PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Understanding the investigators: a qualitative study investigating the barriers and enablers to the implementation of local investigator-initiated clinical trials in Ethiopia
AUTHORS	Franzen, Samuel; Chandler, Clare; Enquselassie, Fikre; Siribaddana, Sisira; Atashili, Julius; Angus, Brian; Lang, Trudie

VERSION 1 - REVIEW

REVIEWER	Stephen Allen Prof of Paediatrics and International Health College of Medicine, Swansea University, UK I have no competing interests.
REVIEW RETURNED	11-Aug-2013

RESULTS & CONCLUSIONS	The participants identified enablers and barriers to research (e.g. lack of awareness, confidence and motivation). However, it was not clear whether they were talking about themselves specifically or research inactive colleagues. A limitation of the study was that only clinical staff with an interest or previous experience of trials was included as participants. It would also have been valuable to include other staff as they may provide different insights into barriers to undertaking research. This could be included in the discussion of the study's limitations.
GENERAL COMMENTS	This is an interesting study. Although only a small number of local staff was interviewed, this generated important information that has direct relevance to developing clinical research in low resource settings. The emphasis on the whole research system – rather than just building investigator capacity – was particularly valuable. I have just a few comments: "Limited resource allocation" and "limited material capacity" are included in the same sentence (e.g. Abstract, Results, 2nd sentence and Page 10, lines 23-6). Are these not the same thing? The meaning of "sharing of burdens" was unclear (Abstract, Conclusions, penultimate sentence; Page 3, line 46). Article Summary; article focus: specify "clinical" in "Investigator-initiated trails…" (Page 3, line 4). Article Summary; Key messages: "Clinical trial implementation is influenced by factors at all levels of the research system" seems self-evident. Is this meant to mean that factors were identified at all levels of the research system that impaired undertaking clinical trials?

	The terms “Northern” and “Western” are used interchangeably – suggest select one of the other. The statement that disease management studies are “simple” is incorrect – or at least does not apply to all such studies (Page 4, line 15). Page 7, Lines 38-40. This sentence appears to describe methods rather than results. Page 8. Perhaps the section “Initiating an idea: Awareness, confidence and motivation” should be included under the preceding section: Human and Material Capacity. Figure 2; Page 18. The classification of “Senior and Junior medical researcher” as Non-trial roles is confusing. The meaning of “FIT” and “LIT” should be specified.

REVIEWER	Raffaella M Ravinetto Head of the Clinical Trials Unit Clinical Sciences Department Institute of Tropical Medicine in Antwerp, Belgium I know Trudie Lang, the last author, and even if we never had any joint publications I am an active member of her Global Health Network platform
REVIEW RETURNED	12-Aug-2013

THE STUDY	- This paper addresses a very important topic, and may help to reenforce the advocacy for strengthening research capacity in the South, with the ultimate scope of designing a public health-oriented research agenda. Findings from Ethiopia could help to improve the local strategies, and in the middle or long term they could be extrapolated to other context (the presence of coauthors from Cameroon and Sri Lanka is promising in this sense). - The research question is clearly defined. However, there is throughout the paper a kind of negative perception of any research carried out with foreign organizations (e.g., "foreign research organizations with their own agenda"). I would recommend to take in consideration also the increasing phenomenon of non-commercial North-South partnership in research, where local and foreign partners may join forces to address public health relevant research questions (e.g, INDEPTH, WANETAM....), and which could be seen as a complementary model beside IITs for promoting public health-oriented research and the interest of Southern populations (by the way, most respondents had positive experience with international collaborations, and the GHN platform also represents a positive model). - It is recommended that a few concrete examples are given of what is meant throughout the paper by "simple" or "pragmatic" trials (operational research? Implementation studies? Effectiveness studies?) - Some of the terms used in Table 2 needs a definition, otherwise they seem to overlap (e.g, trial manager vs study coordinator)

