Author's response to reviews

Title: A cross-sectional analysis of HIV & hepatitis C clinical trials 2007-2010: The relationship between industry sponsorship and randomized study design

Authors:

Neela D Goswami (neela.goswami@emory.edu)
Ephraim L Tsalik (e.t@dm.duke.edu)
Susanna Naggie (susanna.naggie@dm.duke.edu)
William C Miller (bill_miller@unc.edu)
John R Horton (john.horton@dm.duke.edu)
christopher d. pfeiffer (pfeiffer33@gmail.com)
charles b hicks (charles.hicks@dm.duke.edu)

Version: 2 Date: 1 January 2014

Author's response to reviews: see over
Dear Editors of Trials,

Thank you for your continued consideration of our manuscript, entitled “A cross-sectional analysis of HIV & hepatitis C clinical trials 2007-2010: The relationship between industry sponsorship and randomized study design” for publication in Trials. We appreciate the time and effort the reviewers and editors put into the manuscript and have performed major revisions in response to their comments. We have responded to reviewer comments line-by-line below and tracked changes in revised manuscript:

**Reviewer #1: Dimitrios N. Lathyris**

1) The authors in the background section should insist more on the current knowledge of positive or negative influence of industry sponsorship in infectious diseases studies (especially HIV and hepatitis C) and better justify the selection of HIV and hep C studies.

   *We have revised the background to include two more references regarding industry sponsorship of infectious disease trials and changed the structure to specifically address selection of HIV and hep C studies. A paragraph has also been added regarding reasons that there are not specific studies looking at influence of industry sponsorship on HIV and hep C studies.*

2) Data are presented in a descriptive and understandable way. But, in multivariate analysis, the non-statistically significant, in the univariate analysis variables, presence of a data monitoring committee as well as exclusion of persons older than age 65 were included and sample size though statistically significant in the univariate was excluded. I believe that it is important for the authors to justify this selection or correct it. Also, I think that wherever significant PR are presented, “p” should also be added.

   *Sample size was statistically significant and actually was included in the multivariable analysis. The text describing this in the results section used the word “enrollment size” instead of “sample size,” which may have led the reviewer to think sample size was not included in the final analysis. We have changed all the terms to “sample size” to make this more clear. Presence of a data monitoring committee as well as exclusion of persons older than age 65 were included in our “gold model” (despite being nonsignificant on univariate analysis) since we could accommodate extra variables and there has been suggestion that these variables could be associated with industry sponsorship and study design. We did not include p-values as this would be redundant with the PR and 95% CI presented (non-significant values have CI including 1).*

3) The discussion should concentrate more on the most important results of the study, especially on the first paragraph, and comment on the influence of industry sponsorship on the elaboration of HIV and hepatitis C trials, primarily.

   *We have revised the discussion to address this critique.*

4) In general, the abstract convey the authors’ ideas, but the choice of HIV and hepatitis C studies should be more emphasized.
The abstract has been modified to emphasize the importance of HIV and hepatitis C for the current analysis.

Reviewer #2: Joel Lexchin

1) This is another in a series of studies that looks at whether industry involvement in clinical trials produces bias results. As the authors note most previous research has looked at published trials whereas this one utilizes a clinical trial registry and removes the influence of publication. The use of the registry is both one of the strengths and weaknesses of this study. The authors are interested in whether there is a difference in randomization but because they are only looking at the registry they cannot tell how randomization was described and it is possible that there was a systematic difference between how industry sponsored studies defined randomization compared to non-industry sponsored studies. The authors also used the sponsorship field to determine industry involvement but that also means that other relationships between the trial and industry were not examined, e.g., the presence of authors who either worked for industry or authors who had other types of relationships with industry. Both of these issues need to be addressed by the authors.

*We have added these important concerns to the limitations section of our discussion.*

2) Presumably the authors focused on the question of randomization because the use of a RTC design would be more likely to yield less biased results but the authors should state that explicitly.

*This clarification has been added to the methods section.*

3) Lines 269-271: The authors should refer to the recent Cochrane review by Lundh et al that looked at the results and outcomes of studies funded by industry compared to those with other sources of funding. The conclusion was that the industry bias associated with favorable results and conclusions may be mediated by factors other than traditional measures of the risk of bias (e.g. lack of concealment of allocation, blinding and drop-out) and sample size.

*We appreciate this reference, and it has been added to the discussion.*

Reviewer #3: Luigi Naldi

1) I wonder if the source of studies is the most appropriate one. It is expected that trials registered in clinicaltrials.gov are mainly randomized ones. For other kind of research approaches such as observational studies or post-marketing safety studies registration is not as compelling as for randomized studies.

*We agree that analysis of a larger database of both interventional and non-interventional trials would be interesting, particularly with the outcome of randomized study design, but are limited by availability of the clinicaltrials.gov database only.*
Editorial requests:
1) Please include a Conclusions section as the last section of the text. This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

A conclusion section has been added.

Sincerely,

Neela Goswami, MD