in mortality with a conservative or deresuscitative fluid strategy compared to a liberal strategy or usual care (RR 0.92, 95% CI 0.82 - 1.02). There was a significant reduction in ICU length of stay (mean difference (MD)-1.88 days, 95% CI -0.12, -3.64) and an increase in ventilator free days (MD 1.82 days, 95% CI 0.53, 3.10) with a conservative or deresuscitative strategy compared to a liberal strategy or standard care [5].

## Hypothesis

In critically ill patients, a post-resuscitation fluid strategy comprising conservative fluid administration and active deresuscitation reduces net fluid balance, is safe and improves outcomes.

## Objectives

1. To determine the feasibility, safety and clinical outcomes of conservative fluid administration and deresuscitation compared with usual care in critically ill patients
2. To explore biological effects of conservative fluid administration and deresuscitation.

## Study Methods

### 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. The intervention will consist of 2 stages: (1) conservative fluid administration and, if appropriate criteria are fulfilled, (2) deresuscitation in the form of diuretics or fluid removal using RRT to target a negative fluid balance.

### Randomisation

Patients will be randomised a minimum of 24 hours and a maximum of 48 hours following ICU admission. Randomisation will be stratified by study site. Subjects will be randomised in a 1:1 ratio using blocks of variable size.

### Sample Size Calculation

Based on data from a recent observational study in a similar population [2], we anticipate a fluid balance in the 24 hours up to day 3 (primary outcome) 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 principles

The study will be analysed on an intention to treat basis. Multiple imputation will be used to deal with missing data. A p value of 0.05 will be considered as significant. A single final analysis is planned at the end of the trial.

Outcome measures and analysis

The primary endpoint is the fluid balance (mL) during the 24-hour period up to the beginning of study day 3 [continuous variable, measured using a Student's t-test for independent samples].

| Secondary Outcomes | | |
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| **Feasibility outcomes** | | |
| Cumulative fluid balance (mL) from ICU admission until the beginning of study days 3 and day 5, and at ICU discharge | Continuous variables | Independent samples t-test (or non-parametric equivalent) |
| Rates of recruitment as a proportion of patients screened and as a proportion of all patients admitted to ICU (per site) | | Descriptive only |
| Incidence of significant protocol violations (total number of patients, per site, and by nature of protocol violation | | Descriptive only |
| **Safety outcomes** | | |
| Incidence of serious adverse events (SAEs) (number of patients with SAEs as a proportion of total) | | Chi-squared test / Fisher's exact test |
| Incidence of adverse events (AEs) (number of patients with AEs as a proportion of total) | | Chi-squared test / Fisher's exact test |
| **Efficacy outcomes** | | |
| Change in SOFA scores from baseline to the beginning of day 3 and beginning of day 5, overall and individual organ sub scores | Continuous variable | Multiple regression analysis (with baseline scores as co-variate) |
| Mortality (28-day and 180 day) | Discrete variable | Chi-squared test; Kaplan-Meier survival curves; log-rank test +/- Cox proportional hazards model if assumptions met |
| Duration of mechanical ventilation in survivors and non-survivors | Continuous variable | Independent samples t-test (or non-parametric equivalent); Kaplan-Meier survival curves; log-rank test; +/- Cox proportional hazards model if assumptions met |
| Length of ICU stay | Continuous variable | Independent samples t-test (or non-parametric equivalent); Kaplan-Meier survival curves; log-rank test; +/- Cox |

