Author’s response to reviews

Title: Ethics preparedness: facilitating ethics review during outbreaks - recommendations from an expert panel

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Author’s response to reviews:

Editor Comments:

Thank-you for your submission. The reviewers agree that this paper highlights an important issue regarding ethics preparedness for research during outbreaks. You will see that Reviewer 1 has made numerous suggestions regarding the structure and emphasis of the paper. The paper makes some critically intended claims, but does not support them. In your revisions, please either make the paper more descriptive in tone, or (if you choose to keep the more normative terms) justify these and also make explicit any implied claims. We look forward to receiving your revisions.

REPLY Thank you for the opportunity to resubmit our paper, by clarifying the different issues raised in particular by the first reviewer. Given the substantial reorganization of the manuscript, it is not possible to submit a readable “track changes” version; however, we have highlighted the major changes in yellow. We hope that this will be acceptable to the Editors.
Reviewer reports:

Angus Dawson (Reviewer 1):

Thanks for the opportunity to read this paper. It reports on discussions and a series of recommendations from an expert panel looking at research ethics during outbreaks. My main comment relates to the fact that the purpose of the paper is not clear and there is a sliding around in relation to the focus. The structure of the paper could be improved to better reflect the overall aims. I take it that the purpose of the paper is to report the finding of the workshop (in terms of what topics were discussed and what was said in relation to each of them). However, there is also a set of recommendations that purportedly arose through a process of consensus building. I accept, and am guided in my review, by the explicit claim that this is a descriptive report and that it does not seek to engage in discussion of substantive ethical issues. (There is a lot to say about the substantive content - but that's for another day).

REPLY Thanks for these very useful comments. We have tried to address them when preparing our revised manuscript, as explained point-by-point below. In general, our aim is indeed to describe the findings of the workshop, for sharing with a broader public the recommendations that were developed at the workshop and that -we hope- could assist National (Research) Ethics Committees (N(R)ECs) when elaborating their own rules and procedures for research preparedness. Procedural guidance is still missing on how to build capacity of (N(R)ECs) themselves, and prepare them to provide a rapid, yet robust review of research protocols. Countries hosting and implementing research during outbreaks need greater support and guidance to develop practical and effective actions aimed at achieving this.

We believe that the timing of the paper is still appropriate, given our experience in the ongoing Ebola Virus Disease epidemic in the Democratic Republic of Congo, where no mechanisms have been put in place for coordination or collaboration between the N(R)ECs of neighboring at-risk countries.

REVIEWER What do you want to achieve in this paper? What's your aim(s)? At the moment this is unclear. Probably the clearest statement is at the bottom of p.8. where it is stated that 'the objective of the workshop was to identify practical processes and procedures related to ethics review that support national and international outbreak preparedness and response and facilitate the timely implementation of research'. * I think this is an aim not an objective (an objective is a means to achieving an aim).

REPLY We thank the reviewer for highlighting the important distinction between aim and objective. The sentence in the originally submitted paper, i.e. “The objective of the workshop was to identify practical processes and procedures related to ethics review that support national and international outbreak preparedness and response and facilitate the timely implementation of
research.” has been modified accordingly: “The workshop aimed to identify practical processes and procedures to facilitate rapid but robust ethics review of research proposed during an infectious disease outbreak; and to formulate recommendations that may assist the timely implementation of research to support national and international outbreak preparedness and response” (lines 80-83 of the revised version).

REVIEWER * This assumes that research is (always?) a good thing. This is never justified.

REPLY We did not assume that research is (always) a good thing, and we apologize if any wording in the original manuscript may have given this misleading impression. In fact, there is rather an overarching assumption that solid ethics review is essential for preventing bad or untimely research from taking place. In the background section of the previous version of the manuscript (now dropped, as suggested), we had recognized that doing research in outbreaks may harm individual and communities, e.g. by diverting attention and energy away from patient care, through humanitarian misconception, by breaching privacy and confidentiality, by failing to adequately and transparently data and bio-samples generated by the research, etc.

To make it more explicit, we have now modified the wording in line 69 of the originally submitted paper, i.e. “While the need to conduct research during outbreaks of emerging infections has long been recognized”, into “While the need to conduct pertinent, scientifically and ethically sound research during outbreaks has long been recognized” (lines 63-64).

Also, the sentence in the sub-chapter “Session 1 – Preparing RECs for outbreak response”, i.e. “The participants unanimously agreed that rapid review of research proposals and protocols should not risk reducing the quality of ethics committee decision-making nor lead to rushed or superficial decision-making” has now been completed as “THERE WAS AGREEMENT AMONG PARTICIPANTS THAT RAPID REVIEW OF RESEARCH PROPOSALS AND PROTOCOLS SHOULD NOT RISK REDUCING THE QUALITY OF ETHICS COMMITTEE DECISION-MAKING, NOR LEAD TO RUSHED OR SUPERFICIAL DECISION-MAKING, NOR LEAD TO THE APPROVAL OF POOR-QUALITY OR NON-PERTINENT RESEARCH” (lines 145-148).

