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Hub: ConDuCT II	Host University: University of Bristol
Supervisor: Jelena Savovic J.Savovic@bristol.ac.uk	Co-supervisors: Julian Higgins, Hayley Jones
Is the project clinical or non clinical? Non-clinical	
Title of PhD project: Predicting direction and magnitude of bias in clinical trials	

Background: Although teams conducting randomised controlled trials (RCTs) aim to minimise bias as much as possible, some desirable features can be challenging to ensure in practice: e.g. successful blinding of all relevant parties and minimal attrition. If one of these features is either infeasible or implementation of it has failed, it is highly desirable to understand the likely effect of this on the estimated intervention effect. Such an understanding would considerably aid decision-making about healthcare policy - either based on the RCT directly or via its inclusion in a meta-analysis. 'Meta-epidemiological' studies offer potential to inform us about the likely magnitude and direction of bias associated with particular undesirable study characteristics. These are collections of meta-analyses in which the association of characteristics with estimated intervention effects has been studied across a large number of RCTs. However, it is uncertain how well the results of such studies are applicable to any individual trial. Ultimately, in predicting the direction and magnitude of likely biases, it would be desirable to produce *bias-adjusted* effect estimates. Again, these could be based on a single RCT or on a meta-analysis. Two main methods have been proposed for this in a meta-analysis context. These differ in that one makes the adjustments based on expert opinion about likely biases in individual RCTs (Turner et al, 1) while the other uses empirical evidence from meta-epidemiological studies (Welton et al, 2).

The MRC-funded COMBAT study (a collaboration between members of the MRC Biostatistics Unit in Cambridge and the ConDuCT II Hub in Bristol), has recently developed an integrated method for that combines the most attractive features of these two approaches: bias-adjustment is based on a combination of meta-epidemiological evidence and on the user's own anticipation of both the direction and likely magnitude of bias. However, users find it difficult to predict these two things and require more guidance.

What the studentship will encompass: The primary purpose of the project is to develop methods for predicting the magnitude and direction of bias in a clinical trial. A key area of work will be the development of guidance for users of the newly developed (HTMR funded) tool for assessing risk of bias in RCTs (RoB 2.0) [available at www.riskofbias.info], which includes an optional facility of assessing the likely direction of any bias. An extensive library of examples will be collated from among our existing meta-epidemiological studies to gather insight into how large apparent biases might have arisen. The work will start by considering each individual domain of bias. The interactions between biases arising from these domains are critical, however, and further re-analyses of the meta-epidemiological data are expected to lead to further insight into the extent to which the biases are additive.

A second main area of work is to further develop methods for bias adjustment, of either an individual trial result or results from multiple trials combined in a meta-analysis. The student will focus on integrated methods, based on a combination of expert opinion and empirical evidence. Of particular interest is to use quantitative estimates of bias as the opinion component of the integrated method for bias adjustment. To achieve this the student will develop a standardised way of converting qualitative RoB judgements (e.g. "high risk of bias in the direction of overestimation of treatment benefit") into a numerical interquartile range estimate of bias on the ratio of odds ratio scale (e.g. "0.71-0.99") and use this IQR as the opinion component for the COMBAT method of bias adjustment. We plan for the student to write software (e.g. a Stata command) for bias adjustments based on an integrated approach.

Details of supervision: Savović will supervise aspects of the risk of bias tool development, meta-epidemiology and epidemiology. Higgins and Jones will supervise statistical, meta-analytical methods and bias adjustment. In addition, Jonathan Sterne, Nicky Welton and Rebecca Turner (MRC BSU Hub in Cambridge) will have an advisory role.

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Supplementary information

1. Describe the alignment of the project with the HTMR Network strategy

The principal alignments with the strategy are:

1 (Promoting high quality collaborative research): We will exploit our excellent links with key researchers in bias in clinical trials and evidence syntheses (e.g. Turner and colleagues at the MRC BSU Hub in Cambridge, Tierney and colleagues at the MRC CTU Hub in London, Emberson and colleagues at the MRC CTSU Hub in Oxford and Kirkham and colleagues at the Northwest Hub in Liverpool), and develop new ones.

2 (Provide advice on methods): The project aims to develop relevant, implementable and acceptable methods for making judgments about the direction of bias in trials included in evidence syntheses and using this information together with the risk of bias judgment to quantify an estimate of bias to be used to adjust for bias in a meta-analysis.

3 (Encourage implementation of effective and appropriate methods): The project aims to lead to a better understanding of the results of clinical trials in the context of potential flaws, through prediction of the likely direction and magnitude of any bias. Methods of 'bias-adjustment' will be further developed and investigated, aiming to produce results that are less biased and less likely to be spuriously precise. In particular, appropriate methods of bias-adjustment will lead to the results of individual trials being more likely to be included in meta-analyses, thereby reducing research wastage. Further, the project could have implications for future trial design and contact, in that it will improve collective understanding of the most important features of RCTs and the likely effects of any flaws.

5 (Strengthen training and capacity in UK): the completing student will acquire the following skill and experience: clinical trial methods, epidemiology, evidence synthesis, Bayesian statistics, meta-analysis and decision theory.

2. Does this project align with the work of a HTMR Working Group; if so, which?

The project fits within the remit of the Evidence Synthesis Working Group. The student will be expected to contribute to this working group.

3. Describe how this project aligns with the host Hub strategy

Theme 1 of the ConDUCT II Hub aims to develop methods for the efficient use of trials of intervention efficiency, though collaboration between health economics, evidence synthesis, and biostatistics. The project aligns well with the Theme’s strategy, developing practical implementable methods for more reliable use of potentially biased trials in evidence syntheses.

4. Detail of any Project specific training offered in the studentship

Our School has a comprehensive and highly regarded programme of over 30 short courses in research methods. In addition, regular interaction with members of the Evidence Synthesis Working Group will provide an excellent training opportunity for the candidate.

5. Are there any prerequisite qualifications or experience for this studentship?

Candidates for an MRC-funded studentship must meet residence eligibility and hold qualifications in a relevant subject at the level of, or equivalent to, a good honours degree from a UK academic institution (see methodology website for more details- www.methodologyhubs.mrc.ac.uk).

For this projects: MSc or equivalent in epidemiology, medical statistics or other quantitative discipline.