Author's response to reviews

**Title:** The case for conducting First-in-Human (Phase 0 and Phase 1) clinical trials in Low and Middle income countries.

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**Author's response to reviews:** see over
Dear editor

We appreciate the thoughtful comments. We have revised the paper, carefully considering the comments the reviewers gave us. We provide the edited text and the specific in text reference for each reviewer’s comment.

We appreciate the possibility for an opportunity to publish our paper in your journal and look forward to hearing from you.

Sincerely
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Response to Reviewer's report
Reviewer: Sam K Newton
Reviewer's report:

1) Page Three line 7 the word “trials” has been written as “trails”.

WE HAVE EDITED THIS

2) Page Three, second paragraph. Mention is made of the TGN1412 trial. It will be appropriate if something was said about what the trial was about.

WE HAVE INSERTED A FEW SENTENCES EXPLAINING WHAT THE TRIAL WAS ABOUT (Pg. 3, Par2):

“Interest in FIH clinical trials has grown recently, in part because of the disastrous experience of the phase I clinical trial of the superagonistic anti-CD28 antibody TGN1412 in the United Kingdom. The drug was developed with the intention to stimulate a specific kind of T-cell at the same time controlling the production of other T-cells in order to suppress the immune system.”

2. Summary and Conclusion
The whole thrust of the argument by the authors is that the situation in developing countries have changed (page four, second paragraph). Even though they list well documented reasons why “First in human” trials have historically NOT been done in developing countries, they argue that the situation is now different. If that is what they mean then this should be reflected in the conclusion.

WE HAVE REVISED THE SUMMARY TO REFLECT OUR MAIN ARGUMENT VIS (Pg 10. Last Paragraph):

“…We have argued that while FIH studies have historically not been done in developing countries, the situation in these countries has changed, and some of the reasons for not conducting FIH in these countries no longer hold true. Hence, for products meant primarily for conditions that are most prevalent in developing countries, more FIH trials should be performed in developing countries, provided the protections are at least equivalent to those provided in similar trials in developing country clinical settings …”
Reviewer's report
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.

We appreciate this comment. indeed, the overarching logic of international guidelines has always been about the protection of vulnerable populations and, although we believe that this remains a central tenet of international research ethics, we also believe that this logic can be appealed to obstruct the development of important capacities in research in developing countries. Our aim, in part, is to provide some tension to these prevailing ways of thinking to provoke some debate and perhaps open up some new avenues for constructive dialogue about critically important dimensions of research policy.”

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.

We see our argument as part of a trend to elaborate the criteria for responsiveness. We think, generally, that trials should be designed and situated in ways that will help to resolve important clinical or public health questions in the local area or region. But we also think that if capacities exist in specific locations that would allow more challenging trials to be conducted on locally important conditions, then this should also be considered, as long as protections are at least equivalent. Hence the main thrust of our argument is for doing FIH trials in the particular low resource countries in which the target disease is prevalent (Pg. 4 ; Par. 3)

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.

WE HAVE INCLUDED SOME REFERENCES AND TEXT RELATING TO THIS:
”… An important consideration also relates to the need to conduct both early and late phase clinical trials among subjects who have the target disease. The ethical issues here may need
further reflection, but scientifically, there are circumstances and arguments where it would be beneficial to conduct such studies among the patient population. For example, if there’s need to evaluate a new product that cannot be assessed in healthy individuals for some reason, including ethical considerations, then it may be necessary to recruit patients with the target diseases. In other cases, it may be difficult to extrapolate the results from healthy individuals to a patient population. In such instances, the results pertaining to a new product maybe either over- or under- estimated [1,2]. (Please refer to Pg 5, Par.2)

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.

THIS PARAGRAPH HAS BEEN EDITED AND THE PROBLEMATIC SECTION DELETED, INCLUDING THE REFERENCE.

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.

WE APPRECIATE THIS COMMENT AND AGREE WITH THE REVIEWER; we HAVE EDITED THE PAPER WITH THE EXPLANATION THAT;

“…Some of our arguments below pertain to all phases of clinical trials but are germane to our main thrust about FIH trials…..”

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.

WE APPRECIATE THIS LEGITIMATE COMMENT, AND HAVE NOW INCLUDED IT IN THE PAPER.

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.
WE HAVE CAREFULLY GONE THROUGH THE PAPER AND MADE THE NECESSARY EDITS

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.