REVIEWER I think the aim is to produce recommendations to assist relevant committees with the ethics review processes in the light of outbreaks etc. This is achieved via the objectives of: * Outlining five key issues; * Discussing challenges etc.; * Reaching consensus on what ought to be implemented…etc. I would suggest a clearer structure for the paper as follows: 1. Report on the background to the workshop (who was invited, aims etc) - i.e. current pp.8-9; 2. Report on what was the focus of the content and what was discussed (the five 'sessions') - i.e. current pp.10-17; 3. Report recommendations. The current 'background' section (current pp.4-8) should be
dropped and the abstract revised to reflect this. This proposed structure would make it much clearer that this is a descriptive report. The current background is mostly a mixture of vaguely worded summary claims, unnecessary detail and occasional quite contentious substantive normative claims (that are not defended - e.g. some things are held to be 'beneficial', 'reasonable' etc). This is not needed for the paper.

REPLY Thank you for this recommendation, which will improve readability and clarity of the manuscript. We have adapted it accordingly. The chapter “Background” has been eliminated, but some parts of it has been cut and pasted in different parts of the revised manuscript, in order to maintain clarity on why such a workshop was organized, and in particular on how the different sections relate to actual problems observed during outbreaks.

REVIEWER In reviewing the content, assuming the proposal above is adopted, special care should be taken to only use descriptive language (e.g. ‘The groups discussed…’) and not employ any normative language (e.g. '(N)RECs should…'). Or if normative language is used – reasons need to be provided why the authors might think such a claim should be made.

REPLY This has now been done, by eliminating normative language throughout the manuscript. However, the verbatim “recommendations” have not been modified, since these have been agreed by the workshop Participants and published in the ALERRT website.

REVIEWER One thing missing is that I could not see any reasons given for the focus on the five 'session' topics. Was this the result of prior discussion, a review of the literature, expert opinion, lack of time? Why were some other obvious topics excluded? Why were these ones included?

REPLY This is now hopefully better clarified in the revised text: “Noteworthy, substantive ethical issues were already being investigated by the Nuffield Council of Bioethics by means of a broader and inclusive call for evidence on “Research in global health emergencies: ethical issues” (http://nuffieldbioethics.org/project/global-health-emergencies). Therefore, building on other groups’ previous and ongoing work on substantive ethics issues, in this workshop, WHO and ALERRT placed the focus on ethics review processes and procedures. While the review of social science research during epidemics is an important area of enquiry, it was decided to focus on a limited number of issues relevant to clinical research, to allow for a pertinent and productive discussion within a restricted time frame. Based on past experience and review of literature, the workshop considered five priority areas requiring additional attention, and where work might be undertaken to facilitate rapid and sound ethics review during outbreaks: 1 - Preparing RECs for outbreak response; 2 - Pre-review of (generic) protocols; 3 - Streamlining the review of multi-country protocols; 4 - Interaction/Coordination between N(R)ECs and other research oversight bodies & public health authorities; 5 - Data, sample and benefit sharing.” (lines 89-101).
These limitations are now made more explicit, compared to the original text. The revised text now reads: “The work that led to the development of these recommendations presents some limitations. As noted above, in view of the time constraints, the number of issues had to be limited, and we could not discuss other aspects of ethics review that could benefit from additional procedural guidance…..” (lines 414-416).

REVIEWER Something needs to said about the building of consensus. How was this done? Was it done formally using some variant of a Delphi method? Why is *consensus* as such the focus? There is no discussion of these methods.

REPLY We recognize that we have used the wording “consensus” in a slightly inadequate way. For instance, when we said it lines 191-2 of the initially submitted paper that “The workshop included plenary presentations, panel discussions and small groups discussions around specific issues and challenges, with the aim of reaching consensus on the five identified themes”, we were referring to the informal decision-making procedure within the group, during the meeting. We did not mean that we implemented formal consensus development, nor evidence-based development or explicit guideline development. For the sake of clarity, the sentence has now been modified accordingly: “The workshop included plenary presentations, panel discussions and small group discussions around specific issues and challenges, with the aim of generating agreement among the participants on the challenges posed by the five identified themes, and practical actions to address those challenges.” (lines 102-104).

On a similar line, the wording “consensus” has been changed into “agreement” throughout the revised manuscript.

REVIEWER I take the point that the focus is here on process. However, procedures still require justification - there is an implicit set of values at work here and they are not made explicit or justified. For example, the assumption is that being transparent etc is easy to do, uncontentious, and should be done. This is hardly obvious.

