Author’s response to reviews

**Title:** Industry-Sponsored Clinical Research outside High-Income Countries: An Empirical Analysis of Registered Clinical Trials from 2006-2013

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**Author’s response to reviews:** see over
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Dear editors of Health Research Policy and Systems,

Please find enclosed a re-submission of our previously submitted article ‘Industry-Sponsored Clinical Research in Less-Developed Regions: An Empirical Analysis of Registered Clinical Trials from 2006-2013’.

We have made extensive revisions to the substance of the manuscript and accompanying files in response to the recommendations of the reviewers. Please see below for a point-by-point response to individual comments (in italics).

Thank you, and we look forward to your thoughts on this work.

Sincerely,

Srinivas Murthy
Response to reviewers
Reviewer#1:

Major compulsory revisions: In a survey like this it is important to provide information about the types of trial - that needs statements in the text and a table. You need to break them down into trials for cancer, CV disease, pulmonary disease etc, by adult vs. pediatric populations (last row in Table 2 is an oddball in a table responding to other properites), by drug, device or nutritional supplement etc.

We agree with this statement, and have modified the text accordingly (p9, para2). Additionally, we are now submitting a supplementary appendix with the requested data elements. We are not including this in the main manuscript due to space limitations and the thought that the included figures are more relevant to the ultimate messages of the article. We did not break all of the trials into disease categories, given the variability in the data presented and difficulty in effectively categorizing diseases, outside of the included categories.

Minor essential revisions:
p2, Abstract: Add total trials reviewed (22,511) on line 14.

Completed.

On lines 15/16: Here and elsewhere you separate Central and Eastern Europe but on your map (Fig 1) you do not separate these areas and you do not describe this separation in the text.

We acknowledge that this is a confusing way of presenting information. In our classification scheme, 'Eastern Europe' is both a major geographic group, as well as a smaller region of countries. The major geographic group consists of countries from Eastern Europe and Central Europe. We hopefully have clarified this in the text throughout by re-naming the major group simply 'Europe (non-Western)’, which includes both country groups Eastern and Central Europe.

On line 8 you define this study as limited to RCTs, yet on line 20 (and elsewhere in the text of the paper) you indicate phase 3 and 4 trials. Phase 4 indicates post-marketing surveillance and I am not aware of any such "trials" as being randomized.

Data in ClinicalTrials.gov is provided by investigators who classify their trials according to phase and design. These trials were in the registry as Phase 4, randomized trials. It is possible that these trials should in fact have been labeled as Phase 3 trials, but this would not alter the presentation of our results as we have analyzed Phase 3 and 4 trials together.
p4 line 11: "First" not "Firstly"

_Changed._

Lines 16/17: Is it really true that trials are more expensive in Western Europe than USA. Only one ref is given - I would have expected the reseverse to be true.

_Upon further examination of the reference, there is insufficient primary data to support the claim mentioned, with the original data source not being clear. We have amended the statement in the text accordingly._

Lines 17-19: Yes but other work has shown that Pharma concentrates its research on common diseases in Western countries rather than those common in lower income countries (see for example Seruga et al, Ann Oncol: 2010;21:895).

_Agree that the classic paradigm has been that common diseases in high-income countries are what are typically studied, and we have documented in prior work a large mismatch in disease burden and clinical research. Part of the motivation for this work is to better characterize the nature of research outside high-income settings. The specific reasons for doing research outside of high-income settings are beyond the scope of this work, and deserve further analysis._

Line 21: Suggest delete "however".

_Changed._

p5, line 16: I think I know what you mean by "correspondence with disease burden" but please rephrase to make this clearer.

_Clarified._

p6, Lines 11,12: You define here only "Eastern Europe" (which apparently includes Siberia on the map in Fig 1, but elsewhere you break the survey down to Eastern and Central Europe. You need to define these two regions if you keep that classification.

_Please see the comment above._

p9, line 9: Again"phase 4 trials"

_Please see the comment above._

p10, line 4: Rarely appropriate to claim to be first - and you have only addressed rather trivial "trial differences" in this paper. You have merely classified the trials by region - this is a first step, but evaluating differences in quality, ethics etc will
be more important for the future.

Have changed the text accordingly to temper the language.

Reviewer #2

The authors of the study "Industry-Sponsored Clinical Research in Less-Developed Regions: An Empirical Analysis of Registered Clinical Trials from 2006-2013" addressed an interesting topic and tried to describe the current patterns of industry sponsored clinical trials in more or less financially developed countries and classified them into 21 regions and five major geographic groups. However, I consider, not only this classification should be re-evaluated, but also the distinction of countries according to their development should be based in three categories-more, middle and less developed, instead of two-more and less. For example, Eastern European group includes countries that entered the EU recently (Poland, Latvia etc.) or long time ago (Greece) and consequently not only follow strict rules regarding industry sponsored studies, but their financial status is not similar to Sub Saharan countries, for example. Furthermore, China, a country with a fast growing economy in the recent years is neither a “more developed” country, nor a “less developed” one.

This is an issue that we have wrestled with greatly during study conception. The primary focus of the study is to examine the prevalence of research that drug companies are sponsoring in regions that are not considered high-income countries. We have made changes throughout the manuscript and the figures to better reflect that this is the major comparison, examining research conducted between these two large groups of countries.

An established methodology for country classification, as referenced in our manuscript, uses established research infrastructure as a dividing line for a dichotomous categorical variable. We used this indirectly, taking an established research groups’ (the Global Burden of Disease) and incorporating our database. We admit that both Greece and Sub-Saharan Africa are included in the ‘outside high-income’ bracket, but we are hoping to make broad comparisons against high-income countries with established research traditions rather than distinguish between those outside of that income bracket. We have changed the phraseology throughout the paper, but have kept the two-group classification scheme for your consideration.

Further, given that less than 10% of all of the trials are performed exclusively outside of high-income regions in this classification scheme, further breaking down the categories would make for difficult statistical comparisons.
Additionally, included studies should be classified according to their subject and the relationship between study subject and country of patients’ recruitment (e.g. a trial that studies malaria will naturally recruit patients from countries where malaria is endemic).

This is a fascinating question that is beyond the scope of this analysis. We are unable to exhaustively link disease with disease burden, outside of relatively few endemic infectious diseases such as malaria, which make-up a very small proportion of the trials included.

Finally, I think that characteristics of industry-sponsored clinical trials should be presented per industry, at least for the 10 larger pharmaceutical industries reported in the manuscript, since it is important to see if any of them recruits more patients than the others from less developed countries.

A figure has been added to address this request. These results are included in the supplementary appendix.

Discretionary Revisions
Countries included in the high income Asia Pacific group should be reported.

The countries within each group are included in the reference to the Global Burden of Disease project. This website is updated with the assigned countries.