Author’s response to reviewer

Title: Protocol for a systematic review of the impact of resuscitation fluids on the microcirculation after haemorrhagic shock in animal models

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Author’s response to reviews:

Reviewer 1

1. You plan to include and analyze studies that compare different types of fluid resuscitation (rather than fluid versus haemorrhage only). I wonder if this analysis currently falls within your current research question. The first research question will be answered by the summary of overall analyses for each outcome measure. The second research question can be tested by comparing subgroups of different fluids (all with "haemorrhage only" controls). But it seems that the analysis described under "other meta-analysis details" is trying to answer a question such as "compared to crystalloid, which is better, PRBC or colloid?". It may fall within the second research question, but it is not entirely clear to me. I suggest rephrasing or adding a third question.

Response: Thank you. We have added a third research question in order to clarify this point.

2. Add "in animal models" or "preclinical evidence for" to the title to signify that this is a preclinical review

Response: The title has now been changed as suggested

3. In line 1 of methods: SYRCLE (no S at the end)
Response: The extra ‘s’ is now deleted

4. In research questions: add "in animal models" or "preclinical evidence for" to signify that this is a preclinical review. This also specifies the population (along the lines of PICO).

Response: This has now been added

5. If you plan to include all types of publication types, how are you going to handle abstracts and letters to the editor, from which essential methodological detail is likely to be missing?

Response: We have now addressed this problem in the paragraph “Type of study (design)” (Page 6). We will screen these abstracts, letters, conference proceedings, but they will be excluded if the essential methodological details are missing.

6. Will you include animals with co-morbidities? I also noticed that you plan to include knock-out animals, but do you think these can be readily pooled with wild type animals?

Response: We have clarified this in the paragraph “type of animal” (page 6).

7. Is it necessary to restrict the search to 1975? This seems a bit arbitrary.

Response: This has now been changed so that this restriction is no longer applied. All ‘restrictions’ have now been combined into one paragraph rather then three separate paragraphs.

8. Could you specify for which outcome measures you expect to use the mean difference / SMD? Also, I would suggest using the normalised mean difference, rather than the SMD, if possible (see the paper on MA methodology by Vesterinen et al.). The SMD often gives rise to skewed funnel plots, making an assessment of publication bias impossible.
Response: The “Effect Measures” paragraph has been changed to reflect this; normalized mean difference will be used instead of SMD.

9. The term clinical heterogeneity pops up in the article, but I guess pre-clinical may be more suitable here.

Response: The phrase “clinical and methodological homogeneity” has been changed to “methodological homogeneity”.

10. When performing multiple subgroup analyses using the same data, it is necessary to correct the P-value. I suggest adding how you plan to do this under subgroup analysis.

Response: We have added some clarification at the bottom of the “subgroup analysis” paragraph to explain that these analyses are hypothesis-generating only, and therefore p-values will not be reported and appropriate caveats will be made.

11. Will you be assessing the impact of any study quality items on the reported treatment efficacy?

Response: We have now edited the “Sensitivity analysis” paragraph to reflect that we will conduct sensitivity analysis based on the risk of bias according to the SYRCLE risk of bias tool.

12. The last lines of the paragraph on other meta-analysis details are unclear to me. I guess that if the same control group is used to multiple experimental groups, the number of control animals could be corrected and the data could be used. Unless you are worried about "same study bias" resulting from including lots of comparisons from a particular study and only single comparisons from the other studies. In this respect, I also am not sure how to interpret the last line of this paragraph. Could you please clarify?

Response: The “other meta-analysis” paragraph has been changed to reflect the fact that we will be performing multiple interventions meta-analysis as described by Caldwell et al (BMJ, 2005)
13. I believe the statistical approach of most tests for funnel plot asymmetry (including Peter's test) assume that the data have a normal distribution. However, 10 studies may be too few to ascertain this. Also, for funnel plots of animal data, many tests are hampered by the small variation in precision (i.e. group sizes in animal models are generally very similar), and the use of the SMD. I would suggest not performing an analysis for publication bias with fewer than 20 studies.

Response: This has now been changed to 20 studies

Reviewer 2

1. Although in the search strategy the authors have stated that there will be no restriction on publication type, can they please explain why they will not be including conference proceedings within the included studies. This excludes grey literature that may be relevant to their research. This is important as they have highlighted that publication bias may be an issue in this research field. They also do not appear to systematically searching the grey literature conference proceedings as part of their search strategy.

Response: In the “Type of study (design)” paragraph (Page 6) we now state that we will screen abstracts, letters, and conference proceedings, but they will be excluded if the essential methodological details are missing.

2. Please clarify why 1975 was chosen as a cut off for dates of studies to be included, this seems arbitrary

Response: This has now been changed so that the 1975 date restriction is no longer applied. All ‘restrictions’ have now been combined into one paragraph rather than three separate paragraphs

3. How will the authors identify whether the same study animals have been reported several times as a slowly increasing cohort of study animals over time? Please clarify
Response: We have now added a sentence for clarification in the “Combining and comparing the data” paragraph; where a number of similar studies (in terms of animal model, intervention and outcomes) are reported by the same study group or authors over time, authors will be contacted to determine whether studies are independent or include previously reported data.

4. Will the titles and abstracts be reviewed by two independent reviewers, unclear at present?

Response: Please see paragraph “Screening phases” in the “Study Selection” section.

5. Please state how heterogeneity will be categorised according to the I2 statistic

Response: This has been clarified in the “Statistical methods to assess heterogeneity” paragraph by using the suggestions seen in the Cochrane guidelines (http://handbook.cochrane.org/; 9.5.2 Identifying and measuring heterogeneity).

6. Please state at least age of study as part of a sensitivity analysis, as well as only including studies that were at low risk of bias according to the SYRCLE risk of bias tool

Response: These have now been added into the “Sensitivity analysis” paragraph (page 10).

7. Abstract: Please provide the CAMARADES reference number for the protocol

Response: We have been in correspondence with the CAMARADES team (via Professor Malcolm Macleod). They do not yet offer reference numbers for the registration of protocols. This is a work in progress. Instead, they have instructed us to input: “submitted to the CAMARADES registry of systematic review protocols (http://www.dcn.ed.ac.uk/camarades/research.html#protocols)”. This has been added to the bottom of page 2.
8. Background P3 line 45 additional unnecessary ‘is’

Response: Now removed.

9. Methods: Place and location of protocol registration is not present on page 4 of the protocol as stated in the checklist. Please amend

Response: This is now inserted at the bottom of page 2 (please see above Comment 7).