	- It is not clear if the sentence at page 11 on Ethiopian culture ("a nation that historically discourage...") is based on the study findings, on existing literature or on the personal opinion of the authors. - The two mentions of DFDi, especially the one in the conclusion, are not clear - they should be better linked to the rest of the paper
RESULTS & CONCLUSIONS	- While the research question clearly concerns the Ethiopian context, the discussion and conclusion (not the abstract) seem to suggest that answers have been provided at a broader level "for LMICs". However, the study clearly focuses on Ethiopia, with quite a small sample size. If the Authors think that their findings and suggestions for improvement are also already relevant for other contexts, they should elaborate and justify this. Also, the statement at page 10 that the study "provides evidence that IITs would generate highly useful and applicable data" does not seem consistent with the rest of the paper: this message rather comes from the background and rationale, while the study looks at obstacles to IITs. - It is not always clear how the different findings have been prioritized in the discussion. For instance, the problems related to ethics and regulatory review are not analyzed in details in the discussion, nor ways to improve the current shortcomings. Nonetheless, this is an important and complex finding, since the external review has been indicated as an obstacle, but it remains essential to protect the local populations from non-pertinent research including North-driven research agendas. For instance (2), lack of resources and of salary incentives have been identified as obstacles to IITs, but there might more discussion about concrete measures to overcome this obstacles in the specific Ethiopian context, e.g. on ways to attract external funds for local Investigators. For instance (3), at page 8 vulnerable populations are mentioned, but this challenge is not retaken in the discussion. However, this could be a crucial point for local investigators in LMICs (e.g,how to serve the interest of these populations, who are at risk of exploitation in research but also desperately in need of research addressing their health problems?) and might have deserve more discussion - Findings are complex, due to the complexity of the subject of the research, so it could be helpful that in the discussion a kind of global overview was given of the possible mechanisms proposed to overcome the different obstacles, by identifying per each of them the concerned stakeholders (who does what). A summary table could better guide the reader to understand the global picture and the interactions among different local and international stakeholders. - The Authors could substantiate their statement that this is the first study of this kind in LMICs, for instance by describing the literature search they did to prove so. Some authors seem have already described their experience (e.g. Trials 200, 12:145)
REPORTING & ETHICS	The ethical approval in Ethiopia should be attached (only the one in UK is mentioned in the paper). If not available, a justification should be provided.
GENERAL COMMENTS	It would be very useful to share the semi-structured questionnaires, also as a way to repeat similar studies in other countries, and to get comparable data from similar and different contexts Given that the paper aims at giving a compelling voice to local

	investigators, it is somehow surprising that only one author is from Ethiopia and that the majority of authors are based in Europe. It may be recommended to describe the study team roles and responsibilities, so as to explain this apparent contradiction in authorship

REVIEWER	Dr Gail Davey Reader in Global Health Brighton & Sussex Medical School UK Competing Interests: I have three current research collaborations with one author (FE) and one with another (TL).
REVIEW RETURNED	13-Aug-2013

THE STUDY	No patients are involved; this is a qualitative study in which researchers but not patients participated. This is an exploratory qualitative study, so it is not appropriate to define an outcome measure. This is a small, efficient and clearly-outlined study exploring barriers and enablers to investigator-initiated trials in Ethiopia. The authors explain why this is an important area of research and note the very limited evidence on this topic available from LMICs to date. The '10/90 gap' might be more accurately described as 'where only 10% of global health research expenditure is allocated to diseases the *primarily* affect 90% of the world's population', since LMIC populations are also subject to conditions that are also found in HICs and attract considerable funding. I am puzzled about the description of Ethiopia as 'a UK DfID priority funded country for research development', supported by a link to the Royal Society-DfID Africa Capacity Building initiative, a relatively small funding scheme. The description seems a little spurious, and the link with DfID is not developed further until the penultimate sentence of the Conclusion - is this to capture the interest of a British reader? The authors might want to reconsider. In the Methods, para 3, we are told that 'participants said they would speak more openly if discussions were not audio recorded'. The issue of free speech is very important, and I would like to see more discussion of this under the 'Strengths and Limitations' section of the Discussion.
RESULTS & CONCLUSIONS	The barriers to investigator-initiated trials are clearly laid out, and the model generated (Fig 3) is very helpful. The section on enablers is brief, and refers mostly to potential enablers (eg training and experience exchange). I wonder if any existing and locally-specific enablers to trials came out in the interviews? These might include the highly-developed 'recording' culture (paper-based registers and logs dutifully kept even in remote areas) and the hierarchical 'command' culture which enables the rapid mobilisation of whole communities. Under 'Regulatory and other administrative bottlenecks', 2nd para, the Ethiopian Bioethics Initiative is mentioned. A little more explanation of this Initative, and how it might impact trial-readiness

	in Ethiopia, would be welcome in the Discussion. The Discussion is strong, and correctly identifies the need to develop research systems and research culture alongside individual researchers. Altering research culture so that research is more important to promotion is important, but even this will not attract individuals into research if there is a major financial disincentive (compared with, for example, private clinical practice or public health consultancies). The example of Jimma University shows that even altering the value placed on research may not lead to significant changes in research output if other disincentives are not addressed.
REPORTING & ETHICS	No checklist or reporting statement is applicable to this study.
GENERAL COMMENTS	Two small comments on the references - 1. The referencing system used does not appear to separate multiple references within brackets by a comma, which makes the citations unclear in a few cases. This may be an artefact of the online submission, but I hope can be altered in the proof. 2. 'Health' is mis-spelled in ref 23.

