Author's response to reviews

Title: Protocol for a systematic review of prognostic factors and prognostic models for the recurrence of venous thromboembolism (VTE) following treatment for a first idiopathic VTE

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Author's response to reviews: see over
Dear Kerry Dwan,

Re: Protocol for a systematic review of prognostic factors and prognostic models for the recurrence of venous thromboembolism (VTE) following treatment for a first idiopathic VTE

We thank you for your positive comments on our manuscript, and address your minor comments below.

1. Assessment of study quality – make clear which is Cochrane and which is Hayden et al.

We have now responded to your comment by highlighting which in which domains questions from the Cochrane tool will be used. The domains presented are broadly those presented by Hayden et al. for the assessment of study quality in prognostic studies, which is most appropriate to our review, and so elements of the Cochrane tool have been fitted into these domains.

2. Assessment of study quality – it is not clear what you mean by the final sentence in section a, are you assuming all studies with no protocol are high risk of bias. Where does this fit into your list above this?

We agree that this sentence does not read as intended, we do not consider that all studies which do not report a protocol can be considered as ‘at high risk of bias’, and as such we have removed this statement.

3. Evidence synthesis – be wary of selective reporting of adjusted versus unadjusted analyses.

This is an area to take caution as highlighted, and we intend to investigate the possibility of selective reporting of results as part of our quality assessment process, which covers a range of domains, and quality questions, including the reporting of prognostic factors, outcome measures and statistical analyses.

4. Evidence synthesis – more detail could be provided on the assessment of heterogeneity.

We believe that the level of detail provided to describe our investigation of heterogeneity, is sufficient within our protocol as shown on page 7-8, where we discuss;

“Heterogeneity will be quantified statistically (e.g. using I^2 and tau-squared statistics). For each candidate factor a 95% prediction interval will also be calculated for its prognostic effect in a single setting, in order to indicate how the effect may differ from the average in a different setting or population.

For each meta-analysis with sufficient numbers of studies (at least 10), sub-group analyses and/ or meta-regression will be used to explore whether the following pre-specified variables explain any of the heterogeneity: population parameters, outcome event, length of follow-up, and study quality (risk of bias).”

We also mention that we would not consider meta-analysis if the studies selected are too heterogeneous to consider synthesis at all;
“Where appropriate (for example, where there is some degree of homogeneity or it makes clinical sense), prognostic effect estimates (such as odds ratios, hazard ratios) will be pooled across trials”

5. Evidence synthesis – it is usually good practice to state how you will look at the different subgroups i.e. how will length of follow up be split?

We agree that this is important, and have pre-specified particular areas we intend to investigate on page 8;

“For each meta-analysis with sufficient numbers of studies (at least 10), sub-group analyses and/or meta-regression will be used to explore whether the following pre-specified variables explain any of the heterogeneity: population parameters, outcome event, length of follow-up, and study quality (risk of bias).”

The different subgroups will be split accordingly such as investigation high vs. low risk of bias, short-term vs. long-term follow-up, various outcome events (recurrence and other adverse outcomes), population parameters such as gender.

6. Evidence synthesis – you state you will perform a sensitivity analysis of study quality earlier and subgroup analysis here.

This is true and we have done so because we only intend to perform meta-regression/sub-group analysis when there is sufficient data to do so, i.e. when there are at least 10 studies in the meta-analysis. Where this prerequisite is met, subgroup analysis/meta-regression will be used to investigate the impact of studies at risk of bias directly. However, where this prerequisite quantity of data is not met, we are still interested in investigating the effect of studies at risk of bias on our meta-analysis results, and will assess this through a sensitivity analysis.

7. How will you deal with missing data?

We intend to investigate the potential causes of heterogeneity between the studies included in any meta-analysis, and this may also help to identify the possible causes of missing data. As part of the sensitivity analysis described on page 6, we could assess the impact of including and excluding studies with various levels of missing outcome or prognostic factor information.

In terms of prognostic models we mention on page 7, that we will be considering the completeness of data and the handling of missing data in our assessment of quality for studies which develop prognostic models.

We also plan to investigate the possibility of missing study data and its impact through the use of funnel plots to investigate publication bias.

We thank you again for your helpful comments,

Yours faithfully,

Joie Ensor