Reviewer’s report

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

Version: 2 Date: 26 February 2013

Reviewer: Michelle Mello

Reviewer’s report:

This is a well-written paper on an interesting topic by obviously thoughtful authors. The section on waiver of fiduciary obligations is especially well crafted.

However, overall, I’m not convinced of the argument that there is a sharp ethical distinction between Phase III and Phase IV. I also don’t see why the authors’ prescribed duties don’t also attach to Phase III. Shouldn’t physician-researchers always be convinced that a trial’s design maximizes participant benefit and minimizes risk? Perhaps these issues, as elaborated further in the comments below, could be further developed in a revision of the manuscript.

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.

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.

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.

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.

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.

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

Discretionary revisions:

Abstract: The abstract says “In this chapter” - Is this a previously published book chapter adaptation? I just thought the journal should be made aware of that, if so.

Page 1: What’s a “career researcher” in this context? Academic physicians are no less “treating physicians” than those in the community. Currently their obligations to patients do not depend on the % time they spend on research.

Page 2: re: “…the common setting…is the physician’s clinic”: As opposed to what? Are you asserting that premarket trials rarely take place in clinics? Is that true?

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

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