| | | |
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| | | proportional hazards model if assumptions met |
| Incidence of new acute kidney injury defined as KDIGO Stage 3 (before and after correction for fluid balance) up to the beginning of day 5 | Discrete variable | Chi-squared test |
| Cognitive dysfunction at 180 days | Discrete variable | Chi-squared test |
| Health-related quality of life (HR-QoL) at 180 days | Ordinal variable | Mann-Whitney test |
| Incidence of anxiety and depression | Discrete variable | Chi-squared test |
| Incidence of Post-traumatic stress disorder | Discrete variable | Chi-squared test |
| Exploratory outcomes | | |
| Plasma levels of markers of endothelial injury (Angiopoietin I/II and Ang-1/2, Syndecan-1, total protein, plasma albumin, and protein permeability (albumin:α2-macroglobulin ratio)), absolute levels and change from baseline | Continuous variables | Independent samples t-test (or non-parametric equivalent); Repeated measures ANOVA if applicable. Scatterplots and Pearson's correlation coefficient or non-parametric alternative if applicable. |
| Plasma levels of Inflammatory mediators e.g. CRP, TNFα, IL6, IL8: absolute levels and change from baseline | Continuous variables | Independent samples t-test (or non-parametric equivalent); Repeated measures ANOVA if applicable. Scatterplots and Pearson's correlation coefficient or non-parametric alternative if applicable. |
| Cardiac function (echocardiographic measures including left ventricular ejection fraction, E/E' ratio) | Continuous variables | Independent samples t-test (or non-parametric equivalent) |
| Renal function and injury (plasma and urine levels of Cystatin C and NGAL), absolute levels and change from baseline | Continuous variables | Independent samples t-test (or non-parametric equivalent); Repeated measures ANOVA if applicable. Scatterplots and Pearson's correlation coefficient or non-parametric alternative if applicable. |
| Cerebral oximetry (NIRS measurement of regional cerebral oxygen saturation), mean and minimum $rScO_2$ level, proportion of time spent with rScO2 below thresholds of 50%, 65%, and 75% | Continuous variables | Independent samples t-test (or non-parametric equivalent) |
| Tissue oxygenation (NIRS measurement of muscle tissue oxygen saturation), mean and minimum $rScO_2$ level | Continuous variables | Independent samples t-test (or non-parametric equivalent) |

Subgroup analyses

We will compare the primary outcomes and clinical outcomes between treatment groups in the following subgroups: patients with and without Acute Respiratory Distress Syndrome, Sepsis, Traumatic Brain Injury, and with hyper- and hypo-inflammatory phenotypes as previously defined [6].

Secondary analyses

Secondary multiple regression analysis will be performed with treatment allocation as the main exposure. The following key covariates will be forced into the model: age, APACHE II score, presence of ARDS, vasopressor use at baseline. Additional covariates for inclusion in the model will be selected based on clinical plausibility.

We will undertake a secondary per-protocol analysis. This information will be valuable in differentiation between treatment failure (the treatment did not have the intended effect) and process failure (intervention not delivered as intended).

If there is evidence of a difference in the outcome of cognitive dysfunction between treatment groups, we will use path analysis to attempt to ascertain whether the effect of treatment group assignment on cognitive function is mediated by cerebral oxygenation.

For the exploratory outcomes, we will undertake secondary analyses using multivariate regression analysis with fluid balance as the main exposure and treatment group assignment as a covariate.

At a later stage, we will investigate the relationship between cerebral and tissue oxygenation and cardio-respiratory physiological variables such as heart rate, mean arterial pressure, and arterial oxygen saturation.

## Dummy Tables and Diagrams

The following are indicative of the approach used to present data, rather than the precise format.

Figure 1. Study flow diagram.