REVIEWER	Datiko, Daniel University of Bergen
REVIEW RETURNED	16-Aug-2013

GENERAL COMMENTS	**General comments** The study addresses one of the major deficiencies in research in the country and gives account to real problem and tries to find out the bottlenecks and possible solution. It has involved Addis Ababa and Gondar one of the areas with rich experience of conducting operational researches including clinical trials. However, it does not include major areas of the country specifically Jimma and did not interview potential sources form the ethical review board and the schools to check what is going on. More is said on the administrative part and training needs is not clearly shown. The strength of the study is it addresses key issue and highlights the need and potential enablers and barriers. I am afraid that the findings are over stated and may not reflect the existing situations. For example how many trails were applied and how many were rejected how long did it take and what were the problems is not

	checked. **Introduction** 1. More note about the local clinical trials capacity and what we know so far in terms of their contribution to policy 2. Paragraph one: line 5 often not relevant to LMICs : is over stated as the main clinical practices we have is based on international experience and some LMICs 3. Paragraph 3 line 7, …a U.K ……research development …..do we need this **Methods** Study area omits most parts of the country focused on Gondar and Addis Ababa, why are other areas omitted or not involved Paragraph 3 line 5 no audio recorded why and what are the limitations related to this. It should clearly come out. This shades haziness on the description that we have in the article as it may be the feeling or assumed expression of the participants. The clinical trailists involved could understand the importance and consent for recording. **A role for investigator-initiated trials** Line 1 ….and regretted the lack of local evidence to guide policy ….does this mean that policy is not supported by evidence or could have been supported by clinical trial Knowledge about research priority with regard to clinical trial is not shown in the study? Does it show that the country does not need clinical trial and does not have policy outlines or the investigators failed to pick it?

	Human and material capacity The investigators blame the curriculum for not including clinical research and extra time is requested by participants so that clinical trials will be done. Do they have any comment from the institutions working on this as they have interview areas where medical schools are based? Does extra time guarantee clinical trial? Why was not it possible to conduct clinical trial as part of the routine work? More notes on this? The term phobia as described here does not make sense better replaced by different wording or go back to the original document o check **Regulatory and other administrative bottlenecks** I am not convinced that the regulatory system does not have guideline and creates major bottle neck. May be the team from Gondar could complain with regard to the team in Addis mostly they are expected to be part of the review team…is there anything like this which appeared during the interview? **The research system** Paragraph 2 adverse regulatory and administrative systems: more negative and give s no credit for the work done in the country. It should modified and check in the light of the services the system has offered. **Building a receptive research environment**

	Paragraph 3 …..the sentence which states……discouraged personal autonomy is not clear or needs to be better expressed **Prioritizing research systems** Mentions Jimma University for the best practice but ignored hearing from the investigators applauded **References** In the references please add some policy documents and tools available le in the country

VERSION 1 – AUTHOR RESPONSE

Reviewer: Stephen Allen
Prof of Paediatrics and International Health College of Medicine, Swansea University, UK I have no competing interests.

Comment 1:
The participants identified enablers and barriers to research (e.g. lack of awareness, confidence and motivation). However, it was not clear whether they were talking about themselves specifically or research inactive colleagues.
Response 1:
We have revised phrasing in sentences to clarify this. (Page 8; Section- Initiating an idea: Awareness, Confidence and Motivation)

Sentences changed to: “Participants reported that limited awareness of trial research among their colleagues was a common reason for trials not being attempted”….. “If individuals had considered conducting a trial, many participants said that most researchers were not confident to initiate one themselves”….. “Even when potential investigators felt ready to conduct a trial, many participants said that the motivation for undertaking them was insufficient and this discouraged their colleagues from attempting them”.

Comment 2:
A limitation of the study was that only clinical staff with an interest or previous experience of trials was included as participants. It would also have been valuable to include other staff as they may provide different insights into barriers to undertaking research. This could be included in the discussion of the study’s limitations.
Response 2:
Other staff and stakeholders were not included in this study because, as a formative study, it was limited in scope. Subsequent research in other settings, to be published shortly, has included these stakeholders among others.

