Author's response to reviews

Title: Clinical Trialist perspectives on the Ethics of Adaptive Clinical Trials: A Mixed-Methods Analysis

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Author's response to reviews: see over
Dear Editors,

We thank the editors and the reviewers for their careful and thoughtful review of our manuscript. We have provided a point by point discussion of the feedback and provide description of what changes have been made to the manuscript responsive to these excellent suggestions. I have marked reviewer comments (or my understanding of them) in quotes. Also, it is worth noting that a number of topical papers came out in Feb 2015, and at the time of our initial submission these were not available to us. We have cited them, since they are relevant, of course.

Major Compulsory Revisions:

Reviewer 1: “There is a need for ... addressing the bigger picture here that needs more treatment by the authors.

We think that in response to subsequent feedback from reviewer 2, we have addressed this bigger picture, by using

Reviewer 2: The remainder of quotes in the major compulsory section are concerns of reviewer 2

“Abstract: from the claim that adaptive trials involve specific ethical considerations, it does not follow that we need better understanding of the ethical aspects, nor that these ethical aspects have to be clarified by means of experts' views. Another obvious way to do that is literature review or normative reflection.”

We have rephrased the background in the abstract to make this more sensical. We do not disagree that a literature review or normative reflection is an option, albeit it was not the design of this study. Below in the main manuscript section we have made revisions to provide more assessment from the ethics community.

“Abstract: that there are 53 experts is not a result (not an answer to the research question) but part of the methods.”

We have adjusted the manuscript accordingly.

“The ethical benefits are relatively abstractly formulated "accelerating the bench to bedside process", "moral buy-in that achieves the effective teamwork in ACT"; without further explanation it is unclear what the authors mean; I would use the wording of the findings presented in the main document in order not to confuse the reader and to avoid making it more complex.”

We have adjusted the results and conclusions section of the abstract to better match the
We have eliminated this as requested.

We have removed the underlining. There are still some investigators who want to design “adaptive” trials that involve ad hoc looks, but we agree most are focused on pre-defined trial designs.

We have rewritten this sentence to refer more directly to the ethics of clinical trials, broadly considered by scientific, individual and collective aspects.

We have included more references, deleted a paragraph, and looked carefully for “advantages” and changed to “potential” or possible advantages. We believe the background is now substantially improved.
"- "given the ethical imperative to ensure subjects have the necessary information to make an informed decision, most study designs mandate informing the participants that they might not benefit personally from enrolling". It does not follow from the claim that participants have to be adequately informed that most study designs require (which are also no moral actors) to inform participants that they might not benefit.”

I have deleted this sentence. It does not follow well and does not add to the background.

"the section which begins with "ACTs have different ethical nuances" - in the former sections the authors predominantly emphasized the advantage of being enrolled to the seemingly more favorable arm. In this section this is presented as a second issue "for example, some adaptive design strategies increase...” The first is making an informed decision, and also the latter part of this section is on complex decisions. The structure of this section is therefore inconsistent.”

This paragraph has had some additional content and references added and we think it flows better now and is more consistent.

"- “in a study which involved deferred consent" - this situation is not unique to ACTs and therefore not a valid argument in the ethical evaluation of ACTs.”

We have taken this out of the background. While the situation is not unique to ACTs, it may present a design feature that the public would prefer relative to standard fixed designs. We do not yet have empirical evidence to back up this hypothesis (our group is actually starting up a three-armed trial using response adaptive randomization with exception from informed consent for patients with seizures).

"- "understanding clinical trial expert ethical comfort with ACTs" - for the reader who has not read the remainder of the paper it is unclear why a research team would not be satisfied with an ACT."

This was within a section that was deleted per a previous request.

"- "participants were asked to consider ethical advantages and potential ethical disadvantages from the perspective of patients, researchers and society". Since this has been the purpose of the study from the start it is self-evident that the results are also presented according to this categorization. At the same time, since ethics is per definition impartial, embracing the perspectives of all stakeholders and focuses on the what and why and not on who, it is not of particular interest to hear what different stakeholders regard as an ethical advantage from the perspective of a certain stakeholder in the debate, but what the stakeholders who are interviewed see as "ethical" issues. A common strategy used in ethics is to organize the results according to the principles mentioned in the well-known Emanuel framework
(social value, favorable risk-benefit, informed consent, fair subject selection etc). I do not know whether it is still possible to analyze the results in this way, but that would make much more sense from an ethical perspective.”

