Reviewer’s report

Title: Methodological challenges in European ethics approvals for a genetic epidemiology study in critically ill patients: the GenOSept experience

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Reviewer: Jennifer McCormick

Reviewer's report:

The authors have characterized the research ethics review process for a multi-national multi-site clinical trial within the European Union. While the findings are not surprising, it is critically important that studies like this are conducted to that there are empirical data supporting claims that many in research claim: that policies for research ethics reviews (or IRB reviews in the US) lead to procedures that can be burdensome to researchers (sometimes participants) and can slow or even prevent some research from happening.

I have a few comments that I think might improve the manuscript.

In the section European research: regulatory framework, I would suggest a bit more description of what it is consists of. CUrrently this section seems to describe only the European Clinical Trials Directive 2001. For example, it would be helpful for some readers to have a better understanding of whether every country each has its on regulations in addition to the EU Directives and if Countries don't does this mean that individual institutions within those countries can create and adopt their own research ethics policies or whether they merely adopt the larger EU policies. On Page six the authors state that the 2001 Directive was "transposed into the national laws of each EU member state" and it is not clear to me what "transposed into" means in this context. It also might be helpful to some readers to have a few sentences explaining why the key ethical issues you list are key ethical issues and how the Directive impacts each (if at all)>

In the methods section in the second paragraph describes how the collected data from the GenOSep study will be 'anonymized'. I encourage the authors to use the term 'de-identified' rather than anonymized. It seems that the de-identified data will still have links to identifiers. In addition, questions of whether any data can be completely anonymous are continually arising as more data bases are becoming 'de-siloed) (i.e. combined or used together) and advances in informatics occur.

In this same paragraph, i believe there is either an extra word (lawyer? perhaps) or the word lawyer is in the correct place and used follow the word academic.
In the results section... Table 2 is very nice. I would encourage the authors to consider including another, complementary table, that has nice aggregation of the various variables that are described within the text, e.g. number of ICU involved, Number and % of countries with a centralized RECs only, etc. It is essentially using the headers of Table 2 as the variables or headers of the proposed new table with some additions ,e.g. having both centralized and local RECS, having Both Lay and Legal on the RECS. I leave this to the discretion of the authors and editors. I don't believe there is any reference to Table 1 and this it isn't clear what value it adds.

More results section... Page 11 third paragraph describe the various reasons why applications were rejected. I would suggest moving that paragraph to follow the paragraph in Approval Outcomes since this is where you provide the quantitative data on acceptance/rejection. Tangentially, I would note that the applications rejected on the basis of the genes selected for study are interesting... REC reviews are typically about participant safety and wellbeing, not the science itself, unless that science causes significant risk to safety or well-being. Finally, at the top of page 10 the authors note that Hungary review took more than two years --- if the authors have any qualitative data for explanation as to why, that would be great to include.

More results section... at the bottom of page 11 through page 12 the authors include a discussion of additional challenges and issues. were these actually asked for in the survey and reported? if not, I would suggest that this discussion be incorporated into the discussion section; as it reads now, it seems to be more a discussion point than an actually result of the survey.

This comment has to do with some of the language used in the results section and the Discussion section. on page 11line 17-18, the authors use the phrase guidance at the national level; on page 10 line 13-14 the authors state that centralization of approval did not ... . To someone who is not familiar with how countries within the EU operate in terms research ethics review, it is a bit confusing --- if a country has national guidance does that mean centralized review too? or can a country have national guidance that is used by the local institutions. The first paragraph of the discussion gets at this too; the authors say that nine countries have national guidance --- Table 2 states 11 countries have centralized/national reviews. In addition, the authors state Italy has national guidance but in the table it is noted as a country with local review --- so the local review is with the national guidance? I am making perhaps a big deal out of this because of what I believe the stated question was: does centralized review improve the review process? this is different than centralized/national guidance or EU wide guidance vs national guidance. It seems that the survey asked about the review --- whether it was centralized to the national or a regional level or at each local institution, not whether the policies for Research ethics review were national or local. I believe adding a bit more to the introduction as suggested as well as making it more clear where the data for national guidance come from and how it relates to level of review, would clear this up. Also this first paragraph of the discussion - the last sentence mentions heterogeneity of the RECs make up; heterogeneity has the connotation of much more diversity than what is documented by the study. I would suggest re-phrasing to something along the lines of 'the lack of standardized membership requirements for RECS'.
Overall, I found this a rather interesting manuscript, given that I am from the US and the type of scholarship and work I do.

**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?**
If not, please specify which controls are required in your comments to the authors.

No

**Are the conclusions drawn adequately supported by the data shown?**
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Yes

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I am able to assess the statistics

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