Sentences added to “Strengths and Limitations” section; page 11: Although this limits the breadth of perspectives and generalizability of findings, the study sample accessed diverse experiences……”. AND “Our subsequent research on this topic has been conducted in other settings, including a wider range of stakeholders in order to overcome these limitations.”

This is an interesting study. Although only a small number of local staff was interviewed, this generated important information that has direct relevance to developing clinical research in low resource settings. The emphasis on the whole research system – rather than just building investigator capacity – was particularly valuable.

I have just a few comments:

Comment 3:
“Limited resource allocation” and “limited material capacity” are included in the same sentence (e.g. Abstract, Results, 2nd sentence and Page 10, lines 23-6). Are these not the same thing?
Response 3:
“Limited resource allocation”, refers to the overall provision of finances provided by the decision makers within the research system, and how these are allocated to provide different resources. To clarify and simplify, we have revised “resource allocation” to “funding allocation”.

Comment 4:
The meaning of “sharing of burdens” was unclear (Abstract, Conclusions, penultimate sentence; Page 3, line 46).
Response 4:
“Sharing of burdens” refers to sharing the cost of equipment/resources, salaried time for research support staff, and time burdens for completing administrative procedures and procurement. Term revised to “sharing of financial and project management burdens”

Comment 5:
Article Summary; article focus: specify “clinical” in “Investigator-initiated trails…” (Page 3, line 4).
Response 5:
Revised

Comment 6:
Article Summary; Key messages: “Clinical trial implementation is influenced by factors at all levels of the research system” seems self-evident. Is this meant to mean that factors were identified at all levels of the research system that impaired undertaking clinical trials?
Response 6:
Yes. We agree clarification and a more insightful statement required. Changed to “Barriers to clinical trial implementation were identified at every level of the research system, demonstrating the need for an integrated approach to research capacity strengthening”. (Page 3 Article Summary; Key messages)

Comment 7:
The terms “Northern” and “Western” are used interchangeably – suggest select one of the other.
Response 7:
All use of “Western” changed to “Northern”, in accordance with most recently used terminology.

Comment 8:
The statement that disease management studies are “simple” is incorrect – or at least does not apply to all such studies (Page 4, line 15).

Response 8:
By simple we do not mean easy, but rather Richard Peto's use of the term to mean studies with few endpoints, broad eligibility criteria and often involving approved interventions to investigate comparative effectiveness. The term pragmatic is used to describe trials that measure effectiveness and seek to increase external validity.
The following sentence has been added after the first use of these terms (Page 4; introduction; paragraph 2) "By "pragmatic" and "simple" we are referring to studies that are designed to test effectiveness, have few endpoints and broad eligibility criteria, thereby increasing external validity.[10 ,11]"

10. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? Stat Med 1984;3(4):409-22.
11. Godwin M, Ruhland L, Casson I, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. BMC Med Res Methodol 2003;3:28 doi: 10.1186/1471-2288-3-28.

Comment 9:
Page 7, Lines 38-40. This sentence appears to describe methods rather than results.
Response 9:
Although the line reference is different on our version, we think the reviewer is referring to the study population section, located in results: We justify this because it is common for the study population information to be found in the results section of qualitative articles. This is because the recruitment is not determined a priori and is an evolving process.

Comment 10:
Page 8. Perhaps the section "Initiating an idea: Awareness, confidence and motivation" should be included under the preceding section: Human and Material Capacity.
Response 10:
We appreciate this suggestion, but feel that this section is best left where it is. Human resource capacity typically refers to the quantity of available and suitably skilled workforce. Awareness, confidence and motivation, refer more to individual choices regarding their involvement with trials.

Comment 11:
Figure 2; Page 18. The classification of "Senior and Junior medical researcher" as Non-trial roles is confusing. The meaning of "FIT" and "LIT" should be specified.
Response 11:
Several reviewers found the recruitment matrix unclear. We have completely changed figure 2 and added explanation to the "study population" section. (Page 5, Results, Study Population) -
"Participants had varied job roles. Those currently working on a clinical trial included: Senior investigators (n=2), Trial managers and coordinators (n=5), laboratory personnel (n=5) and research nurses (n=2). We also recruited 6 medical researchers not currently working on a clinical trial, 3 of whom had previous trial experience and 3 that did not. The participants had experience in a diverse range of medical professional experience domains (figure 2)."

