Reviewer's report

Title: Association of Trial Registration with the Results and Conclusions of Published Trials of New Oncology Drugs

Version: 1 Date: 22 October 2009

Reviewer: Benjamin Djulbegovic

Reviewer's report:

This is a well written and important paper. I have no major feedback/critique to offer. My comments are related to my own thinking about the issues the authors described in the paper that may be of potential usefulness to them should they decide to incorporate some of it in the paper.

General comments

1. the key issue in this type of research revolves around hypothesis about the successes of new, experimental vs. standard treatments. Any conclusions are then drawn by comparing observed with hypothesized results. The authors write "We hypothesized that advance trial registration is associated with statistically non-significant efficacy outcomes in published trial reports, when controlling for other known predictors of reported results such as funding source, publication characteristics, and trial design characteristics. “

While I wholeheartedly agree with this hypothesis, the authors should really say why they hypothesized that success of new treatments should, on average, be about equal to successes of standard treatments. To the best of my knowledge, the only rationale for this hypothesis could be found in so called “equipoise hypothesis” [ref #16; see also Cancer Control 2009;16:342-347; J Med Philosophy. 2007;32:79-98; Arch Intern Med. Mar 24 2008;168(6):632-642]

(Sorry for citing my papers, but I am not aware of others that explicitly postulated the hypothesis explaining the pattern of treatment successes observed in clinical trials).

2. If we accept the “equipoise hypothesis”, then the question becomes are the results still consistent with it? Although quantitative data still indicates this to be case, the qualitative data seem to significantly favor new drugs (80% of time in the pre-registration cohort of the trials). The authors (and I am inclined to agree) believe that the result is the consequence of bias in reporting. However, industry folks claim that they are so careful in designing trials that their success rates is much higher than predicted by the equipoise hypothesis. So, who is correct? One reason that I think the observed results are due to biased reporting- notably due to publication bias- is that the authors only studied drugs approved by the FDA. However, drugs that were never approved are neither registered nor published (the FDA refuses to release these data due to “proprietary reasons”). I think this is important to acknowledge.
3. I am curious to learn how the authors calculated the “effect size” i.e. that unregistered trials will be associated with 75% of success rate. This is very important assumption.

Minor issue (points that need clarifications)
- how did authors handle multi-arm trials? Which treatment was selected as new and which as standard RX?
- do you have data on accelerated vs. regular approval? This analysis may be interesting.
- what was percentage of phase 2 RCTs vs. phase III RCTs? Any impact on results?
- empirical evidence shows that blinding is really not important when it comes to “hard” outcomes such as survival. So, not sure that was important to have such elaborate coding for blinding.
- although it goes without saying that survival is the most important outcomes, in most of these trials progression-free survival (PFS) was primary outcome. Will result change if PFS is selected as the most important outcome?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

Although I have over the years interacted with 2 authors of this paper (and co-authored the paper with the senior author of the paper in 2003), I believe that I was able to assess this paper in fair and impartial manner.