Author's response to reviews

Title: Efficacy and safety of damage control in experimental animal models of injury: protocol for a systematic review and meta-analysis

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Author's response to reviews: see over
Dear Dr. Kerry Dwan and the Systematic Reviews Editorial Team:

Re:

Ms. No.: 2979981461438216
Ms. Title: Efficacy and safety of damage control in experimental animal models of injury: protocol for a systematic review and meta-analysis

Thank you for your thoughtful reviews of our manuscript and the opportunity to resubmit a revised version for consideration of publication in Systematic Reviews. We have revised the manuscript as suggested, and feel that the appended document is an improved report, which addresses the Editorial requests and comments and suggestions afforded by Associate Editor Dr. Kerry Dwan and the Reviewer. Please find below an itemized list of detailed responses to each of the Editorial and Reviewer comments, including a description of the changes made to the manuscript (which are highlighted in yellow within the manuscript text and/or tables). Within this itemized list, we first cited each comment verbatim in bold type before providing our response for ease of review.

Handling Editor’s Comments:

1. Abstract – “weighted mean difference” is now just referred to as mean difference. This is also stated in the main text as well.

   Thank you. Weighted mean difference has been changed to mean difference in the abstract and main text of the manuscript as suggested.

2. Abstract – the sentence starting “heterogeneity” does not make sense as
publication bias is added at the end. Please edit.

We have revised this sentence in the abstract as suggested. It, and its surrounding text, now read:

“Heterogeneity will be explored using subgroup meta-analysis and meta-regression. We will assess for publication bias using funnel plots and Begg’s and Egger’s tests. When evidence of publication bias exists, we will use trim and fill methods to estimate the potential influence of this bias on pooled summary estimates.” (Page 3-4)

3. **Background, third paragraph – is “diffusely” the correct word?**

We agree that the word “diffusely” is perhaps not required in this sentence and have therefore removed it.

4. **How are you addressing the secondary review questions?**

We apologize for the lack of clarity. In order to make it more transparent as to how we will address both the primary and secondary research questions, we have revised the first paragraph of the Statistical Analyses section of the manuscript. After also incorporating the suggestions of the Reviewer regarding the use of fixed effect weighting in the presence of little heterogeneity, this now reads:

“To address the primary research question, we will calculate individual study estimates of the relative risk (RR) comparing mortality between animals that received damage control (or a specific damage control intervention) versus definitive surgery (or a definitive surgical intervention). Similarly, for the secondary research questions, we will calculate RRs comparing mortality between animals that received different damage control interventions or adjuncts or a damage control adjunct versus no adjunct. As we expect that there will be “clinical” heterogeneity in the design and/or conduct of the included studies, individual study RR estimates will then be combined using DerSimonian and Laird random effects models [70]. However, in the event that we find little clinical heterogeneity between studies, we will combine individual study RR estimates using fixed effect models with Mantel-Haenszel weighting [71]. Where possible, for both the primary and secondary research questions, we will also use fixed effect or random effects models and the reported within-group mean values to calculate summary mean differences for the above secondary outcome variables.” (Page 15)

5. **Statistical analyses – there are a lot of covariates listed here – these should be kept to a minimum.**

As suggested, we have reduced the number of covariates listed in the statistical analyses section of the manuscript from 8 for randomized controlled trials (9 for cohort studies) to 5 (6 for cohort studies). The statistical analyses section of the manuscript now reads:
“Covariates of interest will include characteristics of study internal validity, including whether randomization of animals to treatment was performed, allocation was concealed, or a sample size calculation was reported to have been done [57]. Other covariates will include characteristics of external/construct validity, including whether an intention-to-treat analysis was used, whether potential confounding factors were well balanced between the groups at baseline or controlled for, or whether there was a delay in employment of the treatment of interest by at least 30 minutes for an intervention designed to be applied in the Emergency Department versus 45 minutes for one designed to be used in the operating room [55, 59, 62, 69].” (Page 15)

6. Although you state that there are a lot of potential confounders, you do not list any that you consider important.

We agree that the most important confounding variables in the component studies should be outlined in the protocol a priori. Thus, we revised the background section to read:

“Further, results of these studies are frequently difficult to interpret due to varying inclusion/exclusion criteria, the lack of a complete description of which set of abbreviated trauma surgical procedures was studied, and the unavoidable presence of confounding by indication (whereby obvious or subtle differences exist in the characteristics of patients who are selected for damage control versus definitive surgery). Common baseline confounding variables in damage control effectiveness studies include differences in the volume of resuscitation provided or presenting blood pressures, core body temperatures, and acid/base and blood clotting measurements.” (Page 7)