Reviewer: Raffaella M Ravinetto
Head of the Clinical Trials Unit
Clinical Sciences Department
Institute of Tropical Medicine in Antwerp, Belgium

I know Trudie Lang, the last author, and even if we never had any joint publications I am an active member of her Global Health Network platform

Comment 12:
- This paper addresses a very important topic, and may help to reenforce the advocacy for strengthening research capacity in the South, with the ultimate scope of designing a public health-oriented research agenda. Findings from Ethiopia could help to improve the local strategies, and in the middle or long term they could be extrapolated to other context (the presence of coauthors from Cameroon and Sri Lanka is promising in this sense).
Response 12:
We thank the reviewer for this comment. Since the reviewer shows interest in the future research, we have added details of future research.
“Our subsequent research on this topic has been conducted in other settings, including a wider range of stakeholders in order to overcome these limitations.” (Page 11- Strengths and Limitations)

Comment 13:
- The research question is clearly defined. However, there is throughout the paper a kind of negative perception of any research carried out with foreign organizations (e.g., "foreign research organizations with their own agenda"). I would recommend to take in consideration also the increasing phenomenon of non-commercial North-South partnership in research, where local and foreign partners may join forces to address public health relevant research questions (e.g, INDEPTH, WANETAM....), and which could be seen as a complementary model beside IITs for promoting public health-oriented research and the interest of Southern populations (by the way, most respondents had positive experience with international collaborations, and the GHN platform also represents a positive model).
Response 13:
We recognise that there are many good partnerships and that they have a great deal to offer, in complement with local investigator-led studies. However it is widely acknowledged that some partnerships are less equal than rhetoric suggests, including in terms of setting the themes of research. The purpose of this paper is to give more perspective from the “Southern end”, which includes appreciation for international collaborations that support Southern-led initiatives.

Comment 14:
- It is recommended that a few concrete examples are given of what is meant throughout the paper by "simple" or "pragmatic" trials (operational research? Implementation studies? Effectiveness studies?)
Response 14: (Same as response 8)
By simple we mean we do not mean easy, but rather Richard Peto’s use of the term to mean studies with few endpoints, broad eligibility criteria and often involving approved interventions to investigate comparative effectiveness. . The term pragmatic is used to describe trials that measure effectiveness and seek to increase external validity.
The following sentence has been added after the first use of these terms (Page 4; introduction; paragraph 2) “By “pragmatic” and “simple” we are referring to studies that are designed to test effectiveness, have few endpoints and broad eligibility criteria, thereby increasing external validity.[10 ,11]”

10. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? Stat Med 1984;3(4):409-22.
11. Godwin M, Ruhland L, Casson I, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. BMC Med Res Methodol 2003;3:28 doi: 10.1186/1471-2288-3-28.

Comment 15:
- Some of the terms used in Table 2 needs a definition, otherwise they seem to overlap (e.g, trial manager vs study coordinator)
Response 15: (Same as response 11)
Several reviewers found the recruitment matrix unclear. We have completely changed figure 2 and added explanation to the “study population” section. (Page 5, Results, Study Population) - “Participants had varied job roles. Those currently working on a clinical trial included: Senior investigators (n=2), Trial managers and coordinators (n=5), laboratory personnel (n=5) and research nurses (n=2). We also recruited 6 medical researchers not currently working on a clinical trial, 3 of whom had previous trial experience and 3 that did not. The participants had experience in a diverse range of medical professional experience domains (figure 2).”

Comment 16:
- It is not clear if the sentence at page 11 on Ethiopian culture (''a nation that historically discourage...'') is based on the study findings, on existing literature or on the personal opinion of the authors.
Response 16:
We agree this needs clarification. This point was raised by participants during discussions over the feasibility of audio recording. Statement added; page 5; methods; paragraph 3 – “This was because they would be uncomfortable criticising partners or regulatory bodies while being recorded. One participant explained that this worry was a result of the legacy left by previous authoritarian regimes.”).

The suggestion that previous regimes that discouraged personal autonomy could reduce the ability of individuals to act as agents in change is the supposition of the authors. Sentence changed to: “We also propose that previous regimes that actively discouraged autonomy, could have left a legacy that reduced the ability of individuals to act as agents in change”. (Page 10, Building a receptive research environment, paragraph 3)

Comment 17:
- The two mentions of DFDi, especially the one in the conclusion, are not clear - they should be better linked to the rest of the paper
Response 17:
All references to DFID removed, as reviewers agree they are distracting and unnecessary.

