Author’s response to reviews

Title: Individualised prediction of psychosis in individuals with at risk mental states (ARMS): protocol for a systematic review of clinical prediction models

Authors:
Laura Jayne Bonnett (l.j.bonnett@liverpool.ac.uk)
Filippo Varese (filippo.varese@manchester.ac.uk)
Catrin Tudur Smith (cat1@liverpool.ac.uk)
Allan Flores (Allan.Flores@liverpool.ac.uk)
Alison Yung (alison.yung@orygen.org.au)

Version: 1 Date: 27 Aug 2019

Author’s response to reviews:

Dear Dr van Smeden,

Re: DAPR-D-19-00012 - Prediction of psychosis in individuals with at risk mental states (ARMS): protocol for a systematic review of prognostic models

Thank you for considering our manuscript. We have now revised the manuscript to take account of the comments of the referees. Point by point responses to the reviewer comments can be seen below.

We hope that these changes to the manuscript will be to the reviewers’ satisfaction.

Reviewer #1
1. It is not completely clear to me whether the authors will only focus on prognostic models (aimed at making individualized predictions) or are also including prognostic factor studies (with multivariable models, but focused on identifying predictors only). Please specify this more clearly in the aim, abstract and title.

   We have updated the title, abstract and aim to make it clear that we are interested in prognostic models which make individualised predictions rather than multivariable models which identify predictors only.

2. "The review will include any prospective studies" - why not also include retrospective studies, like registry studies? Or retrospective cohort studies?

   We have updated the protocol to include retrospective studies as well as prospective studies.
3. I am afraid the search strategy will miss important studies because the search terms for prognostic models are incomplete. I would advise the authors to take a look at existing search filters for prediction studies (such as https://doi.org/10.1371/journal.pone.0032844) and adapt the search strategy. Thank you for highlighting this interesting paper. Our search strategy was built using a 2016 peer-reviewed systematic review of prognostic models: https://bmjopen.bmj.com/content/6/5/e011190. Using our current strategy we identified 666 studies on 29th July 2019. Using the Ingui filter the number of hits on the same day was 580, and it was 627 using the Haynes filter. 363 hits were included using all three strategies. Only 45 studies were included in the Haynes and Ingui strategy, but not in ours. A review of titles suggests that these studies are not relevant to our review. Therefore, we plan to keep our search strategy unchanged.

4. Regarding assessment of study quality, the description of PROBAST is incomplete and only includes items of the fourth PROBAST domain on analysis (sample size, missing data, etc.). Are the authors planning to skip the other domain (predictors and outcomes)? Please specify this.

Apologies for our omission. We have rectified this within our revised protocol.

5. The meta-analysis methods are outdated. The DerSimonian and Laird model is not advised for meta-analysis of prognosis studies. Please read the papers by Debray et al. https://doi.org/10.1136/bmj.i6460 and https://doi.org/10.1177/0962280218785504) and update this section.

Our use of the term DerSimonian and Laird was incorrect for this meta-analysis. We have now modified the text to reference the methodology of both Debray and Snell.

6. If there are models available for this population and outcome, I do not think the development of a new model can still be justified, it would be much more appropriate to select the best model and validate and update this model (e.g. recalibration, extending the model etc.). This way, previous research will not be completely ignored and the authors are then really building on existing evidence.

Upon reflection, we agree with the reviewer. We have therefore modified the text within the Discussion section accordingly.

7. In the abstract, please specify 'appropriate guidelines' in the methods section.

We have updated the methods section of the abstract to specify the prediction model risk of bias assessment tool (PROBAST).

8. It would be helpful if the research aims are also described in the PICOTS format (see https://doi.org/10.1371/journal.pmed.1001744)

We have updated the research aims to more clearly include all elements of the PICOTS format.

9. In the description of the patient group (methods) it would be helpful to read something about when the model will be used (which moment in time) and are there any restrictions for using the model, i.e. specific groups of individuals for which the model cannot be used?
We have added a statement to the patient group section which explains that eligible prognostic models will include patients at risk of transitioning to psychosis, and thus recruited to the study at the time of the ARMS assessment. There are no groups of ARMS individuals for which any prognostic model predicting transition to psychosis cannot be used. Therefore, we have added such a statement to the protocol.

10. In 'primary and secondary outcomes of our review' - I wonder whether predictive performance is the only outcome the authors are interested in? I would also be interested in the quality of the developed models (in terms of: where appropriate methods used to develop the model) and the feasibility of using the model in clinical practice. I hope the authors agree with me.

We are in agreement with the reviewer’s proposed secondary outcomes and have thus added these to the protocol.

11. "Disagreements will be resolved through discussion or referral to a third reviewer and then a second subset of studies will be selected for checking" (page 7, line 5-10) - Please specify how this second subset of studies will be selected.

In line with a comment made by reviewer 2 we have now decided that two reviewers will undertake the data extraction. Therefore, the line about checking a second subset of studies has now been removed.

Reviewer #2
1. The purpose of the systematic review is generally described, but there is a lack of clarity on what specific question that review is trying to answer. The authors need to frame their question following the PICOTS. This would make it easier to assess the search strategy.

In line with a comment from reviewer 1, we have restated the aims of the systematic review according to the PICOTS – see “Research aims”

2. Context around the patient population being assessed with the ARMS criteria is needed. It is unclear why it is necessary to examine tools being administered after the ARMS criteria versus other tools that are similar to the ARMs criteria and may be used to assess initial diagnosis. There may be tools comparable to the ARMS criteria that have better predictive accuracy. This comment would be addressed in part by providing a specific question regarding what the systematic review is answering.

