Reviewer’s report

Title: Protocol for a Systematic Review of Prognostic Models for Recurrent Events in Chronic Conditions

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Reviewer: Jack Wilkinson

Reviewer's report:

The authors have submitted a protocol for a systematic review of recurrent events for chronic diseases. With the caveat that I have no idea whether or not similar reviews in this area exist, this sounds like an important topic.

I have some queries about the goal and design of the review, some of which could possibly be clarified through some changes to terminology used in the protocol. I hope the authors feel comfortable in any response to say if I have misinterpreted or am otherwise just mistaken - a great opportunity for me to learn from the discussion.

It took me a while to work out exactly what the content of the review would be. I think this is partially a matter of terminology. The title speaks of this being a review of prognostic models. I don't really know the answer, but I wonder if we should make a distinction between particular models (for a particular application: particular disease, setting, outcome, covariates etc) and methods for constructing such models?

What was confusing was that the title made me think I was going to read a review about the former, rather than the latter. But then the authors stated their aims to be things like to "evaluate existing methodology"(line 68) and to "provide insight into the development of new methods" (line 28, and abstract). I took the latter to mean that they will use the results to inform their own method development (for example, by establishing the state of the art). However, when we look at the methods of the review (inclusion criteria etc) it does indeed seem that the authors intend to perform a review of particular applications, rather than of methodologies per se.

I think this prompts the question of whether the decision to search for particular applications, rather than for methods and stats papers, will allow the authors to address their goal of identifying available methods? Presumably some of the relevant work will be methodological rather than applied, and I wonder if the search strategy and inclusion criteria employed by the authors will catch these papers (or indeed, if they are turned up by the search, would they be excluded if they didn't include a genuine model development on real data? - and would that be the right thing to do?)
I think my main concern would be that the authors might look at which methods have, as a matter of fact, been used, identify apparent gaps in the methodology on this basis, and to start doing methods work on that basis. Meanwhile, the same work may have been done (perhaps, tested and rejected) already, in the stats journals. I worry that if the authors do not pick up this literature as part of their review, they might waste time duplicating existing work.

Indeed, the authors say (line 14): "whilst various prognostic models for recurrent events have been applied in research, most are underutilised." Does this mean that there are many methods, but they haven't been applied in clinical research? Or does it mean that there are many models (developed for particular applications, particular settings, diseases, outcomes, predictors etc) that aren't used in clinical practice. If the latter, a natural question is, how do we know this? If the former (methods are not used to develop particular applications), then will these methods appear in a review of applications? I am raising these points so that the authors can consider whether or not their proposed approach will give them what they need.

Some other features of the protocol strike me as perhaps unnecessary for the authors' goals.

- The authors plan to extract performance measures for the various models (c-statistics or whatever). So we will end up with a review containing information on the performance of different models for different disease areas? Is this useful? If we want to conduct a review for clinicians and patients working in a particular clinical area, then shouldn't we have a dedicated review for each condition and population?

- Otherwise, if this really is a review of methodology, then isn't this a bit like, say, a review of methods for analysing crossover trials including the estimates of all the different treatment effects from the different studies (of different treatments in different conditions etc…)

- Similarly, why are we critically appraising the studies? Again, this would make sense if we were doing a Cochrane-style prognostic review of models for a particular health condition - the goal there would be to inform patients and clinicians about the quality of the evidence. Does this have any place in a methods review? Is it a good use of the authors' time?

- Thinking more about this point - hopefully the authors will not present this review as offering information for clinician and patient stakeholders. This would require clinical expertise. Moreover, restricting findings to studies that looked only at recurrent events (and not, for example, first event only) would result in a review containing an unusual subset of the prediction studies in that disease area, so overall conclusions are unlikely to be reliable in that regard.

- To be clear, I *don't think* that the authors do have these intentions, but some of the methods they describe would be more appropriate if they did - I'm raising these points so that the authors may reflect on whether or not their design is likely to address their objectives.
I think this protocol would really benefit from the authors being a bit clearer about what their objectives are (review of methods or particular models) and reflecting on whether they have selected the most appropriate methods to meet that objective. At present, a clear distinction is not made, and I am left somewhat confused about what the authors hope to achieve (and so, whether or not they are likely to achieve it). If the authors wish to identify the cutting edge in methods in this area, I would encourage them to move away from Cochrane-style methods for prognostic reviews and to consider conducting a methodological review. If, on the other hand, the authors want to review current practice (and to then comment on the state of play using their expertise of what could or should be done), then I think that is a good objective too. Again however, I wouldn't really see the value of quality assessment of studies (unless the authors wish to critique study design in this field? But not what they have described as their aims) or performance assessment of models for that goal. Finally, if the authors want to provide information for clinicians and patients (which is where it would make sense to look at study quality and model performance) then I would suggest that this probably isn't a great idea. Bespoke reviews would be needed for the individual chronic conditions, drawing on topic experts. I'm 99% sure that this isn't the authors intentions, as stated previously, but the current description leaves some room for the reader to doubt.

Jack Wilkinson

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