Reviewer’s report

**Title:** How do multi-stage, multi-arm trials compare to the traditional two-arm parallel group design - a reanalysis of 4 trials

**Version:** 1  **Date:** 4 November 2008

**Reviewer:** Mark Brady

**Reviewer’s report:**

This manuscript compares the conventional designs that were used in four cancer trials with a new approach which implements interim analyses and rules for dropping experimental arms based on an assessment of the treatment’s effect on an intermediate endpoint. In the examples provided, the new approach performs well. Moreover, in the cases described using the intermediate endpoint in the interim analyses may actually improve the operating characteristics when compared to using the ‘final’ endpoint in the interim analysis.

**Major Compulsory Revisions:** None

**Minor Essential Revisions:** None

**Discretionary Revisions:**

1. Consider a fuller explanation of the allocation ratio, p and its relationship to the first equation. As currently written, if the allocation ratio is 1:1, explanation is not clear about what value of p is used in this equation.

2. All of the trials described in the manuscript involve patients with advanced cancer. In these cases progression-free survival is probably a reasonable intermediate endpoint to implement in future study designs. However, in general the value of this design depends on selecting a ‘good’ intermediate endpoint. What considerations should be given for selecting a good intermediate endpoint? For example, a suitable intermediate outcome is not only an event which is believed to be in the causal pathway to the final outcome. It must also be an endpoint that the intervention could possibly influence. Moreover, when the intermediate outcome is a sufficient, but not a necessary event in the causal pathway to the final event, the value of this design may be limited.

3. eI is used described as the expected number of events in the control group at the interim analysis. From equation 1 it appears the eI is estimated under the null hypothesis. From the tables it appears that eI is the expected number of events in the control group, under the alternative hypothesis. Is this so? If it is, please explain.

**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 in relation to this paper.