Reviewer’s report

Title: Exempting Low-Risk Health and Medical Research from Ethics Reviews: comparing Australia, United Kingdom, United States and The Netherlands

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Reviewer: Nicki Tiffin

Reviewer's report:

This study presents a review of Ethics review exemptions for health research involving human participants, as permitted in Australia, UK, USA and the Netherlands.

The comparison of related legislation in these areas can be useful to highlight common trends as well as differences in different countries.

Specific Comments:

1. The title of the manuscript refers to "ethics reviews" and yet the paper only describes medical/biomedical research ethics and documents for the UK and Australia; whilst general research involving humans in US and Netherlands. It is unclear whether the documents are equivalent or whether there are other more general human research-related policies for a wider range of human-related research ethics in the UK and Australia. This should be clarified in the Introduction section to provide context for the comparison that follows.

   It is unclear whether the reviewed NHS (UK) document covers all biomedical research ethics in the UK, or only research involving NHS facilities/staff/patients? How does this relate to research undertaken outside the NHS? It would also be interesting to understand who (what governmental organisation?) is responsible for deciding the exemptions and providing oversight of their implementation.

2. There are sections of the Methods that should rather form part of the Introduction as they describe background information and not what was done in this analysis (highlighted in attached copy of the manuscript).

3. Fields in Table 1 require more information or clarification for several fields. Explanations or general descriptions are missing (highlighted in attached copy of the manuscript).

4. The results section can be better organised: It would seem more logical to first present each of the country-specific findings, and then describe commonalities/differences across the four afterwards.
5. It is unclear who determines whether data are sensitive and by what criteria, in the case of the Netherlands WMO.

6. In the Discussion section, it is noted that including more countries in the comparison would yield more diversity than currently discussed, but it is unclear why more countries were then not included in the analysis if they would provide some missing complexity and diversity? The reference to MSF practices is interesting but unclear how it relates to National legislation in different countries: presumably MSF must work within the legislative requirements of the countries in which it operates?

7. In the Discussion section, it is noted that criticisms of current practices in ethics reviews exist, it would be helpful to provide a few lines on what those criticisms are. In line with this, it would also be interested to understand why the Netherlands is changing legislation on exemptions: more information on what prompted the change and whether new legislation is likely to lead to fewer or wider exemptions.

8. In the Discussion section, there is discussion of the rationales for the exemptions, and their lack of clarity. In the Methods and Results, however, there is no analysis of rationales described or presented and it is unclear from which analysis the conclusions about the clarity of rationales is drawn.

General comments:

9. Genetic sequencing and genotyping are becoming increasingly used in research and health diagnostics. They also render all samples potentially identifying as they can be used to reidentify or match the sample to an individual. Furthermore, studies have shown how easily individuals can be re-identified from longitudinal clinical data even where identifiers are removed. It would be topical and interesting to therefore consider the definition of "identifying" - many efforts are now directed towards data perturbation and other approaches to prevent such de-identification because of the risks to personal privacy arising from re-identification - and how the different areas of legislation address this issue (or not).

10. Integral to the points about ethics review raised here, informed consent is a key factor in what research may or may not be done, and whether secondary use of data and samples can be undertaken. Whilst a detailed analysis of informed consent is not the subject of this study, it is unclear where the issue of informed consent sits within the context of ethics review exemptions and it would be elucidating to have this issue at least briefly discussed in the context of ethics review exemptions for research involving human participants.

11. Whilst proposing a standardised set of exemptions, it would be appropriate to consider how these might impact vulnerable populations, and whether those vulnerable populations might differ between different countries and legislative areas.
12. The "partial" and "proportional" ethics review approach is mentioned in the Methods and Discussion section but would be better articulated in the Introduction. This information could also be provided as a glossary in a new table which defining the different types of review and giving an example for each. This would be a useful resource for readers.

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