Author’s response to reviews

Title: Ethical issues of informed consent in malaria research proposals submitted to a research ethics committee in Thailand: a retrospective document review

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Responses to Editors and Reviewers

METH-D-16-00199

Assessing informed consent in malaria research proposals submitted to a research ethics committee in Thailand: a retrospective qualitative review.

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BMC Medical Ethics
Editor Comments:

While this manuscript has the potential of informing malaria researchers regarding various ICP issues, there are some important areas that would require clarification for the readers.

First, is this an internal quality assurance review rather than a research study? Was REC approval obtained for this study?

Thank you for your kind comment. This was one of the matters discussed among researchers when we decided to do this study. This study was intended to be a research study. Data collection and analysis performed during the study was not part of routine work. It was particularly designed to develop or contribute to generalizable knowledge, particularly for malaria researchers. We also understand that research conducted in conjunction with program evaluations or quality assurance measures may or may not subject to IRB review, and if it is a project intended to develop or contribute to generalizable knowledge, it should be submitted for IRB review. However, it is debatable whether this type of “document review” study is a human study and requires ethical approval, or not (it has been discussed a lot in several webpages/research groups). For this study, the researchers (except the blinded coders of the quotations extracted from the proposals) are persons who work in the ethics committee as voting or non-voting members; thus, by default, they have all read or seen the proposals with the names of their submitters. However, when they extracted the quotations from the proposals and notification letters to the principal investigators, they checked whether the quotations came from which identifiable study number, but not the names of the study investigators. The researchers in this study (who are FTM-EC members) did not therefore seek formal FTM-REC approval documentation but informed and asked for permission orally from the FTM-EC panels for document review. Although there was no formal research ethics review given the nature of the project, the researchers were bound by all of the usual research ethics, research integrity and publication ethics guidelines, to ensure no violation of confidentiality. We have inserted text related to this concern in the “declarations of ethics approval” section.

As I inquire in the specific comments below, it is unclear whether the study looked at only what the REC wrote back to the researchers, or whether it studied the original documents that researchers submitted to the REC. If the former, the manuscript needs to be clear about this throughout the manuscript.

Thank you, we may not have been entirely clear in the methodology. Indeed, we started data collection by looking at notifications to principal investigators, but we also looked back and confirmed and extracted some parts from the original proposal. We have now revised it as shown in the abstract and several places in the methodology/discussion section.

Some more specific comments for various sections of the manuscript...
Background:

- There are important differences between kindness and ethical consent process. Kindness is distinct from beneficence regarding participants’ best interest.

Thank you for pointing out this distinction. We fully agreed that “beneficence” means doing no harm, maximizing benefits/minimizing risks, and NOT acts of kindness or charity, but rather a concrete obligation. What we mean by “kindness” in the text is not charity-related. To avoid misunderstanding of the term used, we change the word “kindness” to “beneficence” as per the editor’s suggestion.

Also, distinguish ineffective communication and unethical behavior.

Thank you for the clarification of this point. We have now the manuscript, distinguishing these two concepts.

- IC being based on a partnership between the investigator and study participants: this needs more explanation. The partnership might be an ideal, but many have argued that IC is a matter of protecting participants, who are vulnerable, rather than a partnership between equals.

- Research is a privilege, not a right: privilege to whom? Research may not be a right, but protection of research participants is generally accepted as a right.

Thank you. These comments are very important and we have elaborated on this matter as per the editor’s suggestions. We seek your permission to use some of your phraseology in the text added to the manuscript.

- “Malaria researchers would therefore benefit from a list of common problems in the ICP elements in different types of proposals.” Are malaria researchers facing different ICP problems compared to other researchers?

We have deleted this sentence and inserted the rationale for conducting the study with a focus on malaria research. This revision should also respond to comments by reviewer #1.

Classification

- Need a table showing the numbers for each category included in this study

Thank you for this suggestion. We had moved the first paragraph in the results section about different study types to the “Sources of info…” section, as per another comment by the editor. We then calculated the numbers and percentages for each category in that paragraph. We also
added another table (Table 2(b)) as per another editorial comment about the analysis of ICP elements by different study type. We trust that the numbers for each category of study are now clear.

Sources of information and data analysis

- “This study was based on a documentation review. The documentation included notifications to researchers, informing them of review outcomes and ethical issues of concern to REC members. The notifications to researchers included detailed information from the REC review about protocol content, PIS, ICF/IAF, and other documents or materials (e.g., advertisements and handouts).” Please clarify whether you only reviewed the REC notifications or if you also reviewed the original protocols submitted by the researchers. If the former, please clarify throughout that the content analysis is only about what the REC said about these ICPs, NOT the ICPs themselves.