WE HAVE EDITED THESE WORDS

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.

WE APPRECIATE THIS COMMENT. IN OUR REVISED VERSION, WE HAVE INCLUDED THIS IMPORTANT REASON (Pg. 6, Par. 2)

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.

WHILE WE AGREE WITH THIS COMMENT;

Our paper is built on this understanding but goes further to argue for a change in people’s mindset, not just in trial location, but about where innovation comes from and re. licensing and other IP innovations that might, in fact, contribute to expanding market opportunities. There are several south driven innovations (Examples of Brazil, India, China—cited in the paper), which should promote this change in mindset. Moreover, NOT being able to host FIH trials is very likely to perpetuate a two-tiered mindset in which the only valuable innovation comes from the North and the South must wait to “catch up”,
Reviewer 3

The authors do not even mention concerns about exploitation that pervade the literature on globalization of clinical trials. The concern is taking advantage of vulnerable populations in countries with limited health care access by studying products that will benefit people in richer countries and bring profits to Western pharmaceutical companies. Maybe they intend to carefully circumscribe the set of trials they mean to include but that is not clear to me (see #2)

WE HAVE CLARIFIED THIS THROUGH OUR DISCUSSION IN THE PAPER.

However, our paper pushes the debate on clinical trials in developing countries further. The WHOLE debate has been framed as one of exploitation. We agree that there is rampant exploitation in the South, in myriad modalities, and we might even concede that FIH trials will be as vulnerable to exploitation in the South as any other trials and the international research ethics community will need to continue to try to figure out what to do about it. BUT…there is also some hazard, we think, in sustaining the status of developing countries as ONLY being capable of fighting exploitation by managing the language of research ethics guidelines and also by building meaningful scientific capacity.

2. I would recommend that they be clearer about the subset of products to which they want their recommendations to apply. On page 3- they say”…for products meant primarily for conditions that are most prevalent in developing countries…”, on page 8, they add “…and unlikely to ever be used in the developed world”, and on page 7 refer to EMEA guidelines for products “…not expected to be licensed in the EU”. The difference between these could be important. HIV, for example, is most prevalent in developing countries, but a major global health problem including in developed countries, whereas trypanosomiasis, for example, is most prevalent in the developing world and products to prevent or treat it are unlikely to be used in the developed world. Accordingly, there are differences in pharmaceutical company interest and investment, and different worries about taking advantage of people and subjecting them to risk for the benefit of others. Further, regulatory agencies may have different requirements for testing products that they ultimately will be asked to license (if proven etc) compared to those they never expect to license. Also, are the authors specifically speaking about trials that involve a Western sponsor/funder/manufacturer and developing country sites?

WE HAVE REITERATED IN THE CONCLUSION THAT WE ARE TALKING PRIMARILY ABOUT “…products meant primarily for conditions that are most prevalent in developing countries”

In the text we mentioned the other categories i.e. a) “those that are unlikely to be used in the developed world” and b) “not expected to be licenced in the EU” in specific contexts. a) to buttress the argument for local regulatory agencies to take more responsibility for such products; and b) to demonstrate that it is possible to develop cooperative mechanisms to address clinical trial needs in developing countries
With regards to the last comment, we include the above category as well as trials that are initiated in developing countries.

“…We need to seriously debate where FIH trials should be done first, whether they are sponsored by Western multinational pharmaceutical firms, smaller Western firms, or firms and research institutes in emerging economies such as China, India, Brazil, South Africa, or (at present less likely but not totally excluded) by such entities in less economically developed countries…”

3. They do not mention that the majority of products tested at the phase 1 level do not end up being approved, or discuss the rationale for including healthy subjects since the purpose of phase 1 is to gather info about toxicity and pharmacokinetics. Commentators worry about exposing “vulnerable” people to risk in phase 1 studies that by design have no therapeutic intent.

WE HAD MENTIONED ON PG. 3 THE PURPOSES OF FIH:

“…FIH trials are studies where an investigational medical product (drug, vaccine, medical device, etc), previously developed and assessed through in vitro or animal testing, or through mathematical modeling, is tested on human subjects for the first time [Error! Bookmark not defined.]. In drug development, such trials involve administering single low, sub-therapeutic doses to a small number of healthy volunteers (10 to 15) to gather preliminary data on the product’s pharmacokinetics and pharmacodynamics. These trials help researchers identify the drug candidate with the best pharmacological parameters to take forward for further development and which ones to leave out…” (Pg. 3, Par. 2)

Especially for phase 0 and FIH for many products, healthy people anywhere can help prove a concept or gather preliminary data on safety.

