Reviewer’s report

Title: Model Consent Clauses for Rare Disease Research

Version: 0 Date: 22 May 2019

Reviewer: Raffaella Ravinetto

Reviewer's report:

This is a well-written paper, that addresses an important topic.

It may be surprising that, given the specificities of research in this field, there is no mention of engagement with patients (and/or patients' families and patients' associations), and of co-designing consent documents with them. I understand that this is outside the main scope of the Task Force meeting that already took place, but these elements could be briefly addressed in the discussion, and they should be noted in the limitations. Perhaps, it could be planned to discuss the Task Force findings (and, particularly, the wording and contents of the "clauses") with patients' representatives at a later stage.

On a different note, it is said that "to maximize the impact of these initiatives in contributing substantive amounts of quality data for research use, practical "standardized consent clauses" are essential to enhance data interoperability as well as to meet the informational needs of participants, ensure proper ethical and legal use of data sources and participants' overall protection". The concept of standardization may be questionable, since informed consent document should by definition be tailored to each specific research, and to contextual features, such as any local cultural concerns, possible differences in the level of research literacy, etc. It seems that here and elsewhere in the manuscript, including in the conclusion, it is more appropriate to talk of "model consent clauses" (which is the wording used in the title and methods) instead of "standardized consent clauses".

Concerning the section "Emerging Trends in Rare Disease Research with Consent Implications" (FIGURE 1), it is said at the first point that because of increasing complexity, "the study purpose and potential benefits must be clearly stated to manage participant expectations.". Limiting to "patients' expectations" may entail the risk of neglecting/overlooking aspects that are not covered by "patients' expectations", but that patients need to know to make an informed decision. It seems that it would be more adequate saying that "the study purpose and potential benefits must be clearly stated to manage participant expectations and to provide them with all the information needed to make an informed decision" (or equivalent wording). (Also note that point 1 is copy-pasted into point 2)
At point 3, I understand the logic for that "family members are often recruited using one consent document to address ethical and administrative challenges". However, it is not clear if this is a recommendation to use a common document and to do a joint consent interview: please clarify. Relatedly, may there be case where an "index patient" does not want to share the information about the disease with family members? Would there be provisions/suggestions to address such cases? Also related to family consent, are there any specific concerns/recommendations for minors' assents, and perhaps provisions to secure consent of those who turn major of age during the research. If these and other procedural aspects were not covered in the workshop, perhaps they may be addressed at a later stage?

On a minor note, when it comes to Generic Core Elements, it could be interesting to know whether this general structure is inspired by existing model templates for research consent (e.g. the one of WHO).

In some of the "sample clauses", it is added "[add permission option if needed]", which may wrongly suggest that permission/consent for other aspects is not needed. Perhaps the researchers mean that in these cases, and most likely for other clauses, in addition to general consent for the proposed research, there should be an additional opt-in/opt-out option. Please clarify.

Sample clause 9 on "risks and benefits" is not explicit on risks - what are the risks should be briefly developed.

The conclusions seem to suggest that the proposed template will (also) help to shorten the informed consent forms, a statement that does not seem to be substantiated by the text. I suggest dropping this in the Conclusions. This would not diminish the value of the paper, which is of proposing a template/model clauses to guide researchers to give to these patients all the information they need to make a decision, and that may be incomplete if researchers stick to "traditional" templates that do not consider the specificities in this kind of research.

The report of the Taskforce meeting should be provided as supplemental material.

A section on Limitations should be included.

**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.

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

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