Comment 18:
- While the research question clearly concerns the Ethiopian context, the discussion and conclusion (not the abstract) seem to suggest that answers have been provided at a broader level "for LMICs". However, the study clearly focuses on Ethiopia, with quite a small sample size. If the Authors think that their findings and suggestions for improvement are also already relevant for other contexts, they should elaborate and justify this.
Response 18:
We do not think that the specifics of the findings can be directly applied to other contexts. However, the broader themes are likely to have relevance to other settings, particularly those with similar resource constraints, limited prioritisation of research and similar medical education style. However, this would need to be done with caution, and in context with other research. We feel this has been clearly stated in the “Prioritising research systems” and “Strengths and Limitations sections”. However to clarify this, we revised the “Prioritising research systems” (page 11) and “Conclusions” section (page 12) to emphasise that the findings are Ethiopia specific.

Comment 19:
Also, the statement at page 10 that the study "provides evidence that IITs would generate highly

useful and applicable data" does not seem consistent with the rest of the paper: this message rather comes from the background and rationale, while the study looks at obstacles to IITs.
Response 19:
Agree that the statement is too strong. However data on participants views on trials supports this. Revised to “This study highlights that Ethiopian investigators think that investigator-initiated trials would generate highly useful and applicable data, supporting the call for more local evidence generation in LMICs”. (Page 9, Discussion, paragraph 1)

Comment 20:
- It is not always clear how the different findings have been prioritized in the discussion.
For instance, the problems related to ethics and regulatory review are not analyzed in details in the discussion, nor ways to improve the current shortcomings. Nonetheless, this is an important and complex finding, since the external review has been indicated as an obstacle, but it remains essential to protect the local populations from non-pertinent research including North-driven research agendas.
For instance (2), lack of resources and of salary incentives have been identified as obstacles to IITs, but there might more discussion about concrete measures to overcome this obstacles in the specific Ethiopian context, e.g. on ways to attract external funds for local Investigators.
For instance (3), at page 8 vulnerable populations are mentioned, but this challenge is not retaken in the discussion. However, this could be a crucial point for local investigators in LMICs (e.g,how to serve the interest of these populations, who are at risk of exploitation in research but also desperately in need of research addressing their health problems?) and might have deserve more discussion
Response 20:
Since the participants did not discuss methods of attracting funding or dealing with vulnerable populations, we did not feel it would be appropriate to discuss issues in detail solely based on our opinions, or wider literature.
However, we agree the difficulty with ethical and regulatory review is an important issue to participants. We did not discuss this in detail because we did not recruit any regulators as participants (Ethics board members were in the participants), so we could not get a fully balanced argument. However, we do feel there should be more information on initiatives that seek to improve the ethical review situation.
We have added details on The Ethiopian Bioethics Initiative in the “Regulatory and other administrative bottlenecks” section (Page 6; Results- “One participant explained that The Ethiopian Bioethics Initiative is already working towards this. Funded by the European and Developing Countries Clinical Trial Partnership, The Ethiopian Bioethics Initiative helps research sites to form institutional review boards (IRBs) and train the committee members on basic principles of ethical clearance. Under this grant they have established and trained 11 IRBs.) and in the “Prioritising research systems” section (Page 10, Discussion- “Meanwhile The Ethiopian Bioethics Initiative is working hard to strengthen regulatory procedures and provides a successful example of developing ethical review capacity”.)

Comment 21:
- Findings are complex, due to the complexity of the subject of the research, so it could be helpful that in the discussion a kind of global overview was given of the possible mechanisms proposed to overcome the different obstacles, by identifying per each of them the concerned stakeholders (who does what). A summary table could better guide the reader to understand the global picture and the interactions among different local and international stakeholders.
Response 21:
We agree that such a summary would be highly useful. The lead author is currently writing a review article to summarise health research capacity strengthening efforts post the year 2000. However, this is a large, complex topic, and requires an entire article to itself. The purpose of this article is to describe the situation in Ethiopia, from the perspectives of local investigators. We feel that such a summary within this article would be distracting.

Comment 22:
- The Authors could substantiate their statement that this is the first study of this kind in LMICs, for instance by describing the literature search they did to prove so. Some authors seem have already described their experience (e.g. Trials 200, 12:145)
Response 22:
We have rephrased the sentence to: “To our knowledge this is the first empirical research study exploring investigator-initiated trial implementation in Low-and Middle-Income Countries”. (Page 3, Article Summary; Strengths and limitations)
We did an extensive search of the literature on Pubmed and grey literature through Google, using the main search terms of Health AND Research AND Capacity Strengthening AND Developing Countries (also other forms of these terms) as part of the literature review undertaken by the lead author, mentioned in Response 21. Other papers have described personal experiences and others investigate general aspects of medical research, but we found no empirical research studies investigating implementation of investigator-initiated trials in developing countries.