We do agree that FIH where healthy volunteers are necessary, any volunteers (with the required characteristics) can prove a concept. However, the scientific, ethical and pragmatic reasons we provide make a case for considering conducting FIH in low income countries for conditions that are most prevalent in these countries.(Pg. 5, Par. 1)

However, we also need to recognize the significance of global dynamics, both politically and economically. Our paper, seeks to challenge these dynamics, by stimulating debate about the hazards and implications of perpetuating situations in which the world’s richest countries do all the innovating and producing and the developing world takes hand-outs. It may not be perfectly clear at what point any given country is ready to host FIH trials but there is no doubt that the current approach is sub-optimal for the South.

4. They suggest that there is no reason a phase 1 trial shouldn’t be conducted in a developing country “If the necessary conditions exist to ensure high technical standards and safety of research participants..” (p.6) What are the necessary conditions? GCP? And who decides when the standards and safety parameters are adequate?
We appreciate this comment. Indeed some of the conditions are the GCP. As well as the regulatory authorities, physical infrastructure and trained personnel to both conduct and monitor the trials. In some cases, partnership with the EMEA and FDA has assisted in assessing this. And this is what we recommend in partnership building. (Pg. 7 Par.2; Pg 9, par 2)

5. Is there an argument for “first” in developing countries as opposed to parallel, for example, or sequential?

Parallel or sequential trials would be fine if it’s part of a transition, i.e. to gain experience, test systems, etc., but the point is to transfer the locus of control and scientific and economic priority setting.

6. Perhaps fleshing out the developing world a little more by discussing differences between emerging economies and poorer economies would be useful. Especially to the extent that infrastructure and capacities might differ, as well as commitment to eventually making available or even manufacturing products that make it through later phase testing to licensing.

WE APPRECIATE THIS IMPORTANT COMMENT WE HAVE EXPLAINED THAT:

“…We expect that some of the most advanced emerging economies will continue to lead [etc/], but the key will be to harness the lessons from these countries in terms of what capacity is needed in science and policy and regulation, etc., so that other less well developed countries will have a path to follow.( Pg. 10, Par 2)

7. Not sure what is meant by “cooperative policy mechanisms”

WE HAVE DELETED THE CONFUSING TERM AND EXPLAINED IT THUS (Pg 9. Par.2);

We believe that trial sponsors, ethics review committees, regulatory agencies and other stakeholders should work together to develop explicit policies and programs that would help advance LMICs’ ability to conduct high quality clinical trials, including specific guidance and capacity for FIH trials. Hence, in the absence of well developed regulatory and science funding policies and legal frameworks and clinical capacity, all these players will have to get on the same page to develop a conducive environment, emphasizing safety, clinical excellence and scientific excellence.

8. They mention that the advantages of more FIH in developing countries extend to both developing and developed countries (p. 8 and 9) but do not specify how

WE APPRECIATE THIS COMMENT
First---this comes in the summary where we are not able to elaborate. Second, through the paper, we have endeavored to highlight the benefits to LMICs, for conducting FIH. These are;

“… LMICs will get medical products that truly reflect the prevailing biological and environmental conditions, and will, over time, benefit from capacity building for their personnel, their infrastructures, including for ethics review, confidence and (institutional/national) pride.

With regards to the high income countries (which discussion was beyond the scope of our paper), Furthermore, those who develop most current products, will be able to sell their products on a firmer scientific (and perhaps ethical) basis, will contribute to the building of infrastructure capacity that will help them do more trials in the future, and will be able to sell more of their products either directly to consumers or indirectly through aid initiatives such as the Global Fund to Fight Aids, Tuberculosis and Malaria- to those countries whose economies are generally growing at faster rates than their own…”

However, our main interest was in the LMICs because one would argue that if the benefits actually do accrue to developing countries in infrastructure or later in health terms, then the west will figure out how to take advantage for its own economic gains.

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2. LevineRJ. Appropriate Guidelines for the Selection of Human Subjects for Participation in Biomedical and Behavioral Research, in; The National commission for the protection of Human subjects of Biomedical & behavioral research; Ethical principles and guidelines for the protection of human subjects of research;The Belmont report. Appendix 1: 1-206 DHEW Publication; 1976’ No (os) 78-0013