Reply to Dodd and Proschan

TO THE EDITOR—We are pleased with the interest shown by Dodd and Proschan [1] and their support for innovative designs to speed up the evaluation of new tuberculosis treatments. We welcome their comments on the control of the type I error rate and the question of bias in the treatment effects in the context of the multiarm multistage (MAMS) design. These are 2 important interrelated issues that need careful consideration when designing and interpreting the results of any adaptive clinical trial.

The objective of our article [2] was to raise the profile of adaptive and other innovative clinical trials designs, as well as to propose a specific implementation of a MAMS design as a useful tool for efficiently identifying regimens for the treatment of tuberculosis. This design and its use in oncology trials have been further described elsewhere [3–5]. We agree with Dodd and Proschan that many methods for eliminating poorly performing regimens in adaptive clinical trials have the potential for inflation of the type I error.
rate, and different trial designs will have different approaches to controlling the type I error and the bias in the treatment effect. The passage they quoted from our article is in reference to this specific implementation of a MAMS design, and we will therefore describe how the type I error rate is implicitly controlled and why there is negligible bias in the treatment effect estimates in this context.

Further work has been done on exploring the bias in treatment effects in MAMS trials, and the manuscript describing this is currently under in press [6]. Choodari-Oskooei et al [6] show that, provided all patients have undergone further follow-up beyond the interim analysis to the planned end of the trial, any bias is markedly reduced at the final analysis and is of no practical importance. This is true for arms that are not dropped at an interim analysis and continue throughout the trial and for those that are dropped at an interim analysis, because in both cases the final analysis will include more data than were available for the interim analyses. The bias is further reduced if the intermediate outcome used for the interim analyses differs from the definitive outcome that is used for the final analysis.

We are eager to avoid misrepresentation and recognize that the statement “the estimates in the arms that are continued remain unbiased” [2pS252] is not strictly correct but should read “the estimates in the arms that are continued remain practically unbiased.” The bias is not exactly 0, but it is of no practical importance.

The introduction of interim analyses to drop only poorly performing arms actually reduces the type I error rate such that the overall pairwise type I error rate will be less than the prespecified level of statistical significance for the final stage. This has been explored and shown in simulation studies [4]. The desired value of the overall pairwise type I error rate is attained by varying the levels of statistical significance in each stage, starting with a large value in the first stage and reducing it with each stage.

The MAMS design is set up as an alternative to conducting multiple, concurrent, 2-arm clinical trials, each evaluating a different novel combination regimen, and therefore strong control of the familywise type I error rate (FWER) across individual comparisons is a secondary rather than a primary concern [7]. However, FWER can be calculated using simulations and, if desired, can be controlled by appropriately adjusting the significance levels at each stage. For example, a simple Bonferroni correction presents an upper bound on the FWER. This is an area of ongoing research.

We are grateful for the opportunity to further elaborate on the operating characteristics of this MAMS design. As part of the PanACEA consortium, we are using this design in a 5-arm phase II randomized controlled trial to evaluate novel regimens for the treatment of drug-susceptible tuberculosis (Pan African Clinical Trials Registry identifier PACTR201205000383208) and look forward to seeing the use of innovative designs by other research groups to improve the treatment of tuberculosis.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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