Author’s response to reviews

Title: Fluid strategies and outcomes in patients with acute respiratory distress syndrome, systemic inflammatory response syndrome and sepsis: a protocol for a systematic review and meta-analysis

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Author’s response to reviews:

Dear Editors,

Many thanks for the helpful feedback received from the reviewers of our manuscript ‘Fluid strategies and outcomes in patients with acute respiratory distress syndrome, systemic inflammatory response syndrome and sepsis: a protocol for a systematic review and meta-analysis’.

Our responses to the reviewer’s comments are found below after each question, and a revised manuscript has been uploaded. Thank you for your further consideration of the manuscript.

Kind regards,

Jon Silversides (on behalf of the review team)

Reviewer #2: Thanks for the opportunity to review this protocol. I think the proposed research is important and will be informative to practicing clinicians and those designing future clinical trials.
Although the protocol is well done I have a few suggestions/points to consider prior to publication:

1) study inclusion - the authors state that studies including perioperative patients or heart failure patients will be excluded. Will studies with mixed patient populations (ie 20% CHF patients) be included?

   We have clarified this in the manuscript. Only studies with >50% of one of the excluded populations will be excluded from the review.

2) Outcomes - Any minimal duration or maximal duration for followup for the primary outcome? What if a study reports multiple time points for mortality outcome data?

   Our primary end-point will be all-cause mortality at the most protracted time-point reported, to a maximum of 90 days. Any studies which report mortality at a later time point will be analysed and reported separately.

   AKI obviously has many different definitions - how will this be handled?

   We anticipate that AKI will be defined either (a) as a dichotomous outcome – present or not present, or (b) incidence for each category of AKI in one of the three most commonly used scales (RIFLE, AKIN and KDIGO) will be presented. If (a) we will report as a dichotomous outcome, if a mixture of (a) and (b), we will refine to a dichotomous outcome, using the category most closely approximating the definition used for (a). If studies report AKI using a mixture of RIFLE, AKIN and/or KDIGO, we will define AKI as RIFLE stage F, AKIN stage 3 or KDIGO stage 3.

3) ROB Assessment - I believe there is an accidental omission as right now this section states that domains will be rated as either low or unclear risk of bias with no mention of an option for 'high'.

   - the Ottawa Newcastle scale has a slightly different version for cohort studies or case-controlled studies

   - only the cohort version is shown

   - I believe case-controlled studies would be included in this review?

   Thank you for pointing out this omission – the manuscript has been amended to state that ROB will be assessed as high, low or unclear.

   The Newcastle-Ottawa scale has indeed two versions as pointed out – we showed only the version for cohort studies as representative but will use the appropriate version for case-control studies, and have amended the manuscript for clarity on this point.
4) Statistical Heterogeneity - the authors state that if high (>90%) then results will be presented narratively - what if heterogeneity is high but can be explained by a priori subgroup analysis? Then will they still not show the quantitative analysis? I would think it would be useful in this case. Potential revision would be if significant 'unexplained' statistical heterogeneity.

We have amended the manuscript accordingly.

5) Analysis Plan - This section requires a little clarification. Do the authors plan to present all outcome data across clinical syndromes (ARDS, SIRS, sepsis)? If this is the case then I'm not 100% convinced how this will enhance generalizability of the results compared to looking at all critically ill patients (including those that don't meet one of the clinical syndromes mentioned). If the plan is to present all outcome data separately then subgroups will be shown within ARDS? eg ARDS children/ARDS adults?

We intend, if possible, to present results across the clinical syndromes listed. We agree that generalisability to a population of critically ill patients would be greatest if studies comprising all critically ill patients were included. Unfortunately, critical illness is not particularly well-defined, and for the purposes of a search strategy including all studies which may have included critically ill patients proved impossible. We therefore focussed on subjects with specific syndromes as being relatively (but not entirely) generalisable to critical illness as a whole.

If sufficient suitable studies are found, we will present the following groups/subgroups:

- All
- All patients with ALI/ARDS
- All patients with SIRS/sepsis
-children (with ALI/ARDS/SIRS/sepsis)
- adults (with ALI/ARDS/SIRS/sepsis)

We will not further subdivide into subgroups of subgroups.

- What factors will be considered to determine suitability of data for subgroup testing? when specifying subgroups a priori it is suggested to hypothesize direction of subgroup effect which will lend to increasing credibility

Suitability of data for subgroup analysis will depend on the number of studies for each subgroup and within-subgroup heterogeneity.

We hypothesise that due to physiological differences between children and adults, that there may be a difference in effect between these two important subgroups, but have no a priori
hypothesis as to the direction of subgroup effect. Based on prior knowledge of the literature and on our clinical knowledge we can hypothesise that the effect will be greater in the ALI/ARDS subgroup than either other subgroups or in the all patient analysis.

- how will you handle outcomes that have both observational and RCT data? Will both be shown?

We will undertake meta-analysis of RCTs only. We have amended the manuscript accordingly.

- for observational data, the authors have mentioned that previous criticisms of primary publications have stated that sicker patients will usually get more fluid which may bias results - will you use raw data or adjusted data (for other prognostic factors, if available) for observational studies?

We will report adjusted data only.

6) Certainty in Evidence assessment - do the authors plan for any assessment of the evidence across outcomes? eg GRADE as per point 17 of the PRISMA-P guidelines

For each outcome, we will grade our confidence in the body of evidence according to the GRADE scale. We have amended the protocol accordingly.

