Reviewer's report

Title: Accelerating clinical development of HIV vaccine strategies - methodological challenges and considerations in constructing an optimised multi-arm phase I/II trial design

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Reviewer: Dennis Dixon

Reviewer's report:

I appreciate the authors' thorough responses to my earlier comments; I have no further points to raise by way of criticism.

The well-written manuscript has lead me to reflect on the present state of the art of designing early trials, not necessarily limited to trials of investigational vaccines. Standard trial designs are inadequate for this trial, as the authors demonstrate by their careful literature search and review. In fact, more and more research plans seem to need one or another departure from standard designs. Maybe the traditional paradigm of choosing a design that (a) has been "credentialed" by publication in a peer-reviewed methodology journal and (b) is as close as possible to matching the actual research objectives of the investigators, even if not a precise match, is obsolete.

Richert et al. illustrate a new paradigm, which may well be their real contribution. They summarize what is already known about the various effects of the candidate vaccine strategies. They carefully state what new knowledge they seek. They describe the proposed trial with all its specifications and assumptions, including those needed for them to study the design's statistical properties. They describe the simulation study they performed, in enough detail that others could reproduce it, and tabulate the results. In fact, not only could others undertake to reproduce their results, it is clear how to proceed to study other specifications and assumptions.

What are the implications of following the new paradigm rather than the old one? Two come to mind readily. With regard to peer review of the clinical trial, evaluation of the design under the old paradigm would very often end with an observation that the proposed study employs a well-established plan as published by Gehan or Simon or Thall (etc.). Under the new paradigm that would almost never suffice, and competent, serious review by a statistical scientist would be needed. I note that, in the U.S., at least, IRB (ethics review) has to address the validity of the science of each project, but many IRBs lack statistics expertise. The situation may be better in the context of reviewing funding applications, although peer reviewers rarely see full protocols in final form.

Another implication is a dramatic decline in articles on experimental design of trials in the statistical and trial methodology literature. Each new trial would follow
the paradigm, but the particulars would be essentially unique. This is a less worrisome consequence, since professional statisticians can presumably find other ways to qualify for career advancement.

Although I would like to know the authors’ reaction to my reflections, that would obviously take them beyond the immediate aims of their manuscript.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.