Thank you. We have noted that we looked at both original proposals and other documents related to ICP throughout the manuscript.

“Information was extracted by personnel with authorized access.” These employees had authorized access for this study? Vs for the purpose of REC review? Please clarify and explain the REC approval process of gaining access to this information for the study purpose. If such approval is not required, please also explain.

To make it less ambiguous, we have changed “personnel with authorized access” to “personnel working in the ethics section of the ORS”. We also inserted the REC approval issue in the “declarations for ethics approval” section, as mentioned above.

Results

- ICP requirements for different study types. The first paragraph belongs to the “Sources of info…”, since this is still explaining which of the 63 protocols were included in your analysis.

Thank you. We have moved this paragraph to the “Source of info…” section, as suggested.

Content analysis of ICP elements

- Need more clarification of the hierarchy of the 5 categories being discussed.

Thank you for the comment. We have elaborated on the five categories of ICP used for presenting our content analysis of ICP issues.
Cost and compensation

“FTM-EC usually requested that the researchers considered revisions in such cases” -- Requested revision of the amount? Or how the compensation is discussed in the ICP?

Both scenarios obtained regarding asking for revision of the amount and procedures/timing of compensation. We added a sentence to clarify this, as per the editor’s comment.

Discussion

- “This study shows that all clinical (IND) studies, and epidemiological studies collecting new information from the study participants, attracted REC comments on elements of the ICP.” It would be helpful to contextualize the findings a bit more: Were some issues more pertinent than others? Just saying that these studies attracted REC comments does not explain whether these studies have more ethical concerns, or that the researchers have not explained these concerns very well. At minimum, it would be important to explain what types of information is flagged more for which types of studies. It is difficult to contextualize your findings with the literature you are citing in this section without knowing a bit more about how different types of research you considered produced what sorts of concerns.

Thank you for this important comment. In fact, we had conducted an analysis of ICP issues by different types of study, but decided not to present this in the first version as there might be too many tables. In response to the editor, to make the discussion clearer and more evidence-based, we would like to add one more table and narrative to the results section. The results should thus explain or clarify our statements in the discussion section, kindly noted by the editor.

- “The results of the content analysis for this study suggest that the risks and benefits were sometimes not clearly or thoroughly explained to study participants, and the FTM-EC therefore requested elaboration and revision of these elements.” Again, knowing whether this issue was more of a concern in certain types of research in your study would be helpful. That would also help to explain how ethically important this concern might be.

We have added a new table to clarify this matter, as mentioned above. We also added material about the importance of balancing risk-benefit, as suggested by the editor.

- Issues about physician-patient relationship: “Most proposals submitted to the FTM-EC did include a statement addressing this, but some used inappropriate wording that required paraphrasing.” Need more explanation of how the wording was inappropriate.

We elaborated further on this matter, as suggested.
- “The results of this study were based on an analysis of the information or content in the proposals.” Were the proposals themselves evaluated? I thought you only looked at the REC documents and that the original proposals were not included. Please clarify.

We started our analysis with the REC documents, but we also re-examined all proposals to identify the ICP elements stated in the proposals themselves. Most of the authors had read and made comments on such issues from the proposal. As shown in our responses to other comments, we have clarified this matter in the research methodology and in the declaration to ethical clearance, as suggested by the editor.

Limitations

- “The main limitation of this study is that it is based on information on malaria research proposals submitted to only one institutional REC…” As per above, please clarify whether you analyzed all the research proposals themselves, or ONLY the REC responses. If you are inferring what was in the proposals from the REC responses, this is another important limitation that needs to be flagged.

Thank you for this comment. We truly appreciate your thoroughness in reading our manuscript. We added the editor’s concern to the limitations of the study section.

