Reviewer’s report

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

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Reviewer: Rieke Van der Graaf

Reviewer’s report:

There is growing interest in adaptive clinical trials. Often they are considered as "more ethical" than conventional clinical trials, although it is still unclear to what extent this claim is correct. This paper contributes to further clarification of the ethical merits of adaptive trials and focuses in particular on the opinion of clinical trialists on the ethical merits, which, I think is important, since there are no other qualitative data of this kind. Having said that, I think that the paper has to be further improved since there are several flaws in the content and the structure of the paper. Therefore, I recommend Major Compulsory Revisions, which I will explain below.

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

Above the background section: avoid the citation; it is unclear what the purpose is of this citation. Moreover, it is not inline with the general conclusion.: -background: avoid underscoring predefined. Adaptive designs are per definition not ad hoc.

- "all trial designs have ethical implications" - what do the authors mean with implications and why implications?

- The ethics literature referred to in the background predominantly stems from statisticians with expertise in ethics, but not from ethicists. Collective ethics and individual ethics are terms that are hardly used in research ethics for example. It is also unclear why ACTs should favor individual ethics. In the end, ACTs are RCTs with adaptations. In other words, randomization is still not based on an individualized judgment of the physician but on calculations and the benefit that is aimed by ACTs remains primarily benefit for science and society, as is the
case in RCTs (although ACTs both may benefit individuals - as RCTs do - and have a higher chance of benefitting more individuals in the trial). One way to avoid the statistician perspective on the ethics of ACTs here but also elsewhere is to refer to some of the papers written by ethicists (a.o. Bob Truog, Rieke van der Graaf, Scott Brian Saxman). None of these papers are currently mentioned in the reference list.

- in relation to the previous comment: the background is rather long, including a short review of some (but thus not all) papers on the ethics of adaptive trials. I would substantially shorten the background and give a more balanced (thus including other papers) overview of the state of the debate and accordingly show why the state of the debate may benefit from qualitative data with experts' opinions on the ethics of ACTs. I would also move the parts which express opinions of the authors to the discussion ("the advantage of fixed RCTs is that", etc).

- "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.

- 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.

- "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.

- "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.

- "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. 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.

-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")

- 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.

- demographic characteristics: this should go to the methods

- 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.

- 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.

- trends according to intragroup and intergroup variations - might be removed to the methods 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.

- 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?
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.

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.

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.

"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.

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

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

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.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I have no competing interests