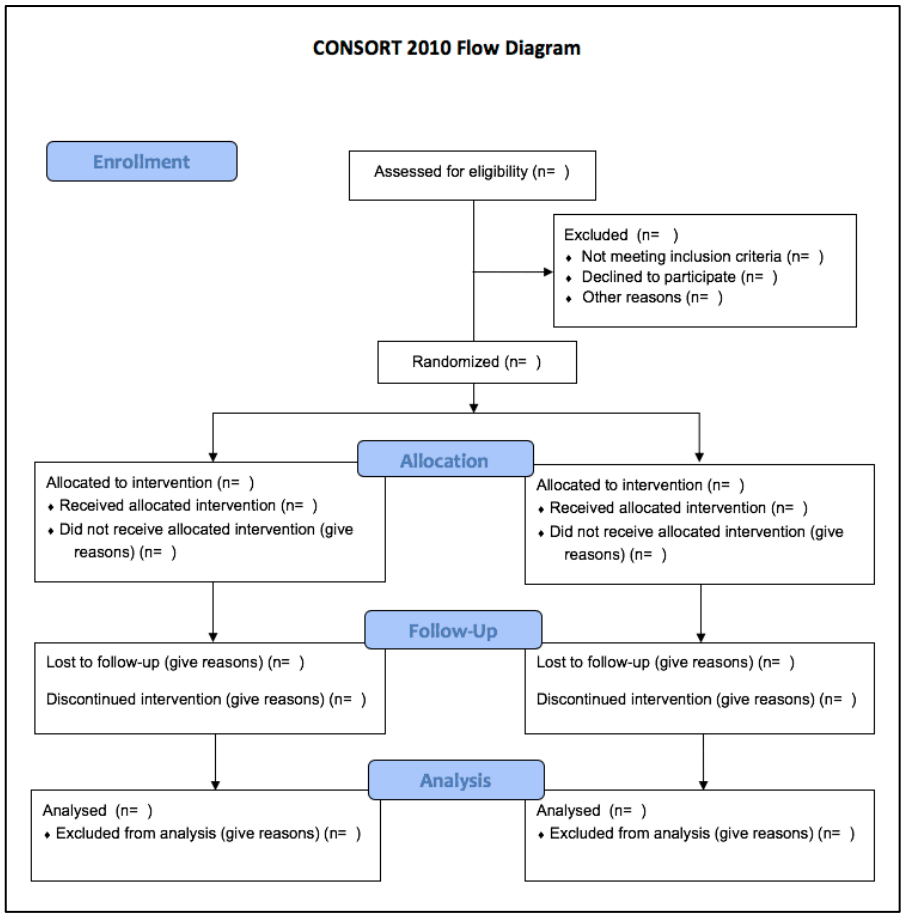

Table 1. Patient characteristics at randomisation.

| Variables | Control | Intervention |
|---|---|---|
| Age | Mean (SD) | Mean (SD) |
| Gender: | | |
| Male | N (%) | N (%) |
| Female | N (%) | N (%) |
| Type of admission: | | |
| Emergency | N (%) | N (%) |
| Elective | N (%) | N (%) |
| Operative status: | | |
| Surgical | N (%) | N (%) |
| Non-surgical | N (%) | N (%) |
| Primary organ system involvement: | | |
| Respiratory | N (%) | N (%) |
| Cardiovascular | N (%) | N (%) |
| Neurological | N (%) | N (%) |
| Renal | N (%) | N (%) |
| Gastrointestinal | N (%) | N (%) |
| Other | N (%) | N (%) |
| Subgroups: | | |
| Acute Respiratory Distress Syndrome | N (%) | N (%) |
| Sepsis | N (%) | N (%) |
| Traumatic Brain Injury | N (%) | N (%) |
| Hyperinflammatory phenotype | N (%) | N (%) |
| APACHE II score | Mean (SD) | Mean (SD) |
| Baseline SOFA score | Mean (SD) | Mean (SD) |
| KDIGO stage: | | |
| 1 | N (%) | N (%) |
| 2 | N (%) | N (%) |
| 3 | N (%) | N (%) |
| Vasopressor use | N (%) | N (%) |
| Serum lactate | Mean (SD) | Mean (SD) |
| Renal Replacement Therapy use | N (%) | N (%) |
| Oxygenation index | Mean (SD) | Mean (SD) |
| Oedema in > 1 peripheral site | N (%) | N (%) |
| Cumulative fluid balance | Mean (SD) | Mean (SD) |