Reviewer reports:

Manasse Bambonye (Reviewer 1):

P.1. Line 1 &2: I do find that the title should reflect the limitations expressed in this research. I agree with the statement that "this study is based on information on malaria research proposals submitted to only one institutional REC, the IRB of the Faculty of Tropical Medicine, Mahidol University, Thailand. It may therefore not be representative of RECs elsewhere in Thailand or around it". That is why for me, the title of this study should reflect this reality. Moreover, this research does not study informed consent as specific variable, but is about decisions rendered by a specific REC in one specific faculty of one university (Mahidol. Then the title as it is seems to be misleading. In reality, the purpose of this study is to summarize issues raised by a REC in one faculty at the Mahidol University as rendered about informed consent and not study about completeness of the consent form compared to those stated in a specific guideline. Additional to that the authors do not justify their choice with regard to retained criteria used in reviewing rendered decisions about consent information provided. I would like to see these issued commented and the title reviewed to reflect their limitation and the real object of study.
Thank you for the comment. Since we have responded to the editor’s comments on several issues related to the study objective and methodology, this revised version, with additional paragraphs in the methodology, results and limitations sections, also respond to the reviewer’s concerns. We also revised the title to clarify that we did perform document review. As per the reviewer’s comment, we added to the limitation section that we did not conduct a comparison of the consent process against any specific guideline, but summarized ethical issues related to the typical standard set of ICP elements used by FTM-EC when reviewing research proposals. In recognizing the limitation of this study, we also changed REC to FTM-EC throughout the study where appropriate.

Purpose of this study:

The objective of this study is somehow not clear. In fact, it is not clearly stated that there are any problems in conducting research in received complaints or in variations of informed consent formulation that need improvements. We understand that there are lot of studies conducted by faculty is involved or is carrying. It is not enough to state the amount of studies carried out, it has to be an existing large research conducted by the faculty to justify the need to know how the informed consent is respected. If this is one of the purposes, this should clearly mention. Clarification on these issues could be helpful for readers.

Thank you for this comment. In responses to comments by the editor and the reviewer, we revised the purpose and rationale for conduct of this study. This should clarify readers’ expectations prior to reading this paper.

Patricia Marshall (Reviewer 2):

The process of informed consent and its review and assessment in study protocols by Research Ethics Committees (RECs) or IRBs in low- and middle-income countries continues to be an important issue for investigators and members of review committees. In this manuscript, the authors examine concerns associated with the informed consent process raised by RECs reviewing malaria protocols in Thailand. The authors conducted a granular analysis of the protocols and have succeeded in shedding light on the review process and outcomes. The paper is well written. The methods are clearly described. I recommend publication with minor revisions.

1. Page 2, line 9: Delete "or communication."

Deleted, as suggested.
2. Page 2, lines 14-15: Delete the sentence that begins "The Faculty of Tropical Medicine's…" It is not needed here.

Deleted, as suggested.

3. Page 2, line 20: Change "…during 2010…" to "from 2010…"

Changed, as suggested.

4. Page 7, line 19: Do you mean "…proposals submitted to Research Ethics Committees from 2010-2015"?

Yes. We revised the wording to make it clear, as suggested. Our document review included documentation from 2011-2015. We sincerely regret our oversight in the first submission and have made the relevant changes throughout the paper.

5. Page 8, line 21 through page 10, Elements of the ICP: This is a very long paragraph (one and a half pages). I suggest breaking this up into several paragraphs. You might consider beginning a new paragraph on page 9, line 11, beginning with "The US FDA guideline…” You could also begin a new paragraph on page 9, line 18, beginning with "The Royal College of Nursing…” Another paragraph could begin on page 10, line 1, "The literature suggests…"

Thank you for the comment. We have created new paragraphs accordingly.

6. Page 11, line 17: the phrase "at times it could be controversial" is not clear in this sentence. Either delete the phrase but keep the reference (#29) or create a new sentence that clarifies what you mean.

Thank you for the comment. We have deleted, as suggested.

7. Page 15, line 17: Begin a new sentence with "Half of the studies…”

Edited, as suggested.

8. Page 21, line 11: Start a new paragraph beginning with "Although the collection…”

Edited, as suggested.

9. Page 24, line 14: What do you mean by "border areas”? Please clarify.

We clarified in the text: “the country’s border areas with Myanmar and Cambodia.”

10. Page 25, line 9: What guideline are you referring to?

The US-FDA guideline (reference #6). We have inserted the reference next to the word “guideline” for clarification.
11. Page 28, line 14: Begin a new sentence with "The researchers must ensure…"

Edited, as suggested.

12. Page 40, line 48, Table 3: This table is extremely long. Is there any way to shorten it, for example, by cutting back on how many words are used in the "Purpose" column?

On page 40, line 8, we have shortened the wording from “Procedure for study activities, data/specimen collection” to “Procedure for study activities”

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandviewertutorials/writinginenglish) and our Writing resources (http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English.

We used the “Edanz” editing company to edit our manuscript before submission. For this revised version, an experienced native English-language speaker in the Office of Research Services of the Faculty of Tropical Medicine has approved the edits. Please see the attachment.

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