Reviewer's report

Title: Design of Phase II Cancer Trials Evaluating Survival Probabilities

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Reviewer: Dr PF Thall

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

Compulsory Revisions

1. The "Background" does not adequately explain the motivating problem, that designs based binary outcomes may be impractical when only event times are relevant, and that the goal is to improve upon common practice by using the event times themselves. The point that it is not feasible to suspend accrual for a long evaluation period in the middle of a clinical trial seems to have gotten lost.

2. The authors appear to be unaware of some important published work in this area, including Dixon and Simon (1988, J. Clinical Epidemiology, 41:1209-1213), Follman and Albert (1999, Biometrics 55:603-607), and Cheung and Thall (2002, Biometrics 58:89-97). The proposed design should be compared to these methods, especially those that monitor the event time data continuously.

3. Given the mathematical notation, I assume that this paper is intended for statisticians, and moreover that a medical readership is excluded, since non-statisticians will find the notation impossible to understand. If this is not the intent, then the manuscript should be revised to minimize such notation.

4. It should be noted that the design on page 8 is essentially a time-to-event version, accommodating the additional issues of accrual and follow up, of Simon's 1989 two-stage design for binary outcomes. Specifically, the possible decisions at the two stages and the optimization paradigm on page 9 are precisely those of Simon.

5. Details of the numerical optimization procedure should be provided, since this is not straightforward. Also, some examples of the necessary computer run times would be very helpful.

6. The table legends and footnotes should explain more specifically and completely what is in going on in each table, so that they are self-contained.

7. Can the authors provide usable software for those who wish to apply this procedure? This is a critical issue.

8. The authors use a large number of acronyms. These should be defined in each of the tables where they are used, either in the legend or in footnotes. Otherwise, the reader must go through the irritating process of identifying the various acronyms in order to interpret the tables. Also, the tables would be much easier to read if most of the numerical values were rounded to fewer decimal places, since it seems that no substantive meaning would be lost.

9. The sensitivity analyses on page 15 suggest the importance of basing the method on a Weibull or other non-exponential model. Since possibly historical data certainly the stage 1 data should provide...
information about both the distributional form and the accrual rate, one could improve the design's performance by using this information to modify the design at time $t_1$, in the spirit of L. Fisher's "self-designing" trials. Since the last sentence of the manuscript touches on this, hopefully the authors plan to develop these very useful extensions in the future.

10. The apparent increase in both the null and alternative rejection probabilities over their nominal values for $DA/x^* > 3$ when $a = b = .10$ but not when $a = b = .05$ is perplexing (Table 2). Can the authors explain this?

Discretionary Revisions

1. Methods: The first sentence should more properly read "...clinical trial designs" rather than "...clinical trials"  
2. The first paragraph on p. 3 really describes the solid tumor setting. There are numerous other settings where "activity" is defined differently.  
3. page 4: It would help to note where the 53 and 42 come from.  
4. page 7: It should be noted that $l$ is the derivative of $L$.  
5. page 7, 2nd line after display (1): "...asymptotically standard normal"  

Competing interests:

None declared.