Reviewer #3: This is a protocol for a review on "Fluid strategies and outcomes in patients with acute respiratory distress syndrome, systemic inflammatory response syndrome and sepsis"

This review is likely to be of interest to intensivists.

However there are some amendments required to the protocol. Major amendments include:

Background

1. There are a variety of definitions for sepsis, infection associated with organ failure is only one of the definitions. The authors should highlight this fact and also state they are using the definition that includes associated organ failure for this systematic review.

The manuscript has been altered to clarify the definition being used.

2. How will it be identified by the authors that the initial fluid resuscitation phase has been excluded from the studies. What definition will be used to define this?

We have deliberately not defined the resuscitation phase based solely on time criteria, as there is no clear definition. Reviewers will therefore make a judgment on each study based on (a) the time period over which the intervention of interest takes place, (b) the strategy employed, and (c) the reported intent of the investigators. We would expect interventions of
interest to begin after the initial 24 hours of ICU admission and last for 3 days or more, and we anticipate that in reality it will be fairly apparent to the reviewers, who are clinicians in the field, whether the study is dealing with resuscitation or with ongoing fluid management.

Outcomes

3. What does mortality (as defined by the authors) mean? Do the review authors mean all-cause mortality (time-scales as defined as the studies)? If so any analysis should be clustered over short medium or long time scales. If the authors mean different types of mortality then these should not be combined.

For the purposes of our review, mortality refers to all-cause mortality.

We anticipate that mortality will be reported at a range of time points: in the ICU literature these are most frequently short- to medium-term time points: 28 days, 30 days, 60 days or 90 days. Some evidence supports treating these time points as equivalent, since this does not change the conclusions of systematic reviews compared to treating each time point as a separate outcome (Roth and Herkner, presented at Cochrane Colloquium, Vienna, Oct 2015). This is clinically plausible in the case of this review, since it is likely that the fluid strategy used in ICU will have the greatest effect on short-term mortality (the period in ICU and shortly thereafter), and is unlikely to have a late (>30 day) effect.

As is common in reviews of critical care interventions, our primary end-point will therefore be all-cause mortality at the most protracted time-point reported, to a maximum of 90 days. Studies which report mortality at a later time point will be analysed and reported separately.

4. If the review is assessing respiratory dysfunction, is it not number of days on a ventilator rather than ventilator-free days?

Ventilator-free days (VFDs) are often used in critical care studies as a means to handle the competing risks of liberation from the ventilator and death. Patients who die are treated as having zero VFDs.

Study selection

5. Please state why 1980 has been chosen as a cut-off point was there any significant change in management of patients at this time point? Please state why this time has been chosen

We wished to capture studies which are reflective of modern critical care practice, which is a rapidly evolving field. There is no clear cut-off point by which this can be defined, so post-1980 was chosen as an arbitrary, though we believe reasonable, selection criterion.

Analysis
6. A cluster RCT could be used for studies that try to answer this review's questions, therefore the authors need to pre-specify how they would take account of cluster RCTs in the analysis. Based on prior knowledge of the literature, we do not anticipate that any cluster RCTs will meet criteria for inclusion in this review. If we find and include cluster RCTs, we will not attempt to meta-analyse these.

7. Time to event data should preferably be analysed as hazard ratios if data are available. Please add this to the analysis plan as the authors plan to extract mortality data. If time to event data are available for an outcome, we will use hazard ratios rather than risk ratios to compare groups.

8. State how the review would deal with an outcome with rare events (e.g. using Peto)

We do not anticipate that any of our outcomes will be rare events. If so, we will use the Peto method to estimate odds ratios.

9. Quality of included studies. The authors have not included an assessment of overall quality of the data but only included an assessment of risk of bias of RCTs. Overall quality assessment for pre-specified outcomes should be performed using a GRADE assessment to highlight the quality of evidence for each outcome. Quality of evidence may differ from outcome to outcome. For example all-cause mortality is not at risk of bias if the study is unblinded, whereas mortality due to a specific type of mortality may be at risk of bias if the study is unblinded. Please amend.

For each outcome, we will grade our confidence in the body of evidence according to the GRADE scale. We have amended the protocol accordingly.

10. "If two or more studies are available for an outcome, their results will be combined in a meta-analysis". Please clarify that this should only be done if it is appropriate to do so. It may not be appropriate even if there is no statistical heterogeneity if there is clinical heterogeneity or the outcomes are not similar enough (different types of mortality, or mortality over different time scales).

The manuscript has been amended as suggested.

11. Please state how the data would be presented if a meta-analysis could not be performed

The following tables will be used to present individual studies:

1. Characteristics of interventional studies table: authors / year / number of patients / inclusion & exclusion criteria / intervention strategy / comparator strategy

2. Risk of bias in interventional studies
3. Summary of estimates of effect in interventional studies

4. Characteristics of observational studies

5. Risk of bias in observational studies

6. Summary of estimates of effect in observational studies

12. Please give examples of sensitivity analyses that will be performed if possible for example only including studies at low risk of bias

We will undertake a sensitivity analysis including only randomised controlled trials after exclusion of studies with high or uncertain risk of bias, as assessed using the Cochrane risk of bias assessment tool.

13. For subgroups that have been pre-specified they should be performed if data are available

We have amended the manuscript as suggested.

Minor amendments

1. Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol

This has been included in the manuscript.