Reviewer's report

Title: The case for doing first-in-human (phase 0 and phase I) clinical trials in developing countries.

Version: 1 Date: 15 May 2011

Reviewer: Robert Levine

Reviewer's report:

Major compulsory revisions

1. The authors should take into account the positions taken in the leading international research ethics documents (Helsinki, CIOMS, ICH) pointing out that their recommendations are inconsistent with these positions and presenting their reasons for adopting differing positions.

2. The authors should clarify whether their argument supports doing FIH trials in the particular low resource countries in which the target disease is prevalent or whether, instead, their argument supports doing such trials in low resource countries generally. Some of their arguments seem relevant only to the former position and some others seem more generally applicable.

3. Page 4, paragraph 2: compelling scientific and pragmatic reasons are offered to support the argument that FIH studies should be done in low resource countries. Most of these reasons would also support an argument to discontinue doing all FIH studies in so-called "healthy volunteers". One is really interested in the results of such studies carried out in persons who have the target disease. Well-developed arguments on this point were published in the 1970s by Azarnoff, Oates and Levine, among others. Reference should be made to these arguments.

4. Page 5 paragraph 1: reference is made to the trials of rotavirus vaccine. The serious adverse effects were not seen in FIH studies and so its relevance to this discussion is questionable. Further, reference to "a few adverse events" seems to trivialize the really dangerous events that were observed. You should delete this reference or make its relevance clear.

5. At least some of the supporting literature for your argument is not concerned with FIH studies but rather with later phase drug studies. You should make clear which these are and indicate why you consider it relevant to cite these studies. Either that or remove them.

Minor essential revisions

6. It would be worthwhile to address the crescendo in clamor emanating from the low resource countries to conduct all early phase drug development research in their countries. Evidence of this is easily found by checking out the advertisements presented on the Internet primarily by commercial firms. However, there is also evidence that some nations are trying to attract drug
development research as a source of revenue.

7. The authors should be attentive to typos that are not caught by computer spell checkers; e.g., reference is made to "trails" of new drugs on page 1.

The authors should also carefully check the links provided in their references; e.g., the one in #35 does not function.

8. "Reputationally" (page 4) is a suspect word that does not appear in standard dictionaries that I checked. Also on page 4 there is an inapt use of a metaphor, what you call a "chicken and egg" situation.

9. Page 4, paragraph 1: reference is made to the concern of some companies that their conduct of FIH studies in low resource countries may be detrimental to their reputations. I think their major concern in this regard has been omitted-- that is that they may be made to appear to be exploiting "vulnerable" persons in low resource countries.

9. Page 7, last paragraph, line 3: I doubt that doing FIH trials in low resource countries will "increase economic activity by encouraging research into more innovative products". Most low resource countries do not have the resources to carry out such research and this obstacle will not be resolved by relocating the FIH trials. On the other hand, wealthy industrialized countries where most therapeutic innovation takes place will be spurred by incentives other than the location of the FIH trials.

**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