Author's response to reviews

Title: Ethical challenges for international collaborative research partnerships in the context of Zika in the Dominican Republic: a qualitative case study

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Reviewer reports:

Reviewer #1: This is a well written paper, that timely addresses an important topic in international medical research. The attention for some ethically important aspects such as capacity building and community engagement are especially important. Some recommendations may be formulated for improvement of the paper:

- In the Methodology, it should be explained how the sample size was determined. At lines 142-145, it is not clear if the contact with the key-informants was preceded by a contact with/agreement by their institution (please clarify). Concerning lines 147-8, please briefly clarify if information on "health research, policy, education and practice and from local to international funding agencies" was collected based on formal search (or otherwise, briefly describe how the documents were selected).

Authors: The sample size was determined by selecting one single participant from each organization that was previously identified. We did group interviews when the institution asked for the inclusion of more than one participant. In lines 197-201 you will find the new description on how sample size was determined. The contact with the informant was preceded by a contact with the institution. They designate who was going to be interviewed. We realized that previous lines 147-8 where rather confusing, since in plain language we did the usual literature review looking for national and international papers, and documents related to our topic. As the literature review is expected, we omitted this info from the actual paper since did not add something new.
- In the Ethics Section, please add a statement about protection of participants' confidentiality. It would also be useful to explain if/at what stage the recorded information was coded or anonymized.

Authors: Added in line 223-4.

- It may be worthwhile to remind, either in the Introduction or in the Discussion (or both) that the Zika epidemics was preceded by the Ebola outbreak in West Africa; and to shortly elaborate on whether the lessons learned in the Ebola epidemics have/have not informed the management of the Zika epidemics, in particular concerning research's planning, priorities settings, governance. To date, the Ebola outbreak is only briefly mentioned at lines 88-89.

Authors: In the revised version, we have extended the references of the Ebola outbreak in West Africa. Mostly in the introduction Lines 96-102. Also, we reflect in discussion, line 501.

- The recommendation at lines 455-6 (that ECs should revise collaborative agreements, to ensure that they are fair) is very interesting and may deserve some more elaboration: would ECs need some more specific training, to get familiar with critical elements such as benefit-sharing in international research? Should this be done at national level or regional level (to ensure a common approach and understanding but the different ECs)? …. In addition, given the identified weaknesses concerning community engagement, the Authors could consider recommending that ECs would also look into "community engagement" aspects when revising protocols.

Authors: We have extended the discussion on RECs responding your very useful comments. We did not realize that in fact ECs could play a vital role reviewing such collaborative agreements and we have come up with some ideas with the hope that they are acceptable for most ECs. Definitely, training and more interactions between ECs could be helpful for them. Please, find in our discussion section these and other considerations at lines 580-606.

- Lines 439-45: these findings may lead to further reflection on other critical aspects, for instance unbalance in authorships, and also on ethical issues related to data sharing and biobanking: if data and/or samples repository will be located in third countries instead of the outbreak countries, there is a clear risk of disempowering the local research community. Even if these aspects were not covered at the time of the survey, the authors could consider planning further analysis/research, e.g. within the working group mentioned in the Conclusions.

Authors: We include this comment in the paper (Introduction Line 592-594) as one of the possible aspects to review by ECs.

- The focus of the paper is on the Dominican Republic, but it could be useful to discuss whether public health-oriented research agendas for outbreaks could also be discussed and agreed at regional level.

Authors: Recently a paper was published by Aarons D. (2017) regarding a model for collaboration between ECs in emergency situations. We found interesting to include this discussion. Also, in the paper we pointed out that WHO / PAHO play a role setting the research
agenda in the region and worldwide in the case of Zika outbreak. We hope that this point that research agenda was in fact regional is clear enough in our writing.

- Pratt and Hyder published in 2016 a target article in the Am J of Bioethics (Governance of transnational global health research consortia and health equity. AJOB 16(10): 29-45), which focuses on global health research partnerships and in particular on how their governance should be structured to advance health equity. It was followed by a number of replies (Pratt & Hyder. Response to Open Peer commentaries on "Governance of Transnational Global Health Research Consortia and Health Equity", AJOB 2017 17:1, W4-W6). It is suggested that this set of papers may be considered to support some aspects of the Discussion.

