Reviewer's report

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

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Reviewer: Edward Mills

Reviewer's report:

In this manuscript, Wason and colleagues raise an important point in how adaptive trial designs are not a universal cure for all clinical trial investigations. They provide their guidance on identifying situations where adaptive trial designs may not be appropriate with real-life examples. Similar to Wason and colleagues, I too am enthusiastic and advocate the use of adaptive trial designs for most clinical trial investigations. Overall, this is a very interesting manuscript that should be published by BMC Medicine. I commend the authors here for this paper, and I believe it also will become highly cited. I just have some comments, clarifications, and suggestions that I believe will improve this manuscript's overall readability and delivery of its overall message.

* In the section, "Long-term outcomes", the authors discuss the importance considering the delay between recruitment and assessment of outcomes, and how the outcome being used to make adaptations should be observed sufficiently quickly compared to the total recruitment length of the trial. They provide their first real-life example of two-arm, phase 2 immunotherapy trial (ISRCTN: 11889464). In this example, they discuss why a single-stage fixed sample design with a maximum sample size of 70 participants was chosen over another design that would have potentially allowed for early stopping for futility after 46 participants (23 per arm), based on projected recruitment rate of 2 participants per month.

  - The current figure is not very clear. I would recommend a different figure than Figure 1 provided to illustrate how at the time of 23 months (when 46 participants are observed for at least 12 months), all of participants would have already been recruited at projected rate of 2 participants per month.

  - It would be important to highlight the potential savings if projected rate for recruitment was erroneous; for instance, if the actual recruitment rate of 1 participant per month is observed, there would have been some potential saving gained from a planned interim futility analysis. As well, there would have been some savings if an outcome of 6-month PFS rate that is correlated with 12-month PFS rate was used as an intermediate outcome for adaptation.
More detailed figure legend would be beneficial to explain Figure 2 for expected sample size (2a) and proportion of patients allocated to effective dose (2b).

In lines 163-168, the authors mention that the actual time taken to conduct the interim analysis in their example of TAILoR trial. If the authors of this manuscript were the investigators of this trial, it would be nice to mention the time taken for the interim analysis, given that this trial has already been published.

In section, "Limitations due to additional administrative and logistical complexity", the authors discuss logistical challenges associated with conducting data collection and cleaning in a timely manner to first conduct the interim analysis during the trial, as well as the challenges of having data monitoring committees (DMCs) and trial steering committees (TSCs). But it should be noted that ensuring high-quality data collection and having independent DMCs should be standards (as the investigators of the STAMPEDE trial were able to) that all clinical trial research should strive for. These attributes will not only benefit future adaptive trial designs but also non-adaptive, single-stage fixed sample designs.

The last section of "Weighting the pros and cons of adaptive designs" is really important. I recommend the authors to build up on this section. If they are constrained against by BMC Medicine's word limit, I would recommend taking the section out on the BATTLE-2 trial. In such a biomarker-guided trial, there are other issues of ensuring good quality genomic data that I feel is beyond the scope of the manuscript.

In this section, it would be nice to the authors to mention how no methods (adaptive or non-adaptive) should be a default. Careful considerations of recruitment, data quality, choices in outcomes, administrative and logistical complexity while following the KISS (keep it simple, stupid) principles using simulations and other ways should be a standard practice that future investigators should adopt for their trial planning.

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