Reviewer's report

Title: The fiduciary obligation of the physician-researcher in phase IV trials

Version: 3 Date: 13 July 2013

Reviewer: Michelle Mello

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Below are my first round comments and my reactions to the authors' responses.

Major compulsory revisions:

Page 1: I don’t think I agree with the assertion, “This entwinement is highlighted by the fact that these studies occur within the doctor’s clinic, and thus the physician-researcher conflict is especially present in phase IV.” There may be greater blurring of roles, but there should be less of a conflict of interest in phase IV since the drugs are presumed beneficial and the post-approval study may be observational, not randomized.

OK as revised.

Page 1: You initially couch the paper as being about phase IV “studies,” which include non-trials. Later, you confine it to trials. This shift to trials only greatly affects the analysis. Be consistent. Why give a definition above that doesn’t pertain to the focus of the analysis? Also, it seems your analysis is limited to non-placebo-controlled trials. Correct? Please clarify.

OK as revised.

Page 4: re: Section III: I take the point. Yet none of this is distinctive to Phase IV research. Thus, it’s not clear that it advances the paper’s thesis.

OK as revised.

Page 7: re: “Simply put, in phase IV, physician-researchers ought to be more inclined towards practice than to research”: I don’t understand why this distinction is being made here, after you’ve agreed that there is a high similarity between the two in the context of Phase IV trials because they are usually therapeutic.

OK as revised.

Page 7: re: “Hence, in this phase ... the fiduciary obligation of the physician to treat...is not easily waived as in other phases”: I don’t appreciate a distinction
here. Both in Phase III and Phase IV, the doctor is willing to enroll a patient in a potentially therapeutic trial because he’s in equipoise as to which therapy is best. It’s just that the risk of losing a therapeutic benefit is lower in Phase IV because both comparators have established efficacy. But I don’t see that as “not waiving therapeutic obligations”, versus waiving them in Phase III.

Ideally this response would be incorporated into the manuscript, i.e. as a response to an anticipated counterargument.

Page 8: This section’s recommendations seem rather self-evident. Perhaps the authors can explain if they depart from current practice.

OK as revised.

Minor essential revisions:

[None requested.]

Discretionary revisions:

All comments marked as discretionary revisions have been satisfactorily addressed.

**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:**

'I declare that I have no competing interests