Authors: Authors are in debt with this suggestion. We learned a lot from this articles and hopefully we achieved a higher level of discussion. However, we need to mentioned that we have made an extensive literature review before writing the first version of the paper. We found out that the issue of not including these important literatures was that we had a hard time getting access to them. Even when asking for help to our librarians in two different universities, it was quite difficult even for them. In the paper, we mentioned that this one of the very basic issues we confront in our country, access to scientific literature.

Reviewer #2: This paper addresses important issues regarding the design, conduct and funding of research in the developing and/or under-resourced countries of the world. The work is in the setting of urgent health crises, but is potentially generalizable for not only clinical research but other types of international collaborative research projects. The approach of the authors is to use semi-structured interviews yielding qualitative data, and to work with both individual interviewees as well as focus groups. The authors cite a focus on ethics as the organizing principle for their investigation and write that "the term collaborative research denotes a requirement that the clinical research be considered ethical".

Although I am very sympathetic to the subject and the importance of both the highest ethical principles in clinical research and the need for collaborative research as a means of addressing critical problem efficiently, especially in low resource environments, this paper has significant deficits. With significant revision, however, it is likely to meet standards for publication.

First, there is a lack of definition in the paper and a failure to set the scene- What ethical principles are the authors addressing, in specific; Why is this methodology suitable to do so?; What is the research funding environment like in the DR and what types of collaborative research are ongoing there? What is the currently existing research infrastructure and to what extent is it supportive of collaboration?

Authors: We had worked extensively in reviewing, clarifying and extending our thoughts to make them more clear to our intended readers, as our reviewers. As a consequence, we change the structure of the paper. Health equity, justice and fairness are the ethical principles we bring into the discussion. Now you will find at lines 140-67 an extended description of the DR environment not only in terms of health research collaborations but on Science and Technology and basic health indicators.
R: The second set of questions have to do with the sample: why were the interviewees chosen for invitation and who was not invited (e.g., other agencies, NGOs, academics, etc.) and why?; was there agreement or discord among the interview responses?; and what categories of stakeholders were not included at all and why (e.g., mothers, pediatricians, vector control, etc.)?

Authors: Institutions that make up the structure of a National Health Research System (as defined by WHO) was the target population of the study; not individuals. Based on this, research stakeholders were clearly defined under this conceptual basis. So, we included various sector government, NGO’s, academics, agencies, medical societies, health care providers, patients (represented by a patient organization). All of them related having health as their core mission. We almost achieve to include every agency working on health, some returned our invitation letter stating that they do not work anymore on health. Our sample is highly representative of research stakeholders in the Dominican Republic.

In that way, it was difficult to encounter differences or similarities between interviewees. Basically, they were concerned with some specific issues related with their institutional mission. For example, with NGO’s, providers and patient group the topic most relevant was related to community engagement. With health researchers, they were concerned with obtaining funding, fairness in contracting, etc., and so on. It was kind of difficult to see a common line of discussion in our sample.

Who were not included in our sample? We did not include mothers, pediatricians, vector control, etc., because we were concerned mostly with those participants involved at the institutional and policy level side; not individuals and each participant should represent an organization within the health sector with a clear link with health research.

R: Third are questions about data analysis and portrayal - the paper would benefit from more detailed discussion of how the 5 domains were arrived at, some semi-quantitative analysis of the responses if possible, and a linkage between the data and the ethical principles they are ostensibly discussing. Issues having to do with equity, participation, resource allocation, fairness, capacity building, etc. are present in the discussion and ought to be brought out more clearly. Distinguishing between the ethics of immediate response to crisis and the ethics of clinical research is important and, in this paper, is subject to a confusing conflation.

Authors: We could not focus on semi-quantitative analysis for the reasons mentioned before in the previous question. The variety of responses did not support the semi-quantitative analysis. We extended the results and discussion on the 5 domains.

A clear distinction between the research ethics in emergency situations and the ethics of clinical research is not always present in our paper. This is due to the nature of the responses of our interviewees. Most of the time they were responding in general terms, not focusing on emergencies context. We could not get rid of that in our analysis. The scope of the findings could be extended to health research broadly defined.

R: Finally, although it may be beyond the scope of the research, it does appear that the authors have ideas of how this can be done better. I wish they would say so more explicitly.
Authors: In this version, we have worked hard to be more explicit in our approaches.