Table 2. Key outcomes

| | Control | Intervention | P value |
|---|---|---|---|
| Primary outcome | | | |
| Fluid balance over 24 hours up to Day 3 (mL) | Mean (SD) | Mean (SD) | x.xxx |
| Feasibility outcomes | | | |
| Cumulative fluid balance from ICU admission up to Day 3 | Mean (SD) | Mean (SD) | x.xxx |
| Cumulative fluid balance from ICU admission up to Day 5 | Mean (SD) | Mean (SD) | x.xxx |
| Clinical outcomes | | | |
| Mortality at 28 days:<br>Total<br>Acute Respiratory Distress Syndrome<br>Sepsis<br>Traumatic Brain Injury<br>Hyperinflammatory phenotype | <br>N (%)<br>N (%)<br>N (%)<br>N (%)<br>N (%) | <br>N (%)<br>N (%)<br>N (%)<br>N (%)<br>N (%) | x.xxx |
| Duration of mechanical ventilation in survivors | Median (IQR) [#], N=x | Median (IQR)[#], N=x | x.xxx |
| Length of ICU stay in survivors | Median (IQR)[#], N=x | Median (IQR)[#], N=x | x.xxx |
| Change in SOFA scores baseline to day 3 | Mean (SD) | Mean (SD) | x.xxx |
| Change in SOFA scores baseline to day 5 | Mean (SD) | Mean (SD) | x.xxx |
| Incidence of new AKI (KDICO Stage 3)<br>Before correction for fluid balance<br>After correction for fluid balance | N (%) | N (%) | x.xxx |

*Individual SOFA organ function scores to be reported in an appendix. [#]Mean (SD) to be reported if normally distributed

Table 3. Process measures

| | | | |
|---|---|---|---|
| Recruitment rates (% of screened patients / % of admitted patients)*:<br>Total | xx.x% / yy.y% | | N/A |
| Number of protocol violations* (% of included patients):<br>Total<br>Eligibility<br>Study conduct<br>Other | <br>N (%)<br>N (%)<br>N (%)<br>N (%) | <br>N (%)<br>N (%)<br>N (%)<br>N (%) | N/A |
| Incidence of adverse events:<br>Number of patients experiencing AEs<br>Protocol specified expected AEs<br>Total of AEs[#]<br>AE 1[#] | <br>N (%)<br>N (%)<br>N (%)<br>N (%) | <br>N (%)<br>N (%)<br>N (%)<br>N (%) | <br>x.xxx<br>x.xxx<br>x.xxx<br>x.xxx |

| | | | |
|---|---|---|---|
| AE 2[#]<br>AE 3[#]<br>Other | N (%)<br>N (%)<br>N (%) | N (%)<br>N (%)<br>N (%) | x.xxx<br>x.xxx<br>x.xx |
| Incidence of serious adverse events (% of included patients) | N (%) | N (%) | x.xxx |

*Data to be reported by site in appendix. [#]3 most frequent reported individually. Full list in appendix to main manuscript. Full list of AR, SARs, and SUSARs in appendix (if any).

Long term (180-day) outcomes, and exploratory outcomes, will be reported in a separate manuscript.

References

1. Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. Critical Care. Critical Care; 2015;19:251.

2. Silversides JA, Fitzgerald E, Manickavasagam US, Lapinsky SE, Nisenbaum R, Hemmings N, et al. Deresuscitation of Patients With Iatrogenic Fluid Overload Is Associated With Reduced Mortality in Critical Illness. Critical Care Medicine. 2018;:1.

3. Murphy CV, Schramm GE, Doherty JA, Reichley RM, Gajic O, Afessa B, et al. The Importance of Fluid Management in Acute Lung Injury Secondary to Septic Shock. Chest. 2009;136:102–9.

4. Vaara ST, Korhonen A-M, Kaukonen K-M, Nisula S, Inkinen O, Hoppu S, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. Critical Care. BioMed Central Ltd; 2012;16:R197.

5. Silversides JA, Major E, Ferguson AJ, Mann EE, McAuley DF, Marshall JC, et al. Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. Intensive care medicine. 2017;43:155–70.

6. Famous KR, Delucchi K, Ware LB, Kangelaris KN, Liu KD, Thompson BT, et al. Acute Respiratory Distress Syndrome Subphenotypes Respond Differently to Randomized Fluid Management Strategy. Am. J. Respir. Crit. Care Med. 2017;195:331–8.