Comment 23:
The ethical approval in Ethiopia should be attached (only the one in UK is mentioned in the paper). If not available, a justification should be provided.
Response 23:
This study began as an informal pilot, to generate ideas, questions and guide planning for a subsequent larger study. OXTREC approval was gained through an expedited review because it was classified as minimal risk. We did not apply for Ethiopian ethics approval because of the exploratory and minimal risk nature of the work. However, during the pilot work in Ethiopia, it became clear that useful information was being generated and the researchers we worked with suggested it would be useful if the findings were written as an article and published. They informed us that this would be appropriate without Ethiopian ethics approval, if each participant was fully informed that the study only had Oxford approval, and still agreed to take part. After verbal consent, each participant was subsequently contacted to explain this and to gain written confirmation of consent.

Comment 24:
It would be very useful to share the semi-structured questionnaires, also as a way to repeat similar studies in other countries, and to get comparable data from similar and different contexts
Response 24:
We strongly agree and would encourage other groups to replicate our study in their settings. Such an activity is currently being organised with a group in Peru. However, the semi-structured questions from this study were a work in progress. The development of these questionnaires was an outcome of this formative work and the questionnaires have subsequently been used and adapted in 2 further studies to be published shortly. We therefore feel it will be more appropriate to share the final validated questionnaires, in the subsequent article, rather than share the questionnaires from this study.

Comment 25:
Given that the paper aims at giving a compelling voice to local investigators, it is somehow surprising that only one author is from Ethiopia and that the majority of authors are based in Europe. It may be recommended to describe the study team roles and responsibilities, so as to explain this apparent contradiction in authorship.
Response 25:
The reason there are 4 authors from the U.K. is that SF (the corresponding author) is a PhD student, and BA, TL, and CC are his supervisors. They therefore have contributed a lot to the study. However, if SF was an established independent researcher, less supervisory input would have been required and there would have been fewer U.K. based authors, giving a more equitable balance of author

location. The author's roles in the study have been indicated in the contributions section (page 12), and we have added student and supervisor responsibilities.

Reviewer: Dr Gail Davey
Reader in Global Health
Brighton & Sussex Medical School
UK

Competing Interests:
I have three current research collaborations with one author (FE) and one with another (TL).

This is a small, efficient and clearly-outlined study exploring barriers and enablers to investigator-initiated trials in Ethiopia. The authors explain why this is an important area of research and note the very limited evidence on this topic available from LMICs to date.

Comment 26:
The '10/90 gap' might be more accurately described as 'where only 10% of global health research expenditure is allocated to diseases the *primarily* affect 90% of the world's population', since LMIC populations are also subject to conditions that are also found in HICs and attract considerable funding.
Response 26:
Changed in manuscript (page 4, Introduction, paragraph 1)

Comment 27:
I am puzzled about the description of Ethiopia as 'a UK DfID priority funded country for research development', supported by a link to the Royal Society-DfID Africa Capacity Building initiative, a relatively small funding scheme. The description seems a little spurious, and the link with DfID is not developed further until the penultimate sentence of the Conclusion - is this to capture the interest of a British reader? The authors might want to reconsider.
Response 27:
All references to DFID removed, as reviewers agree they are distracting and unnecessary.

Comment 28:
In the Methods, para 3, we are told that 'participants said they would speak more openly if discussions were not audio recorded'. The issue of free speech is very important, and I would like to see more discussion of this under the 'Strengths and Limitations' section of the Discussion.
Response 28:
We have added the participants' explanations for this in to the methods section, ("This was because they would be uncomfortable criticising partners or regulatory bodies while being recorded. One participant explained that this worry was a result of the legacy left by previous authoritarian regimes" – page 5) and added the following sentence to the "Strengths and "limitations Sections" (page 11) – "Inability to audio record the discussions may have had some impact on the accuracy of notes taken. However, we felt it was more important to ensure open and frank dialogue and the detailed notes were subsequently reviewed by participants to ensure accurate representation".

Comment 29:
The barriers to investigator-initiated trials are clearly laid out, and the model generated (Fig 3) is very helpful. The section on enablers is brief, and refers mostly to potential enablers (eg training and experience exchange). I wonder if any existing and locally-specific enablers to trials came out in the interviews? These might include the highly-developed 'recording' culture (paper-based registers and

logs dutifully kept even in remote areas) and the hierarchical 'command' culture which enables the rapid mobilisation of whole communities.
Response 29:
We did not mention that rapid recruitment was possible due to large pools of patients who would usually give consent readily. This has been added to the “Operational hurdles” section (Results, page 7 – paragraph 2) and the paragraph restructured to emphasise operational enablers. No mention of command or recording culture was made by participants.

