Author’s response to reviews

Title: Pre-clinical evaluation of therapies to prevent or treat bone non-union: a systematic review protocol.

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COMMENT#1:

The plan to seek missing data from study authors is an excellent approach. However, how you will achieve the other plans regarding handling missing data is unclear given that you will only have group level summary data, for example the use of last observation carried forward. I am not familiar with how data are presented in animal study papers so perhaps the individual animal data are presented in papers that would permit this approach or you plan an approach I am not familiar with - could you please add a bit more information to clarify what you plan to do and/or reference the approach you will take as appropriate. It may be worth considering defining what your main analysis will be and then using other approaches as a sensitivity analysis.

RESPONSE: A number of other protocols of systematic reviews of animal studies have been reviewed and their approaches to missing data scrutinised, in order to address the above comment. The editor is correct in stating that use of ‘last observation carried forward’ and other similar methods to handle quantitative data is not applicable in the context of this review. This is because missing data will be summative, and not a situation where a ‘number’ or ‘unit’ will be missing. Other protocols for reviews of pre-clinical studies refer exclusively to management of missing data regarding elements such as no mention of randomization, or no mention of blinded outcomes. In such instances (and in the absence of being able to source this missing data), the domain is labelled as ‘high risk’. The impact of this missing data is then assessed when carrying out risk of bias analysis. The request by the editor to include a reference to illustrate how to
handle quantitative missing data is therefore no longer applicable, given the nature of the missing data that the review will encounter. The paragraph on 'Missing Data' has therefore been rewritten to reflect our new approach.

COMMENT#2:

The rationale for establishing the quality cut-off for inclusion of studies in the meta-analysis based on how many studies you find is problematic as it leaves your study open to criticism for not specifying this a priori. A pragmatic approach might be to specify what you will do if there are sufficient studies and what you plan to do if this is not possible e.g. pool studies regardless of quality.

RESPONSE: The ‘Assessment of Bias’ paragraph has been rewritten to take into account the above comment. In particular, we have stated a priori that key domains that are assessed as ‘low risk’ for bias will be analysed separately to ‘high risk’ or where the risk of bias is ‘unclear’. However, we have also detailed our plan of action in the event that such an approach generates too few papers to meta-analyse. In this event, we will pool all studies regardless of bias.

COMMENT#3:

The sentence "During proforma completion, missing data that is required for analysis will be attempted to be obtained by contacting the study authors" is a bit clunky. I suggest something along the lines of "we will seek missing data required for the analysis from the original study author"

RESPONSE: The sentence has been reworded to the following: ‘During proforma completion, we will seek missing data that is required for analysis from the original study author’.

COMMENT#4:

The sentence "Sub-group analysis on the primary outcome of bone formation may be based (but not inclusive) on the following criteria" - it is not clear what the wording in brackets means - could you please make this clearer.

RESPONSE: The sentence has been reworded to the following: ‘Sub-group analysis will be considered where studies can be grouped according to the following characteristics’.

COMMENT#5:

The sentence "The decision as to which domains are of highest significance with regards to the subject of our review, will be informed by the likely magnitude and direction of the bias". It is
not entirely clear what this means - do you mean that based on the findings of the assessment of bias you will identify what they key sources of bias are in this body of evidence?

RESPONSE: The paragraph ‘Assessment of Bias’ has been reworded to make the above point clearer. The phrase ‘likely magnitude and direction of bias has been removed’, and we have specified a priori which domains will hold greatest magnitude in relation to their likelihood of identifying bias. In particular, a reference has been included to illustrate which domains are likely to contribute most significantly to bias, based on other systematic reviews of pre-clinical studies.

COMMENT#6:

The sentence "... therefore meta-analysis with studies where there is an absence of such interventions is not advised" - do you mean "interventions" or do you mean in the absence of additional insults. Given that the paper is about evaluating therapies I suggest you stick to using intervention in reference to therapies. If I have understood it properly I suggest rewording to something along the lines of "Such insults will inherently produce higher rates of delayed and non-union therefore it is not advised to combine studies regardless of the energy of the trauma, whether the fracture is open or not or whether infection has been introduced."

RESPONSE: The paragraph (fifth paragraph of Discussion) has been reworded to make it clearer that the term ‘intervention’ refers to a therapy, and an ‘insult’ refers to an addition to the animal model designed to counteract or interfere with the therapy.