While the Statistical Analyses section of the manuscript now includes the following sentence:

“Important confounding variables that should have been considered by study authors include baseline blood pressures, core body temperatures, arterial pH values, and laboratory clotting test results.” (Page 16)

7. Has this review been registered in PROSPERO?

We did not register our review in PROSPERO as the website for the register (http://www.crd.york.ac.uk/PROSPERO/) states that animal studies are not currently eligible for inclusion. In response to the below Editorial request, we therefore now include a statement in the Methods section of the manuscript that the protocol is not registered in PROSPERO. This reads:

“As protocols for systematic reviews of animal studies are not currently eligible for inclusion in PROSPERO, this protocol has not been registered.” (Page 10)
Editorial Requests:

1. Please include your PROSPERO registration number at the end of your abstract. Alternatively, if you have not registered with PROSPERO then please mention this in your Methods section.

   Thank you for this suggestion. We did not register our review in PROSPERO as the website for the register (http://www.crd.york.ac.uk/PROSPERO/) states that animal studies are not currently eligible for inclusion. We therefore now include a statement in the Methods section of the manuscript that the protocol is not registered in PROSPERO. This reads:

   “As protocols for systematic reviews of animal studies are not currently eligible for inclusion in PROSPERO, this protocol has not been registered.” (Page 10)

Reviewer Comments:

Major Compulsory Revisions

None

Minor Compulsory Revisions

1. Data Synthesis section: Avoid the use of “clustered” as this suggests cluster analysis which is not what you are intending to do. Instead stick with terminology such as “grouped”. [Clustered/clusters are mentioned twice within this paragraph]

   Thank you. We agree with the Reviewer. As suggested, instead of using the word “clustered”, we used the word “grouped” in the Data Synthesis Section.

Discretionary Revisions

1. Within the Methods/Design section of the abstract I would suggest that you additionally mention personal contact with relevant researchers in the field

   Thank you for this suggestion. We did not add this statement to the abstract as it was expanded in response to a comment by the Handling Editor. However, as we agree that this should be part of the search strategy, we have added this to the Search Strategy section of the main text of the manuscript. This now reads:

   “To identify studies that are about to be published, we will contact trauma surgery experts, relevant researchers in the field, and conduct manual searches of abstracts for conferences held between 2009-2013, including meetings of the American Association for
the Surgery of Trauma, American College of Surgeons, Eastern Association for the Surgery of Trauma, International Association for Trauma Surgery and Intensive Care, Trauma Association of Canada, and the Western Trauma Association [7].” (Page 11)

2. The background section involves the use of complex medical language. Personally, I would find it beneficial if the language was either toned down, or alternatively, additional descriptions were provided to define the medical terms e.g. Exsanguininating trauma patients (patients who are bleeding heavily).

We agree with the Reviewer. We therefore toned down the language in the Background section of the manuscript or added additional clarifying information wherever possible. This was done in four places on page five, including at the location suggested by the Reviewer (this now reads “Trauma patients who are bleeding heavily” instead of “Exsanguininating trauma patients”) and two places on page 6.

3. Study Selection, 1st paragraph: Please check whether this sentence makes sense – “Injuries of interest will include those resulting in truncal solid, hollow, and/or vascular organ or extremity vascular trauma.”

We have revised this sentence in order to improve readability. It now reads:

“Injuries of interest will include those resulting in solid, hollow, and/or vascular organ damage in the trunk (neck, thoracic, abdominal, or pelvic) as well as extremity vascular trauma [7, 9].” (Page 12)

4. Data Extraction, paragraph 1: I would suggest also testing the design of the form on a random sample of an equal number of RCTs and prospective cohort studies until it is clear that the form captures all relevant information.

We agree. We have therefore revised the sentence in paragraph 1 of the Data Extraction section of the protocol to read:

“The design and reliability of the spreadsheet will be pilot-tested on a random sample of an equal number of RCTs and prospective cohort studies until it is clear that the form captures all relevant information and consistency in data extraction is achieved (κ statistic ≥0.75) [65].” (Page 13)

5. Data Extraction, paragraph 2: Do you plan to collect information about the nature of the induced injury too? I guess these may be included within the characteristics of the included animals but it would be good to see it spelt out.

