Reviewer's report

Title: Approaches to interim analysis of cancer randomised clinical trials: a survey from the Italian National Monitoring Centre for Clinical Trials.

Version: 3 Date: 8 February 2008

Reviewer: Heinz Schmidli

Reviewer's report:

Major Compulsory Revisions

0. General: I would appreciate an overall evaluation of the 86 studies with an interim analysis, with a statement at the end such as: x (p%) of these studies were adequately planned. You could define some criteria you consider essential (e.g. presence of a DSMC, description of statistical monitoring method, etc.). And then define a study which meets all these criteria as adequately planned. With the current approach focusing on one-factor-at-a-time, it is not really clear how many of these studies were correctly planned.

1. Abstract: The background part needs a thorough revision, and should be shortened. The first 2 sentences could be reduced to a short statement that interim analysis are common in cancer trials. The authors should also include the motivation for doing this survey, e.g. identify areas for improvement in current practice, etc.

2. Abstract: In the results part, indicate the percentage of trials with interim analysis, but without a DSMC. Also mention the overall result (point 0 above), i.e. are the majority of trials adequately planned? What are the most concerning cases (e.g. interim analysis without DSMC, no description of statistical monitoring method, etc.)?

3. Abstract: The conclusion needs to be reconsidered. What are the main points that researchers/regulatory bodies should pay attention to?

4. p.4 Statistical monitoring approaches: The description should make clear the distinction between the different reasons for stopping: due to safety issues, for futility or for efficacy. And the different roles of statistics.

5. p.5 Aim of the study: As mentioned above (point 1), a real motivation is lacking.

6. p.6 Methods: As these are all descriptive analyses, p-values should not be reported (confidence intervals, when appropriate). Could you delete a value of p<0.05 was used to determine statistical significance.

7. p.7 Sentence: Comparison of the 150 values and p-values. Please drop chi-squared values and p-values. Percentages are sufficient.
8. p.8 sentence "The median number of interim analyses was 2, etc. Could you be more precise: x (p%) had 1 interim analysis, y (p%) had 2 interim analyses, etc.

9. p.10 paragraph on Montori et al.: this needs clarification. What is the point the authors want to make? The sentence "Trials with fewer events yielded greater treatment effect" is misleading. If there is a very large true treatment effect, then it is likely that the trial will stop early, and hence will have fewer events/patients.

Minor Essential Revisions

1. The title should include "TRIALS WITH TIME-TO-EVENT ENDPOINTS"

2. Abstract: drop "only" in "only 70.7%". I don't think this is a small percentage.

3. Abstract: typo "OaBrien and Fleming"

4. p.3 sentence "conducting an interim analysis may also have some drawbacks. The remarks on bias may be misleading. If this is considered important, then there are statistical approaches to deal with this (cite Jennison&Turnbull, 2000, Group Sequential Methods, Chapman&Hall/CRC).

5. p.4 sentence "treated with scepticism." I think this is a minority view, and this should be made clearer, for example by adding that interim analyses analysis are currently standard practice, with benefits considered to outweigh some drawbacks.

6. p.7 sentence "The median number of patients" Mention that numbers in brackets are quartiles

7. p.8 typo "Overall neither form of monitoring was took place in 30 out of".

Discretionary Revisions

NA

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable
**Statistical review:** Yes, and I have assessed the statistics in my report.