Reviewer’s report

Title: Comparative effectiveness research: what to do when experts disagree about risks

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Reviewer: Richard Ashcroft

Reviewer’s report:

I found this to be an admirably clear and well argued paper, which advances the debate on the ethics of comparative effectiveness research. The argument about how to evaluate claims about relative risks of different interventions and competing evidence about these is important and well laid out.

My only significant reservation about this paper is that it quickly becomes clear that this paper is amongst other things a contribution to the debate about the SUPPORT trial, and continues arguments made with Lantos and others in connection with that trial. While the paper's analysis, I think, stands independently of the debate about SUPPORT, it does nonetheless function as a contribution to that debate and the reader is meant to evaluate the debate about SUPPORT with this paper's arguments in mind. That is the function of the case study: rhetorically, we move from a well understood case to the general principle, and see how the principle is illustrated by the case. Here, however, if is not clear that the SUPPORT trial is a "well understood case" and so in fact the rhetoric works in the opposite direction - we take the principles as understood, and are shown how they apply to SUPPORT. That would imply putting the SUPPORT case at the end, rather than at the beginning. So... I think the authors are being a bit "tricky" here. My observation is about rhetoric rather than logic, and as I say the logic of their argument about evidence, uncertainty and risk seems quite valid. I think the authors should be more explicit about the role SUPPORT is playing in this paper, and at the very least it should be mentioned in the abstract.

My other, minor, observation, concerns the practicalities of ERCs weighing up evidence. This is a line which has a lot of heavyweight support, notably from Iain Chalmers and colleagues, and at its strongest would imply that ERCs should insist on being shown a systematic review of the evidence for the different interventions before approving a trial. This is attractive, from a purist point of view about how these decisions ought to be made. But it seems quite impractical. (That said, I have always thought of SUPPORT that had the investigators looked at the results of other similar trials more comprehensively they might have concluded that SUPPORT was not needed, and even the ethical controversy about the SUPPORT trial had already been run once regarding similar trial in the UK some years before!) So I think the authors need to tighten up exactly what their policy recommendation to ERCs is here, in terms of how they should weigh the evidence up, and what burden of proof they should lay on applicants to show that their study is necessary and worthwhile.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes

**Does the work include the necessary controls?**
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Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:

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