We do also plan to collect data on the nature of the injury induced in the animal model. In order to make this more clear, we revised the sentence as suggested. This now reads:

“We will extract data from included studies on: 1) study characteristics; 2)
characteristics of the included animals and the animal model, including the nature of the induced injury; 3) the treatment that was employed; and 4) mortality and secondary outcome measures (see Table 3 for a detailed description of the data to be collected.”

6. Statistical Analyses section, paragraph 1: If the heterogeneity is minimal you may need to consider using a fixed effects model (generalized inverse variance method) rather than a random effects model. Therefore, I would suggest that you include relevant text to this effect within the Statistical Analysis section.

Thank you for this suggestion. As we expect that there will be “clinical” heterogeneity in the design and/or conduct of some of the included animal studies, we had planned to use a DerSimonian and Laird approach to pooling the risk ratios (and mean differences) for the included component studies. However, as we agree that it may be possible that the included studies exhibit minimal between-study clinical heterogeneity, we have included the relevant text as suggested by the Reviewer. As some of the studies may have low event rates or sample sizes, we wonder whether Mantel-Haenszel may be more appropriate than inverse variance weighting as it has been suggested to be more robust when data are sparse [1]. After incorporating the revisions suggested by the Handling Editor regarding how we address the secondary research questions, the first paragraph of the Statistical Analysis section of the manuscript now reads:

“To address the primary research question, we will calculate individual study estimates of the relative risk (RR) comparing mortality between animals that received damage control (or a specific damage control intervention) versus definitive surgery (or a definitive surgical intervention). Similarly, for the secondary research questions, we will calculate RRs comparing mortality between animals that received different damage control interventions or adjuncts or a damage control adjunct versus no adjunct. As we expect that there will be “clinical” heterogeneity in the design and/or conduct of the included studies, individual study RR estimates will then be combined using DerSimonian and Laird random effects models [70]. However, in the event that we find little clinical heterogeneity between studies, we will combine individual study RR estimates using fixed effect models with Mantel-Haenszel weighting [71]. Where possible, for both the primary and secondary research questions, we will also use fixed effect or random effects models and the reported within-group mean values to calculate summary mean differences for the above secondary outcome variables.”

7. Statistical Analysis section, paragraph 3: consider providing more information about the trim and fill methods you intend to use, especially a reference for these methods.

In response to the Reviewer’s suggestion, we provided two sentences explaining the trim and fill methods we intend to use as well as supporting references. The third paragraph of the Statistical Analyses section now reads:
“When evidence of publication bias exists, we will use the Duval and Tweedie “trim and fill” method to estimate the potential influence of this bias on our pooled summary estimates [75, 76]. In this method, the small outlying study results are first “trimmed” (removed until the funnel plot appears symmetrical) and then the remaining symmetric study results are used to re-estimate the “true” center of the plot [75-77]. Subsequently, the plot is “filled” (the missing outlying study results and their theoretical “counterparts” are replaced around the re-estimated center) and an adjusted pooled estimate is calculated [75-77].” (Page 16)

8. Discussion, paragraph 1: Please consider re-phrasing the following sentence to improve clarity: “Thus, systematic reviews of these types of studies may be used to outline which interventions tested in animal models may not effectively translate into clinical trials…”

Thank you for this suggestion. We have revised this sentence (and its surrounding sentences) in order to improve clarity. The first paragraph of the Discussion now reads:

“Animal experiments are frequently used to evaluate interventions before they are used clinically. Although these studies provide evidence of the performance of interventions under relatively ideal conditions, some are limited by study design-related biases and/or a lack of model construct validity. Thus, systematic reviews of these types of studies may be used to outline which interventions tested in animal models do not yet have enough supporting evidence to warrant evaluation in clinical trials [29, 55-57, 78]. Unfortunately, it has been reported that this may infrequently occur in practice. For example, in a systematic review of 1,026 experimental treatments for acute ischemic stroke, the drugs that were ultimately clinically evaluated clinically were no more effective in animal models than those not clinically evaluated [78].” (Page 17)

9. Author’s information: Is DJR a surgery resident or a surgeon?

DJR is a surgery resident.

10. Reference 21, should “ppen” be “open”?

In reference 21, “ppen” has been changed to open.

Thank you once again for the reviews. The comments have improved our manuscript and we hope that you will find this version suitable for publication in Systematic Reviews. We look forward to your response.

Sincerely,

Nela Cosic, Derek J. Roberts, MD, and Henry T. Stelfox, MD, PhD
References