Author's response to reviews

Title: A Comparison of a New Multinomial Stopping Rule with Stopping Rules of Fleming and Gehan in Single Arm Phase II Cancer Clinical Trials

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Author's response to reviews: see over
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Dr. Melissa Norton,
Editor-in-Chief
BMC Cancer

Dear Dr. Norton,

We are pleased to submit to you the revised manuscript “A Comparison of a New Multinomial Stopping Rule with Stopping Rules of Fleming and Gehan in Phase II Cancer Clinical Trials.” Below is a point by point discussion of the reviewer’s comments. We thank the reviewers for the opportunity to discuss and improve this paper.

Referee 1:

1) Major compulsory revisions:

Response: The paper describing this model (Goffin JR, Tu D: Phase II stopping rules that employ response rates and early progression. J Clin Oncol 2008, 26:3715-3720) provides the details sought by the reviewer, including sensitivity testing of the model using hypotheses varying both response rates and early progression rates. The present paper applies that model to studies with actual patient populations, with the aim of providing to clinical investigators insight into real world applications. To allow the model to be compared to those studies, it must take the same response rate hypotheses and error rates. Only variation in the early progressive disease rate hypotheses remains, and therefore two reasonable (non-extreme) sets are provided. We hope the reviewer will allow possible reference to the prior work rather than a reprise of that work. We have added the following clause to the first sentence of the Methods: “…described here briefly and in detail previously, where variations on the rules and sensitivity testing have been provided”.

2) Discretionary Revisions:

Response: In a full decision-theoretic framework, we agree a cost-benefit analysis would need to be performed. However, this would need to incorporate not just the error rates, but also a plethora of assumptions related to the potential costs of each type of error. We believe this is unrealistic, given these assumptions would need to incorporate the potential benefit (number of patients, magnitude of benefit), negative treatment effects (toxicity, complexity of treatment), costs (which would vary depending on jurisdiction), competing treatments, and so on. As such, we believe that trying to create a common criterion for all these potential variables is impractical, and would prefer to leave the decision to clinical investigators, and acknowledge the subjectivity.
The bivariate endpoint based design suggested (e.g. response and early disease response) is not appropriate for phase II cancer clinical trials. Patients typically have assessment for response or progression every 6-8 weeks and for most treatments, few remain on trial beyond two or three assessments. As such, most patients are defined as having either a response OR early progressive disease OR stable disease and can not have multiple outcomes. We do note that there are alternative designs which incorporate response and other outcomes, such as toxicity (e.g. Bryant and Day, Biometrics, 1995; 51(4):1372-1383).

3) Minor essential revisions:

Item A: Does “efficient” mean “specific”…

Response: Efficient is meant to mean “minimizes resource use”. The sentence has been changed to both clarify “efficient” and to add the word “specific”.

Item B: “when drug is inactive” may be needed behind “minimize the expected number of enrolled patients” (paragraph 2, Background).

Response: Added verbatim with thanks.

Referee 2:

1) “No new knowledge is presented in this paper” AND “An article of limited interest.”

Response: We respectfully disagree. As indicated by Referee 1, this is an article “important to those with closely related research interests.” The cost of bringing one new oncology agent to market is estimated at nearly one billion US dollars, a figure which does not describe the human costs of exposure to failed drugs or to the delay in approval of effective drugs. With recruitment to adult clinical trials typically failing to exceed 5% of the cancer population, the pool of patients is also severely limited. Improving oncology trials is thus critical to improving cancer care.

While the original paper describing this model describes the simulation methods and the resulting rules, the present paper describes the method as applied to actual patient populations. Although perhaps adding little from a purely statistical viewpoint, it provides valuable results to clinical investigators. Many clinical investigators have a weak statistical background and are unlikely to change from classical statistical designs to more efficient designs unless they observe advantages through the use of concrete examples. This manuscript provides these concrete examples and demonstrates situations in which the new rules are more permissive in allowing phase II trials to proceed to stage two of accrual (compared with Fleming) and others in which it is more likely to lead to early stopping (compared with Gehan).

2) The title must mention that only one-sample designs are considered.
Response: The words “Single Arm” have been added to the title.

Other correction:

Two unformatted references at the end of paragraph two of the Background were corrected (El-Maraghi, 2008 and Thesenas, 2004).

We appreciate your consideration of this manuscript and hope that our responses are satisfactory.

Sincerely,

John Goffin, MD FRCPC