Reviewer's report

Title: Developing Methods to Assess Harmful Effects in Systematic Reviews

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Reviewer: Jacqueline Dinnes

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General
1. In general I thought this was a useful piece of work which should help to highlight the issues that reviewers and commissioners and of research need to consider when reviewing harmful effects.
2. The methods were appropriate, however I did find it confusingly written in several places and have made some suggestions below as to how this may be improved.
3. Not sure if the title really conveys the content of the paper – the paper reviews the team’s experience in the area and suggests areas that need consideration when carrying out such reviews but does not really ‘develop’ a method.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
4. pg 6 para 1 Study designs – RCTs – this paragraph was quite difficult to read – information in table form would help here I think (see below)
5. pg 7 para 2 – sentence beginning ‘This reflected the difference in the reviews’ objectives….’ – might be better to describe what they did first then comment on it.
6. pg 11 para 1 – advice from clinicians should be sought - presumably because researchers carrying out systematic reviews often don’t have sufficient topic knowledge to comment fully on the scope of a review before they’ve got some way into the actual work?
7. pg 12 para 2, first sentence doesn’t make sense – do you mean that debate continues over the usefulness of quality scales?

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
8. pg 4-10. the Results section would significantly benefit from a tabulation of what was found in the reviews, for example with the three reviews along the columns at the top, and the different stages of the reviews down the side. This would allow comparison across reviews and also mean you could focus on explaining the reasons for the approaches taken in each review in the Results section rather than having to convey a lot of similar information per review.
9. pg 4-5. Review objectives. You have included both a description of what was done and some discussion as to what perhaps should have been done for epilepsy and smoking cessation but not for schizophrenia. We don’t find out until page 12 that few studies were found for schizophrenia and that an alternative approach may have been preferable. Should include a description of the success/failure of the schizophrenia objectives as you did for the other two reviews.
10. pg 4-5. Review objectives – smoking cessation and epilepsy. For both of these reviews you state that more specific safety issues could have been addressed if the review questions had been more focused, but do not make it clear why this could not be done within the broad scope of the reviews –
presumably it was because too many studies were found to make it feasible? You should include a summary of the number of studies that had to be screened for inclusion, and the numbers that were actually included to indicate the scale of work undertaken for each review.

11. pg 7 para 2 – what is the difference between uncontrolled trials and prospective case series? A box describing what you mean by these, and also PEMs and PMSs would be useful

12. pg 7 para 2 – by how much did the schizophrenia inclusion criteria regarding size and duration reduce the workload? Have you missed anything relevant by restricting in this way?

13. pg 8 para 1 – you refer to a ‘huge volume of data’ in the epilepsy review – it would be useful to know how much

14. you don’t mention any problems in searching for this type of data - isn’t this a key component of the review process?

15. pg 10 para 3 - you argue that clearly defined questions are better than broad ones, but don’t really say how these should be identified – are you saying that a lot more scoping work should go into identifying the right questions? The schizophrenia review clearly benefited from review of a trial protocol, but these are known side effects and surely the point of doing a systematic reviews is both to see if adverse events occur more/less often than previously thought and to see if previously unidentified side effects are occurring? At the same time you say the schizophrenia review was good because it was focused, but later (pg 12) you say that perhaps it wasn’t focused on the right events, so not quite sure what approach you are advocating to deciding on a review question

16. pg 11 para 2. is your point that, where time and resources are limited, inclusion of nonrandomised studies should be directed by review of the data available from RCTs? You’re not making your point very clearly.

17. pg 11 para 2. you also say that non-randomised studies may be of ‘dubious quality’ but that does not mean RCTs will answer the review question adequately as you point out later, on page 13

18. pg 12 para 1. you say the smoking cessation review may have provided clearer conclusions if the data from RCTs had been reviewed first, but I thought that had already been done and that was why you didn’t include RCTs of effectiveness in your review? If you had looked at this data first, how would it have helped make the decision about which nonrandomised study designs to include? I’m afraid I don’t understand the logic. Was it that you would have selected fewer adverse events to look at and so wouldn’t have had to look at so many nonrandomised studies, rather than informing on which designs to include?

19. pg 12 para 2, third sentence. It is unquestionable that reviewers should think about what the quality assessment is for a priori, rather than carrying it out because they think they should.

20. pg 12 para 2, final sentence. Can you suggest how the discrimination of poor from better quality studies should be achieved? Your results section suggests that no such quality assessment tool is yet available. In the meantime, perhaps you should list the sort of questions that you found most useful?

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

None