In line with a comment from reviewer 1, and point 1 here, we have restated the research aims to improve the clarity regarding the specific question this systematic review will answer. We agree with the reviewer that there are other measures that could be used besides the ARMS – basic symptoms for example. Indeed these alternative indicators of risk are comparable, or in some cases have slightly superior predictive power than ARMS. However, ARMS is the most widely used approach worldwide and forms part of national clinical assessment in the UK. Indeed, ARMS is a standard approach within the UK with the whole workforce being trained in the assessment of ARMS. Thus specific calls around prediction of psychosis focus specifically on ARMS. For these reasons we are interested in prediction models which assess a patient population according to the ARMS criteria. We have added relevant text to the introduction.

3. Based on the background, it appears as if the ARMS criteria have been validated. This model provides a baseline as regarding the predictive accuracy of transition to psychosis. The authors should consider including this in the systematic review; if not, a justification as to why it is not included is
needed and details of its predictive accuracy should also be provided.

ARMS criteria were largely developed using clinical insight rather than via statistical methodology. This is a well-known fact within the mental health literature. There is also increased recognition that better prognostic models need to be developed on top of ARMS (E.g. https://doi.org/10.1093/schbul/sbs060 and https://doi.org/10.1176/appi.ajp.2016.15070890). Therefore, the ARMS criteria is not a prediction model suitable for inclusion in our systematic review. Evidence regarding sensitivity, specificity, discrimination and calibration is also unavailable.

4. Why is 12 months considered the primary outcome? The predictive accuracy of the models may change depending on when the prognostic model is administered relative to the initial ARMS criteria assessment.

We have updated the protocol to explain that 12 months is considered as the primary outcome as this first 12 months is the highest risk period for psychosis onset and the time when individuals are most distressed and most likely to engage with services. Other time points will be considered as secondary outcomes.

5. Hand searches of previous psychosis transition systematic reviews and meta-analyses are described. Have any of these reviews summarized prognostic models? If so, this should be acknowledged and the current proposal should describe why this systematic review is necessary or adds value beyond the existing models.

We have described the two existing systematic reviews for prognostic models in ARMS patients in our updated protocol. We have explained that the systematic reviews were undertaken in 2017 and since then many additional relevant prognostic models have been published. We have also described that the publication of the PROBAST risk of bias assessment tool now facilitates thorough assessment of any included models and thus justified the need for the current planned systematic review. Additionally, the use of meta-analytic methods to summarise the performance of the eligible models also significantly expands work within previous reviews.

6. Please justify the data extraction strategy of using a primary abstractor. What is the size of the second subset of studies and will disagreements be checked in the second subset?

We have now reflected on our choice of using a primary abstractor and have instead decided to get two reviewers to independently undertake all data extraction. We have therefore updated this section accordingly and any text related to a second subset has been removed.

7. How will updated models of the same prognostic models be considered in the meta-analyses?

We have now added a sentence to the protocol to explain that if there are updated versions of the same prediction model identified by our review then only statistics for the most recent model will be included in the meta-analysis.

8. The discussion describes the importance of the review in identifying prognostic factors that are important and have consistent prognostic value; however, the methods do not describe how important factors will be identified. Please describe in the methods how a prognostic factor will be judged as being important and/or consistent?
In line with comments made by reviewer 1, and this comment, we have modified the discussion to focus on identifying models which are potentially informative when estimating risk of transition to psychosis. All references to factors with consistent prognostic value have therefore been removed.

9. Author should consider describing the ARMS criteria in a Box in the Background section.

Whilst we acknowledge that understanding ARMS criteria is fundamental to our systematic review and thus or protocol, we feel that the description we have provided within the patient group section is sufficiently in-depth to facilitate this. We do acknowledge that this description appears in the methods section of the manuscript rather than the introduction and have therefore added a note to the introduction, pointing people to the patient group section for further details of the criteria.

10. There is a typo in Patient group in the Methods section: "The review will include individuals …"

Thank you for spotting this – we have now rectified this mistake.

11. It is unclear whether the prognostic tools of interest are predicting first episode of psychosis or recurring episode.

In line with previous comments regarding the PICOTS, we have now clearly stated our aim as identifying models which predict transition to psychosis. This means predicting the first episode, and we have now added “(first episode)” to further improve clarity.

12. The term prognostic model is used throughout the protocol. This implies examining survival analysis-based prediction models. Will you be including models build using logistic regression, and if so, how will you compare them to the survival models?

We admit that the use of the term “prognostic” might be interpreted as examining a survival analysis-based prediction model. Therefore, we have changed “prognostic” for “clinical prediction” (or just “prediction”) throughout the protocol to ensure it is clear that we will be including both logistic and survival models.

Measures of calibration and discrimination should be reported for both logistic and survival models. Therefore, synthesis via a random effects meta-analysis should be possible. Subgroup analyses, looking at validation measures for logistic models separately to survival models will be undertaken if there is sufficient included studies to support this. We have updated the analysis of subgroups or subsets section accordingly.

13. Which reference management software will be used?

EndNote reference management software will be used. We have updated the study selection section accordingly.

14. How will the extraction form be piloted?

The data extraction form will be piloted on a 5% sample. We have added further details of this pilot testing to the protocol.

15. Will information on missing data be collected with the extraction tool?
We will be collecting information about missing data as part of the data extraction process. We have
updated the data extraction section accordingly.

Yours sincerely,

Laura Bonnett
Tenure-Track Fellow