REPLY We did not mean to assume that being transparent is easy to do, and we apologize if our wording may have given this impression. In the revised manuscript, we have tried to make more explicit the (ethical) values (accountability, transparency, consistency and efficiency) underlying the suggested processes. Thus we now clarify that “HAVING A SOP OR FRAMEWORK WOULD PROMOTE CONSISTENCY AND EFFICIENCY OF THE REVIEW, SINCE THE PROCEDURES WOULD BE PRE-ESTABLISHED, AND COULD BE RAPIDLY IMPLEMENTED. IN ADDITION, IT WOULD PROMOTE ACCOUNTABILITY, BY MAKING PROCESSES CLEAR AND TRANSPARENT.” (LINES 155-157). At the same time we have given examples of situations in public health emergencies where transparency as a value
may be harmful, and there is a need for caution. Finally, we now provide a rationale for why transparency in the work of ethics committees may be/ is an important value: “WHILE IT IS RECOGNIZED THAT THERE MAY BE LEGITIMATE REASONS FOR WITHHOLDING CERTAIN TYPES OF INFORMATION IN ANY PUBLIC HEALTH EMERGENCY (FOR INSTANCE, IF IT JEOPARDIZES NATIONAL SECURITY, UNNECESSARILY VIOLATES CONFIDENTIALITY AND PRIVACY, CAUSES STIGMATIZATION, OR MIGHT LEAD TO BEHAVIOURS RESULTING IN INCREASED SPREAD OF THE DISEASE) (30), TRANSPARENCY REMAINS OF PARAMOUNT IMPORTANCE IN THE CONTEXT OF ETHICS REVIEW, AS THE N(R)ECS MAY PRIORITIZE RESEARCH ABOUT THE OUTBREAK, WHICH COULD NEGATIVELY IMPACT OTHER PROJECTS. RAPID SHARING OF INFORMATION COULD ALSO RAISE ETHICAL RISKS IN RELATION TO USE OF DATA. THEREFORE, EFFECTIVE MANAGEMENT OF PUBLIC HEALTH EMERGENCIES DEMANDS OPEN AND TRANSPARENT PUBLIC COMMUNICATION BY N(R)ECS, AND THE UPFRONT DEVELOPMENT OF SOPS OR FRAMEWORK WOULD BE ONE SUCH STEP”. (lines 157-165).

REVIEWER It could be clearly stated what the proposed force or status of the recommendations is supposed to be. Is this general advice? Or is it a proposal for further discussion? Or are they a firm and formal proposal for global action to be implemented immediately?

REPLY For each of the recommendations, still listed in Table I in addition to being now presented in the third (new) section of the revised manuscript, there is a corresponding suggested action, which indicates what we recommend would happen with each recommendation, namely (1) holding regional workshops to draft the model SOP, (2) draft a paper on terminology of the pre-approval, (3) WHO to lead a process for a consultation on “multi-country rapid ethics review” and work on the scope of “other similar emergencies”, (4) specify in the model SOP (point 1) the procedures for communication, (5) specify in the model SOP (point 1) the requirement for submission of preliminary and full data and sample sharing plans, and (6) to do an inventory of resources related to MTAs.

We have clarified in the last paragraph that these recommendations have been made by a group of multi-country/global experts with the expectation that N(R)ECs supported by WHO, relevant collaborative research consortia and external funding agencies (may) work towards bringing these recommendations into practice (lines 422-431).

REVIEWER Why is there a list of substantive ethical issues in the first paragraph of session 5 and not elsewhere in the reported 'sessions'? It is far from obvious to me that these are the sum total of relevant ethical issues and they have a suspiciously 'usual suspects' feel to them. Again,
there is a danger of commitments in relation to substantive ethical claims here - whether explicitly or implicitly - and this needs to be avoided in a descriptive paper.

REPLY Following the reorganization of the paper in line with the reviewer’s suggestions, most sessions are now introduced by a general paragraph that presents the topic.

We recognize that this introductory part remains significantly more developed for session 5, also in the revised version of the paper. We think that this reflects the longer/deeper discussion and reflection that took place at the workshop, in turn probably due to the relative “novelty” of these issues for ethical reviewers (indeed, it is also stated at the end of this session that “This was an area where Participants felt there was a need for more capacity strengthening for (N)RECs members”). (lines 361-363).

Primus Che Chi (Reviewer 2):

REVIEWER *Lines 332 - 334: It would be important to highlight that rapid sharing of new information arising from research will have a potential to influence public decision making only if the relevant national and local authorities/stakeholders have the skills and competences to incorporate/integrate such information into decision making.

REPLY We are a bit hesitant to include this comment in this section, since it was not explicitly mentioned by the Participants as such. Therefore, we included it at the very beginning of the revised manuscript, in the introductory part: “Rapid sharing of new information arising from research has a potential to influence public decision-making, provided that relevant national and local stakeholders have the skills and competences to integrate such information into decision making.” (lines 62-63).

REVIEWER *While the recommendations and suggested actions are important, the authors should equally highlight the need to ensure that NREC or relevant authorities follow-up to ensure that proposed benefit sharing plans in submitted proposal are respected by researchers, post-approval (cf. Recommendation 5a).

REPLY As above, we are hesitant to include a statement which did not clearly emerge from the workshop. However, we added the following when discussing Limitations: “In addition, we did not discuss on if/how (N)RECs may proactively monitor implementation of reviewers’ recommendations by researchers and sponsors.” (lines 419-420).
REVIEWER * Inconsistencies in the referencing (need for consistency): i. Some lists of authors include "and" before the last authors, while others don't. ii. Some have a comma (,) after the last author initial before "et al.", while others don't.

REPLY Thanks, this has now been harmonized.