This is a great point, but unfortunately we mainly focused on the informed consent aspect using our data collection technique. We addressed the question of perceived validity in a companion paper. We have added to the limitations that we would have like to collect opinions under the Emanuel framework for clinical trials ethics and that future planners of ACTs may do well to consider each of the 7 points in the ACT versus the fixed/traditional clinical trial.

“Moreover, at least two of the stakeholders that they identify (patients and society) have not been interviewed. Below I’ve expressed my concerns with regard to the absence of patients in the study, but the same applies to society.”

We have added to the limitations the need to include ethicists who may be better able to ponder society as a stakeholder. We have also added a reference and statement for future inclusion of patient/research advocates in clinical trial planning processes.

“-Settings and participants: why were patients excluded from this survey? It is somewhat remarkable since they are important stakeholders. Moreover, the authors categorize their findings amongst others according to the patient perspective (which now remains biased without the voices of the patients themselves). Furthermore, it is unclear to me whether patient or patient advocates have indeed be absent, since elsewhere the authors mention the presence of patient advocates (for instance shortly above the section "opinions regarding the researcher perspective")”

There were lay patient/research advocates in attendance in many ADAPT-IT discussions and each was provided a VAS survey. There was not direct interviewing of them, as the focus group plan did not include them. We have taken the sentence “No patients were surveyed as part of this report” out of the methods, and as mentioned above, have included it as a limitation.

“- data sources/analysis: in (empirical) ethical papers I have seldom seen this level of statistical/methodological detail of the analysis. It is not incorrect, but the paper can still be transparent and reliable without this level of detail.”

Given the clinical trials and clinical audiences, it is important to us for it to be apparent that we used valid approaches to the textual analysis. If the editors would prefer we shift some of this to a methodological appendix, we can do so.

“- demographic characteristics: this should go to the methods"
We have moved this up as requested. We would be happy to move it back as we have seen papers put this sort of information in both locations and would defer to the editor. As noted above we made a similar change to the abstract.

“- general comment that applies to the results section: the number of the citations should be limited, although it makes the results more vivid, not all of the citations are accurate and/or parts can be shortened. For instance: - ‘response adaptive randomization gives patients a better chance...is the same the citation that follows on potentially reducing the number of patients who get the ineffective drug. Or in the citation that follows - only the last sentence is of importance in light of individual ethics "designed to improve the outcomes of patients". Many citations face similar problems and have to be reconsidered/shortened or eliminated.”

While the concepts are similar, we do think it is important to relate that different stakeholders reached congruent opinions.

“- opinions regarding the researcher perspective: citation “I think that the overall efficiency of the medical research enterprise is something that ought to be important to all of us in the adaptive design part”. This is not specific for the researcher perspective but also for the societal perspective.”

This is true. We have added this to the introductory statement for this citation.

“- trends according to intragroup and intergroup variations - might be removed to the methods section”

This was developed by evaluating the graphical depictions of the participant responses and we believe is most appropriate to include in the results section.

“-discussion: avoid overlap with results, for instance the entire section from " the academic clinicians and the other stakeholders" to "and emphasize potential negative aspects" can go.”

Thank you, that was duplicative and has been removed as recommended.

“- the discussion is categorized according to areas of agreement and disagreement; it is unclear why these themes have been chosen. Again, I would categorize them at least to ethically relevant themes. Although informed consent is one such issue, response-adaptive randomization as such is not. Accordingly, the "ethical" issues raised under areas of disagreement under response-adaptive randomization are heterogeneous. The authors single out one remark (individuals are not worse off before any adaptation) and conclude that participation in ACT is an ethical advantage. Moreover, is the latter their own judgment (which is then somewhat premature here), or is it the result of the interviews/focus groups? Also, when it is an ethical advantage, then what is the disagreement here?”
We think the implied hierarchy (areas of disagreement then several subparagraphs of areas of disagreement) was incorrect and thank you for pointing that out. We now have a freestanding paragraph on major areas of agreement, followed by major topical areas such as RAR. The question about our own judgment is a fair one, therefore we have altered that sentence to be conditional on the trial actually being conducted when the new (or old) treatment is ultimately clearly superior to make this less ambiguous.

