Reviewer's report

Title: When to keep it simple – adaptive designs are not always useful

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Reviewer: Spencer Hey

Reviewer's report:

1. Does the opinion article present a novel argument, or a novel insight into existing work?

In my view, yes, this article does provide a novel argument and insight into the appropriate use of adaptive trial designs. I share the authors' perspective that the methodological literature does tend to gloss over the limitations for adaptive designs. Therefore, I believe that their unpacking the conditions for good use of these designs is a welcome and needed contribution to the literature.

2. Does the piece address an important problem of interest to a broad biomedical audience?

Potentially inappropriate use adaptive designs is certainly an important problem, since it may lead to uninformative, misleading, or unconvincing trials—and thereby contribute to avoidable research waste. Whether this is a topic of broad interest to the biomedical audience is hard to say. But I do think that a broad biomedical audience *should* be interested in the topic and the arguments presented here.

3. Is the article well argued and referenced?

For the most part, this is a thoughtful and well-reasoned argument. However, there is an assumption throughout that adaptive designs are ethically advantageous because they may increase the likelihood that a participant will be allocated to the arm that is eventually found to be superior. Although this is not an uncommon assumption, it is in the very least controversial, and, in my view, it is simply incorrect. There are at least three reasons for this:
(1) Clinical trials cannot be ethically justified by direct benefits to the participants, because benefit is precisely what is being determined by the trial. Therefore, trials are justified by the *potential* benefits to *future* patients. And (part of) what makes a trial ethical is when these potential future benefits offset the actual risks and burdens to which the participants will be exposed. Thus, to claim that adaptive trials are more ethical because they increase the prospect of direct benefit is fundamentally at odds with the widely-held principles of research ethics.

(2) Notwithstanding the above, direct benefit to trial participants is not irrelevant to the ethical evaluation of trials. However, the way that patient benefit is often (although not always) invoked is through the ethical requirement of clinical equipoise, which demands that there is genuine uncertainty in the expert community about the relative therapeutic merits of all arms in a controlled trial. The consequences of clinical equipoise that are most relevant to the argument here (it seems to me) are (a) that patients should not be exposed to anything less than competent care and (b) patients should not be systematically disadvantaged by participating in the trial. In other words, clinical equipoise requires that patients will not be harmed by being allocated to one arm or another.

Adaptive trials interface with clinical equipoise is some interesting and complex ways—and it is probably beyond the scope and interests of this paper to really get into those matters. Nevertheless, I think there may be at least a few points that the authors should consider: On the one hand, adaptive trials which drop arms (like the MAMS design), seem to operationalize clinical equipoise in a really intuitive way: Because as soon as we know that an arm is ineffective, we drop it from the trial. This seems to straightforwardly satisfy equipoise requirements.

However, for adaptive trials that weight allocation in favor of "better performing" arms, the implications of equipoise are less intuitive. As long as there is (and should still be) uncertainty about which is truly the better intervention, then (consistent with point 1 above), there is no good reason to think that patients are benefitting more or less by ending up in one arm or the other. In other words: Because every arm must be consistent with clinical equipoise, then patients are not being advantaged or disadvantaged due to their allocation. In which case, it is mistake to say that there is an ethical advantage by allocating more patients to the superior arm. The (potential) ethical advantage of adaptive designs is rather from minimizing the total patient burden (in terms of sample size, time, number of visits, trial burdens, costs to society, etc.).
Finally, it may be important to acknowledge how adaptive trials can introduce a systematic disadvantage for patients who enroll earlier in the trial. In a MAMS trial, for example, since some arms may be dropped over the course of the study due to lack of efficacy or futility, it would be better for a patient to wait as long as possible to enroll, since this will maximize their chance of getting something that is effective. Assuming that equipoise holds throughout the trial, this temporal asymmetry does not make the trial less/more unethical from that perspective. But it may raise ethical concerns from justice insofar as adaptive trials redistribute some of the burdens of trial participation onto early-enrolling patients, who may be more vulnerable. For some conditions and patient populations, this may not be relevant. But in some kinds of adaptive trials in oncology, for example, I think this can be an important consideration that may intersect with or amplify some of the authors concerns about trial complexity. And this issue also interfaces with validity concerns, if the trial population is changing over time.

Bottom line here: I don't think the authors need to get into all of this. But I do think that at least some of this ethical complexity needs to be surfaced, and that doing so would enrich their analysis and discussion.

For more on many of these points, the authors may find the series of articles from 2015 in Clinical Trials helpful (starting with Hey and Kimmelman's "Are Outcome-Adaptive Randomization Trials Ethical?"), since many of these issues are discussed there as well.

4. Has the author used logical arguments and sound reasoning?

See above.

5. Is the piece written well enough for publication?

Yes, the piece is well-written. I think the discussion of the Birmingham CRUK CTU trial is a particularly lucid and helpful illustration of the issues around long-term outcomes.
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