Reviewer's report

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

**Version:** 2  **Date:** 20 February 2013

**Reviewer:** Mark Yarborough

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This manuscript forwards the proposition that Phase IV research imposes certain fiduciary obligations on physician researchers that may not pertain to physician researchers conducting earlier phase trials. While this thesis is intriguing and of possible merit, this reviewer thinks the following matters warrant further elucidation in the manuscript.

1. Provide a more detailed justification as to why Phase IV studies are ethically different from earlier phase studies. This reviewer was not persuaded on at least two key points the authors appeal to to grant Phase IV trials special status:
   a) that just because the research setting is typically the clinical setting, Phase IV trials are therefore "intimate with practice." Many, if not most, drug trials are done in a clinician's office setting.
   b) that because Phase IV trials deal with approved drugs for approved indications, physician researchers are more constrained and thus less able to conduct research that may compromise therapeutic goals.

In other words, why is the "setting" of research of ethical relevance and why do Phase IV research participants require higher levels of protection when it comes to trying to produce generalizable knowledge? Part of the authors' argument for why Phase IV is categorically different from other Phases is due to the fact that it is research with approved drugs, suggesting that it is wrong to compromise a patient's care when there is an approved therapeutic option. But some patients in Phase III trials forego standard care, even when standard of care is an FDA approved drug, for part or all of the clinical trial's duration. A stronger explanation about what is ethically different about Phase IV research is needed.

2. Is the correct conclusion being drawn from Table 1? The authors state that "it is still without doubt that these various codes require the physician to put the patient first over research interests." One could reasonably claim that the quotes and references in the Table all make the point that the safety of the research participant cannot be compromised for the sake of societal interests and that the therapeutic interests of patients/research participants thus can be compromised, up to a point. Thus, are the authors drawing the appropriate conclusion from the Table?

3. The authors could improve their manuscript by making a stronger and clearer case as to why the topic is important. Explain what is to be gained by viewing physician researchers who conduct Phase IV trials differently from physician researchers who conduct earlier Phase research and what is to be lost by not
doing so?

Level of interest: An article whose findings are important to those with closely related research interests

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