"- what I miss in the discussion is an evaluation of the results in light of what is already known on the ethics of adaptive trials. Thus are clinical trialists right that “use of ACTs can help avoid exposing some participants to ineffective treatments, thus offering a clear ethical advantage”? This benefit has to be offset against the burdens, for instance that trials may take longer when there are frequent interim looks.”

We have added some sentences to the discussion that help frame our findings in the context of what was known before.

"- informed consent: the forest versus trees metaphor is somewhat simplistic. Even if it were ethically acceptable not to explain details of the methods used in the study (which is questionable since e.g. the DoH says that participants should be informed about the methods) it does not follow that the informed consent process for adaptive trials will become less complex. The ethical challenge par excellence is that of fair subject selection in light of the question whether patients will be able to understand that the later they enroll the higher the chance that they will be assigned to the seemingly more favorable arm.”

We have added the context of studying emergencies. People cannot delay the need for treatment in such contexts. There still is a fairness issue, but there is no way for individuals or investigators to “game” the system by delaying enrollment.

"- informed consent: "it has not proven to be substantially more challenging" - obviously to proof that it is more challenging will be difficult as is the case for all ethical issues.”

Proven is the wrong word. We changed to felt.

"- "some considerations may help explain these difference between the two biostatistician groups" : this is indeed the added value, not the lines above (see one of the previous comments). On the other hand, the first explanation seems rather speculative. Why would academic biostatisticians be less able to specifically focus on the research question (response adaptive and interim analyses) than the consultant biostatisticians? The second explanation is somewhat similar to the first, stating that all stakeholders view the issue from their own experience and perspective. That is true for all interviews and focus groups in empirical ethics.
Intuitively I would think that the ethics of ACTs is relatively unexplored in ethics. Some have already formed their opinions, others still have to formulate them, which will show a wider variety in the answers. In other words, it is not surprising to find a wider variety in the answers than on the ethical acceptability of e.g. the idea that individual informed consent may be waived under specific conditions.”

I have added some additional text that tries to develop a hypothesis regarding this cross group difference.

“- study limitations: "small but experienced group": what I understood thus far was that in particular the biostatisticians were experienced and the others less experienced.”

The overall group was experienced in clinical trials, but only a subset had experience with ACTs. We have added a clause that recognizes that a large portion of this project involved people with little or no past experience in adaptive designs.

“- study limitations: "we did not survey medical ethicists". I think that that is a missed opportunity but I can understand that this is not easy to correct. It is also a mistake to think that ethics starts with the ethics review of ethics committees as the authors seem to imply here. Ethicists in an ethics committee have a relatively applied role, whereas academic ethicists will often have a broader view, allowing for critique on ethical guidelines.”

This is a great point. We meant IRB members in the sentence here (and changed it), and added a session about medical ethicists.

“- "this first known empirical study" - this becomes somewhat annoying now. Moreover, it is not a conclusion.”

We have revised the sentence to be more conclusive.

“- the conclusion is divided into what the stakeholders collectively and individually think. Apparently, collectively they do not contribute to the debate (what they express is already well-known). This is somewhat surprising since the areas of disagreement and agreement in the discussion seem to be based on a group level.”

Minor Essential Revisions:
Reviewer 1:
“--While there is some description of the respondents in the beginning of the results section, some more description of in the methods would be welcome. Please be explicit about the relationship between the study sample and the ADAPT-IT team (are they co-investigators, consultants or some combination of the above).”
I have added this.

“What steps were taken to ensure maximal response rate for the surveys? Dillman method reminders? Incentives?”

Additional text added to the methods. Frequent reminders in person and by email were given.

“--How were the four respondents who provided feedback selected—randomly or in some considered fashion?”

Purposively, this is added to the text.

One from each constituent group who had been present across the planning processes for the 4 trials, and was not one of the principal investigators of the overall project. We have added the term purposively to indicate this was not a random selection.

“--While it is obvious that the likert scale anchors of 0 and 100 correspond to "definitely not" and "definitely" respectively, but readers might find it helpful to have this reinforced in the figure rather than just the numerical scale on the vertical axis.”

I have changed the figure legends to reflect this.