Reviewer’s report

Title: Ethics review of studies during public health emergencies - The experience of the WHO Ethics Review Committee during the Ebola Virus Disease epidemic

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Reviewer: SEEMA SHAH

Reviewer’s report:

Dear authors,

I was glad to have the opportunity to review this interesting paper. The idea to draw lessons from the WHO's experience in reviewing protocols during the recent Ebola virus disease epidemic is inspired, and this piece has the potential to make a significant contribution to the literature and future ethics review in outbreaks of emerging infectious diseases. The authors do a nice job of drawing from their experience, identifying some significant challenges of this kind of work, laying out the major ethical issues, and citing the relevant literature. However, the paper is not structured in a way that makes its contributions as clear or well-supported as they could be. Accordingly, I would recommend that the authors modify the structure and argumentation of the piece in several ways that I will describe below.

First, the body of the paper largely focuses on substantive ethical issues (e.g., whether forgoing a placebo control was justified in trials of treatments for Ebola virus disease and for vaccines, if pregnant women and children should have been included in these trials, etc.). However, the recommendations at the end of the paper largely focus on process issues that seem to be designed to speed up review. It would be helpful if the authors separated substantive from procedural issues in the paper, and made a tighter connection between the problems they saw in each area and their recommendations.

With regard to the substantive issues, the recommendation for a global consultation on the inclusion of pregnant women and children in trials conducted during outbreaks seems to be the only one tied to the substantive arguments. None of the recommendations directly address the issues about study design, and it is not clear if the authors think that anything about the review of study design should have been done differently. It is possible that more streamlined review and exchange of information across different review bodies is meant to allow for more thorough scientific review and to ensure that information is shared with ethics review committees, but such an idea is not spelled out. The authors should also acknowledge that there are important trade-offs that were made, but note that they took a defensible position by approving the trial designs presented. An additional article that would be helpful to cite on this point is: Rid A, Miller FG. Ethical Rationale for the Ebola "Ring Vaccination" Trial Design. Am J Public Health. 2016 Mar;106(3):432-5.

Alternatively or in addition, they could bring in other evidence or arguments to support their recommendations. For instance, the Guinea ring vaccination trial was complicated by the fact
that, in my understanding, the study team changed the primary outcome to get definitive results. (See Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!).Lancet. 2016 Dec 23. pii: S0140-6736(16)32621-6.) It is possible that speeding up research review could have helped start the trial earlier in the epidemic when the risk of infection was much higher, leading to more interpretable results. This would be a good motivation for the ideas the authors have for speeding up research review.

With regard to the specific recommendations, some of them are good ideas, and others are less well-supported or less clear about how they would be put into practice. As I have noted, there is also a disjunct between the body of the paper and these recommendations. First, the argument that investigators should take time to make sure their submissions are internally consistent is a little misplaced, at least without more information. For instance, if the inconsistencies that held up review were minor or inconsequential, then they should not have held up review and the problem was with the reviewers. If the inconsistencies were about major issues of ethical importance, only then would it be important for investigators to spend valuable time fixing up the protocol instead of moving the research forward in other ways.

Second, the idea for joint ERC is a good one but subject to several practical and potentially ethical issues. It would take time to constitute such a committee from scratch, and institutions in the U.S. might be concerned about legal liability if they were to rely on this committee rather than their own IRBs (or a standard IRB/ERC). Someone would presumably have to vet the membership of this committee to ensure it meets the standards in some or all research regulations that would apply.

Third, the idea for a joint DSMB and Scientific Advisory committee is an interesting idea, but challenges could arise if the interim data from one trial calls into question the conduct of another, and if the data are considered confidential or proprietary. These challenges might also be a problem for the idea that there should be "direct information exchange between the chairs of advisory, safety review and ethics committees." For an article on this issue, see: Shah SK, Dawson L, Dixon DO, et al. Should sponsors and DSMBs share interim results across trials? J Acquir Immune Defic Syndr. 2011 Dec 15;58(5):433-5.

Fourth, the notion that there should be more than standard support for investigators by ethics committees sounds good in theory, but it is unclear what this means in practice. More specific suggestions would be helpful here.

Finally, the authors put a lot of weight on improving informed consent documents as a way to build trust. The available data do not suggest that many things other than extended time for discussion and test/feedback approaches can really improve understanding, and I don't know of any data that measures whether improving informed consent can build trust. See Flory & Emanuel, JAMA 2004; Nishimura et al. BMC Med Ethics 2013. I suspect the emphasis on improving informed consent documents in the context of research on Ebola virus disease during an epidemic is misplaced, and better community engagement and social mobilization is really
important. If the authors really think improving informed consent could be valuable, they should cite literature in support of this claim.

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Yes

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