**Author’s response to reviews**

**Title:** Assessment of safety and efficacy of mesenchymal stromal cell therapy in preclinical models of acute myocardial infarction: a systematic review protocol

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Editorial Office:

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.

As this is a pre-clinical systematic review it is not eligible for registration with PROSPERO, therefore we have not mentioned this in the Methods section. We do mention that a summary of the protocol will be listed on the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) website.
Reviewer #2:

1. Will you not search trial registries?

We thank the reviewer for their careful consideration of our manuscript.

At the current time there is no trial registry for preclinical studies. We are aware of an international register of preclinical trial protocols in development (www.preclinicaltrials.eu), however this registry is not currently functional.

2. An example search strategy should ideally be included in the protocol.

We have now included this (Line 121). Please see Appendix 1 for an example strategy used to search MEDLINE.

3. Has thought been given to the design of non RCTs that will be included?

The non-RCTs we have included are controlled comparison studies or “pseudo-randomized” studies in which authors report methods used to randomize which are not considered true randomization. Terminology and methodology that is common-place in clinical studies is not routinely employed in basic science/preclinical studies. As previous reviews have shown that a third or less of animal studies report randomization (Van der Worp, 2010), we felt it necessary to include controlled comparison studies (both RCTs and non RCTs) to answer our study question.

The updated manuscript reads as follows:

This broad range of comparative studies will be included in order to answer our study question as terminology and methodology that is common-place in clinical studies is not routinely employed in preclinical studies, and previous reviews have shown randomization is reported in a third or less of animal studies [46]. (Lines 127-130)

4. Risk of bias: Have you considered using the ROBINS-I tool for non RCTs? You state earlier in the manuscript that you will use a modified version of the Cochrane tool but do not describe this modification.
As there is no validated tool to assess Risk of Bias in animal studies, this will be assessed as high, low, or unclear for the six domains of bias identified by the Cochrane Risk of Bias tool (Higgins and Green, 2009). We will include additional domains relevant to animal studies such as: source of funding, conflict of interest, sample size calculations, similarity of groups or adjustment for confounders at baseline, random housing of animals and animal selection at random for outcome assessment, based on our group expertise and elements of the SYRCLE Risk of Bias Tool, an alternative method of assessing risk of bias in preclinical animal studies (Hooijmans et al., 2014).

We have updated the description in the manuscript to reflect this and the text reads as follows:

We will include additional domains relevant to animal studies such as: source of funding, conflict of interest, sample size calculations, similarity of groups or adjustment for confounders at baseline, random housing of animals and animal selection at random for outcome assessment. (Lines 220-223).

5. Data synthesis: you state the ratio for weighted means. Do you mean a mean difference? Why does baseline data matter in the use of standardised mean difference?

Due to the variety of measurements we will be combining we are unable to use mean difference. Ratio methods can be used to analyze continuous outcomes, by calculating a ratio of mean values instead of a difference (Friedrich et al, 2008). Ratio of Means allows for pooling of outcomes expressed in different units and comparisons of effect sizes across interventions. It provides a result similar in form to a risk ratio, which is generally preferred and understood by clinicians. As RoM has been shown to exhibit comparable performance characteristics to Standardized Mean Difference, and it is well suited for small sample sizes that are typical of animal studies, we have chosen this method because of its simplified clinical interpretation. The mention of standardized mean difference was an oversight as the primary measure will be Ratio of Means. The text has been updated to justify the use of Ratio of Means and remove mention of SMD:

Continuous endpoints will be pooled using the ratio of weighted means method with inverse variance random effects modeling [17] . Ratio of Means allows for pooling of outcomes expressed in different units and comparisons of effect sizes across interventions. As Ratio of Means is well suited for the small sample sizes of animal studies, and provides a result in a form similar to a risk ratio, we have chosen this method because of its simplified clinical interpretation. (Lines 253-256)
6. Selective reporting: I'm not sure the test referenced is exactly in relation to selective outcome reporting. There are other sensitivity analyses available, or you can assess the studies using ORBIT (Kirkham et al, BMJ 2010).

Thank you for bringing this study classification system to our attention. We agree that this would be a superior and ideal way to assess selective outcome reporting in clinical trials. As alluded to above, reporting in preclinical studies is generally very poor thus the application of this tool would be difficult. The referenced test for an excess of significant findings does not directly measure outcome reporting and our text has been edited to clarify this.

7. Analysis: has thought been given to confounders and the differences between RCTs and non RCTs and whether different study designs will be pooled?

Potential differences in the design and confounding introduced in RCTs vs non RCTs will be accounted for in risk of bias assessments. We have planned sensitivity analyses that will examine heterogeneity of the primary outcome according to risk of bias assessments.

We have updated the manuscript to include mention of this as follows:

We have planned an analysis to determine the effects of high vs. low risk of bias on the effect size of the primary outcome. (Lines 226-227).

References:


