Author’s response to reviews

Title: Seeking consent to genetic and genomic research in a rural Ghanaian setting: a qualitative study of the the MalariaGEN experience

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Author’s response to reviews: see over
Dear Dr. Henderson,

Thank you very much for your email of October 28th. We are very pleased that the reviewers are so supportive of this article and have detailed below how we have responded to all of their helpful suggestions. We have also noted our responses to your editorial comments.

Referee 1

Major Compulsory Revisions

Tindana, Kass & Akweongo’s 2006 study based in the same two communities is an important foundation for further ethics research in the Kassena-Nankana District. Although this is referenced in the third paragraph of the Introduction (reference 11), it is not referred to again in the Discussion. I feel the authors could explain more clearly how the present study builds on this research. The earlier study clearly established preferred routes for permission-seeking, the vital role that trust in NHRC/VAST plays, preferred consent processes and issues relating to the benefits of research. The present study reiterates some of this (the consent process, routes of permission-seeking, trust in NHRC/VAST), which is fine, but where the present study goes beyond the earlier one, this should be emphasized in the Discussion. Perhaps more importantly, the areas that are new in the present study should receive even more attention: difficulties related to enhancing community understanding of genetics and genomics, the ethics of requesting consent in an emergency setting and issues relating to international data sharing. These are new areas, explored for the first time in these communities, and more could be made of them. For example, mothers agreed that it was acceptable to take blood samples prior to fuller discussion of the research project. This is hugely important information.

1. We agree with the reviewer’s comments on the need to link our current study to previous studies conducted in this setting. We have addressed these comments by including the following paragraphs in the introduction to highlight the new areas explored in this study:

*Previous studies conducted in the KND on informed consent and community engagement [11,23] have described the role of traditional decision-making structures in the consent process, the role of trust in sustaining researcher-participant relationship and some of the constraints of contextualizing current international requirements of informed consent. The focus of this current*
study is to provide insights into specific issues arising when seeking consent to genetics and genomics research in a low-income context, to identify examples of best practice in enrolling participants in this context, and to identify areas that may need further research and discussion in this rural setting.

2. We have also revised the discussion on page 21 with the following paragraph:

Determining best practice in seeking consent given the constraints faced in various research contexts will always be a challenge for researchers. In the KND, previous studies [11, 23] have reported some of these constraints which relate to enhancing general understanding of research. Our current study indicates that in the context of genetics and genomics research, which involve highly scientific research methodologies, the consent process can be further complicated by the difficulties with making the scientific concepts comprehensible to staff seeking consent and to research participants.

Another constraint highlighted in this study is the conduct of research in emergency situations which may make the traditional process of seeking informed consent impracticable.

3. Further down in this same section, we have added the following:

For example, we found that trust and the expectation of health benefits were still important in the mothers’ decision to enrol their children in the MalariaGEN study.

As the biomedical research enterprise moves more into these highly scientific research methodologies, such as those involved in genomic research, there may be the need to focus more attention on other protection mechanisms such as community engagement and strengthening the review processes involved in these types of research projects.

We also believe that further research is needed to address the ethical issues arising in future uses of stored samples and getting a deeper understanding of the meanings behind participants’ responses to these issues.

Reviewer’s comments

Similarly, there is a general view that researchers could conduct ongoing studies with ‘leftover’ samples without seeking additional permission from donors. This is more nuanced, and needs further exploration, but again is very relevant to many other studies that may consider this approach.

4. On page 24 of the manuscript we had indicated that one of the limitations of our study was how we ‘used questions about further research on identifiable blood samples as a proxy to begin exploring concerns about future research using genomic data’. Based on the responses we received from participants, especially the mothers, we believe that most of them have ‘little conception of the potential downstream uses of genomic data generated from their samples’
5. We also agree with the reviewers that further exploration is needed to understand the meanings behind these responses. One of us (PT) is doing this through another research project.

