Author’s response to reviews

Title: Model Consent Clauses for Rare Disease Research

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Fowzan Alkuraya (Reviewer 1): Nguyen and colleagues have risen up to the challenge of charting the course for unifying the language used in research consent forms in the context of rare diseases. As they eloquently explain, this is a timely subject given the growing appreciation of the importance of data sharing in rare disease research. The basic elements they propose to be included and the suggested language in the generic examples given are very well thought out and will likely help researchers develop their consent forms in a way that meets the special needs of the rare disease genetics community. I highly recommend this work for publication. I only have a few minor comments:
1- The Conclusion section of the Abstract is too long. I suggest you limit it to the part starting with "The model consent…".

Done

2- "core elements founds in" should be "core elements found in".

Done

3- Figure 1 looks nothing like a figure. Should it be called "box" or something similar?

Done – “Figure” has been changed to “Box.”

4- There seems to be an error in "Figure 1" where trends #1 and #2 are exact duplicates.

Done – duplication deleted.

Raffaella Ravinetto, PharmD, PhD (Reviewer 2): 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.

- Two out of the 15 Task Force members are representatives from different patient organizations. The article has been modified to highlight this fact.

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".

- Done – “standardized” has been removed and replaced with “model.”

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)

- Done – the sentence has been modified to include “provide them with the necessary information to make informed decisions.”

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 join consent interview: please clarify.

- Done – the sentence has been modified to clarify the point that family members may undergo individual consent “interviews” but are recruited under one single consent document.

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?
- These aspects went beyond the scope of the workshop. A “Limitations” section has been included to address this point.

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).

- The Core Consent Elements were adapted and developed from various consent templates (along with practical knowledge and experience drafting consent forms).

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.

- Done – phrase changed to “[add opt-in/out option if needed].”

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

- If risks are present, they were addressed under each specific rare disease theme (e.g., Audio/visual, collection of data, etc.). We did not include a general clause for “risks” because it did not meet our requirement for “specificity” in rare disease research but can be found in consent forms for other types of biomedical research. However, the section has now been modified to include only “Benefits.”

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.

- Done – reference to “lengthy” consent forms has been deleted.

The report of the Taskforce meeting should be provided as supplemental material.
- Done. The report has been included as “Supplemental Material.”

A section on Limitations should be included.

- Done – it has been included.

“Limitations:

The MCC Task Force recognizes the need for further guidance regarding consent procedures for the recruitment of minors (e.g., assent and re-contact at age of majority clauses) and the nuances pertaining to the communication of results to family members and between family members. These aspects were beyond the scope of the workshop.”