**Reviewer’s comments**

Giving more weight to some of these issues is likely to require re-structuring of the Introduction and Discussion (and also be reflected in the Abstract).

6. As suggested we have re-structured some sections of the discussion and introduction to reflect these revisions.

**Minor Essential Revisions**

A. Please be more precise in the penultimate sentence under ‘Study site’. ‘... with up to 57% of the population having never been to school’ could mean only 1% of the population ...or 56.9% of the population. The Kassenas and Nankanis may differ in school attendance; if so, please give a precise figure for each group.

7. We have obtained the current figures of the literacy rates in the KND and have revised this section as follows (separate literacy figures for Kassenas and Nankanis were not available):

*The current literacy rate in the KND is 59%.*

B. Under ‘Sampling’, the idea of mothers of cases and controls is introduced rather abruptly. It would be useful to add a sentence into para 5 of the introduction (where the MalariaGEN project is mentioned) to briefly explain the study design.

8. In response to the reviewer’s comments, we have revised the paragraph on page 4 which explains the design of the main MalariaGEN project:

All of these factors were relevant in the recruitment of participants into a case-control study to identify genetic factors influencing susceptibility to severe malaria as part the Malaria genome epidemiology network (MalariaGEN) consortial project 1 (see Table 1) ([www.MalariaGEN.net](http://www.MalariaGEN.net)). Cases were children admitted to the Navrongo War Memorial Hospital with diagnosis of severe malaria; and controls were healthy children from the community.

C. (Minor Issue not for Review) This is probably very pedantic, but I was taught that data are plural. This comes up in the Methods (para 1), under ‘Data collection’ (first line).

9. We were taught this as well and are embarrassed it slipped through the copy-editing – it has now been corrected.

3. **Discretionary Revisions**

One very interesting area that is not fully explored is that of conveying genetic concepts to groups with little background in science. The authors note the difficulty of getting across ideas about malaria genetics towards the end of the section ‘Enrolling cases in the hospital’ and throughout the section ‘Knowledge and
understanding of genetic and genomic research’. Views of fieldworkers are quoted, but I wonder if mothers’ conceptions of ‘familial-ness’ were explored at any stage. It would be valuable to know if there is any community familiarity with issues of heredity that are expressed in terms other than those about ‘the blood’. If the authors have any more information on this, they may wish to consider adding it.

10. This is a very important omission and we are grateful the reviewers have raised it. We have now addressed this comment on page 17 of the manuscript:

We found that most mothers could understand a discussion about the genetics of malaria because they related genetics to heredity based on their experiences of diseases that run in families. However, extending this to the broader concept of genomics was more challenging. It was particularly difficult to extrapolate mothers’ knowledge of heredity to explain genomic research where such research involved population level sampling that does not necessarily involve families affected with the disease under study.

Referee 2

Reviewer’s comments- 1. The authors have made some comments at the results section that should be included at the methods or the discussion sections: The first subsection (the consent process) describes different ways used at the MalariaGEN study to provide the information. This should be described at the Method section.

11. We thank the reviewer for this suggestion. The following paragraph has been moved to the Methods section. Further suggestions for moving text from the reviewer are detailed in the order received below with our responses.

During the MalariaGEN study information was provided to prospective participants in three different ways. These were a community engagement process prior to the initiation of the study, a two-stage enrolment process for mothers or caregivers of children with severe malaria who presented at the hospital and an enrolment process at the community level for matched controls (as illustrated in Figure 1).

- Please clarify whether blood samples were collected for research purposes or were first just taken for clinical purposes.

12. Again, we are very grateful to the reviewers for these insightful comments which have helped us to improve the manuscript. We have now rewritten some sections of the results and discussion. We have added the following sentences on page 11:

A single blood draw was made for the purpose of clinical tests and DNA extraction for the research.

13. As well as on page 12:
Blood for patients who did not meet the research criteria or whose primary care giver declined consent was only used for clinical purposes.

Reviewer’s comments- The subsection “Knowledge and understandings of genetic and genomic research” begins with an interpretation of a result (differences at the level of understanding between research staff). Any interpretation of the results should be included at the discussion to make a clear distinction between the results and the possible reasons for these findings.

14. The interpretation of results has been moved to the discussion section.

Reviewer’s comments- The subsection “Sample use and data sharing” refers to the results from a study carried out in Uganda. Again the comparison of the results from other studies should be included as part of the discussion of this research.

15. This has now been addressed in the discussion section.

Reviewer’s comments- Concerning the results on the boundaries between research and therapy, this is an observational study and therefore it does not include any experimental drug. However, I believe that the main issue has to do with the data collected as part of the MalariaGEN study. These data, as it generally occurs in observational studies, will not have any direct benefit for the children included at this observational study. I guess that this idea is difficult to understand in this specific clinical environment. I find it hard to believe that that this issue was clearly understood by mothers of cases and even less by mothers of controls.

16. We agree and have added the following clarification.

Consequently, even studies that do not offer direct benefits to participants, such as the MalariaGEN study, may be perceived as beneficial.

Reviewer’s comments- The first paragraph at the Discussion describes some general points related to informed consent’s issues in genomic research, mainly at developing countries. This idea should be more properly detailed at the introduction. At this section a brief reference to this idea could be made but connecting it more clearly with the results of the study.

17. The idea in the first paragraph of the discussion has been moved to the introduction and a brief reference made to it in the discussion section as recommended.

Reviewer’s comments-3. The limitations of this qualitative study (limitations usually found at this type of research) should be more clearly stated at the discussion. Some of them are:

- The number of researchers, research assistants and research staff is low and any comment would be appreciated.
18. We are grateful to the reviewer for highlighting this point about the number of respondents for this study. Since this research was focused on the MalariaGEN project, we purposively recruited all the researchers, research assistants and research staff of the project in this study who gave consent for their inclusion in the study. Although the number of people in each category seems is low, we were limited by the number of researchers and research assistants working at the Navrongo Health Research Centre. As suggested, we have also highlighted this in our limitations section.

- There are many factors that can be related to the level of understanding and that cannot be shown with this study (such as literacy level and other social and economic factors).

19. We agree with the reviewer and have covered this in the limitations section.

Reviewer’s comments- 4. This study suggests that, in this context (a developing country), the importance of written information is lower than it may be in developed countries. In general, some requirements from international guidelines (influenced by developed countries) are not easily applied at developing countries. At the same time there are other needs that must be fulfilled. I would encourage authors to develop this idea a little bit more.

20. As the reviewer suggests this is a very important issue of broad relevance to consent processes for research in developing countries. We feel that it would be over-reaching the findings of this paper to provide an analysis of how requirements of international guidance should be moderated in developing countries beyond the suggestions already set out in the discussion section.

Editorial comments:

Abstract
Can you ensure that the background section of your manuscript includes the aims of your study?

We have revised the background section as suggested. We have included a fourth heading ‘Methods’ in the manuscript which can be deleted if preferred.

Tables
We notice that you have included the tables as additional files. If you want the tables to be visible within the final published manuscript please include them in the manuscript in a tables section following the References.

This has been done. Please note that we have nested the numbering of references for each table within the table as the placement of the tables in the text is yet to be determined.

General Formatting
Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

We have formatted the manuscript as suggested. The above link was not available when we formatted the manuscript, so we have used the guidelines at http://www.biomedcentral.com/bmcmedethics/authors/instructions/researcharticle#formatting-title which we hope are acceptable.

We hope that you will agree that we have appropriately responded to the reviewers’ very helpful comments and suggestions, and that you will consider this article as suitable for publication.

Attached, two versions of the manuscript; a clean version of the paper, and a version with changes marked.

With best wishes

Your sincerely,

Dr Susan Bull

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