Comment 30:
Under 'Regulatory and other administrative bottlenecks', 2nd para, the Ethiopian Bioethics Initiative is mentioned. A little more explanation of this Initative, and how it might impact trial-readiness in Ethiopia, would be welcome in the Discussion.
Response 30:
We have added details on The Ethiopian Bioethics Initiative in the “Regulatory and other administrative bottlenecks” section (Page 6; Results) and the “Prioritising research systems” section (Page 10, Discussion). Please also see response 20 to reviewer #2 comment.

Comment 31:
The Discussion is strong, and correctly identifies the need to develop research systems and research culture alongside individual researchers. Altering research culture so that research is more important to promotion is important, but even this will not attract individuals into research if there is a major financial disincentive (compared with, for example, private clinical practice or public health consultancies). The example of Jimma University shows that even altering the value placed on research may not lead to significant changes in research output if other disincentives are not addressed.
Response 31:
Thank you for this important point. We completely agree and it needs adding to the discussion. The following sentence has been revised in the “Building a receptive research environment” section (page 10) – “Providing protected time for research and recognising research within careers would help motivate investigators to undertake trials through positive reinforcement, but this alone may not be sufficient without adequate salaries to offset lost revenue from private practice and consultancy work.

Comment 32:
Two small comments on the references -
1. The referencing system used does not appear to separate multiple references within brackets by a comma, which makes the citations unclear in a few cases. This may be an artefact of the online submission, but I hope can be altered in the proof.
Response 32:
Apologies. We have amended EndNote formatting to add commas.

Comment 33:
2. 'Health' is mis-spelled in ref 23.
Response 33:
Apologies. Amended

Reviewer: Daniel Datiko
University of Bergen

General comments
Comment 34:
The study addresses one of the major deficiencies in research in the country and gives account to

real problem and tries to find out the bottlenecks and possible solution. It has involved Addis Ababa and Gondar one of the areas with rich experience of conducting operational researches including clinical trials. However, it does not include major areas of the country specifically Jimma and did not interview potential sources form the ethical review board and the schools to check what is going on. More is said on the administrative part and training needs is not clearly shown.
Response 34:
This is a small formative study, and as such, had limited scope. It was not our intention to provide a representative picture of all research in Ethiopia, but rather to represent local investigators experiences and perspectives. This is acknowledged in the "strengths and limitations" section. Health research is mainly carried out in the cities of Addis Ababa, Gondar and Jimma. We focussed on Addis Ababa and Gondar because as the reviewer points out, they have rich experiences in research. Therefore, we recruited from 2 of the 3 main cities conducting health research.
We describe some findings from a study at Jimma University in the discussion; this was a major global study, and Jimma was their sole case study from Ethiopia. As such we believe that only recruiting from Addis Ababa and Gondar is sufficient for the purposes of our study.
Representatives from ethics review boards (n=3), senior research leaders from medical schools (n=5) and 1 ex government official, were included as participants. This is explained in the recruitment matrix (figure 2). As the other reviewers point out, this figure is not clear, so revisions have been made to this – please see comment 11 amendment.

Comment 35:
The strength of the study is it addresses key issue and highlights the need and potential enablers and barriers. I am afraid that the findings are over stated and may not reflect the existing situations. For example how many trails were applied and how many were rejected how long did it take and what were the problems is not checked.
Response 35:
Review times for specific studies and operational problems are mentioned in the "operational barriers" section. The "regulatory and other administrative problems" section also deals with this in detail. A breakdown of trial registration in Ethiopia is given in the methods (figure 1).
The purpose of the study was to represent participants' perspectives and experiences, and to reflect on these, not to provide a comprehensive regulatory overview. We therefore feel that we sufficiently addressed this area and any further details are beyond the scope of this study.

Introduction
Comment 36:
1. More note about the local clinical trials capacity and what we know so far in terms of their contribution to policy
Response 36:
We agree that this needs to be more explicit. We have added an extra point to table 1 (page 4) providing references discussing the role of local clinical trials in contributing to policy.
• More likely to influence policy [13] and sustainably link research to action [14]

Comment 37:
2. Paragraph one: line 5 often not relevant to LMICs : is over stated as the main clinical practices we have is based on international experience and some LMICs
Response 37:
Within the Introduction, this point is general, not specific to Ethiopia. Within the results, we do not argue that the main clinical practices in Ethiopia are not based on international experience. Rather, the international evidence cannot be contextually tailored and as such is not always relevant. Locally derived evidence that adapts international guidelines would be preferred as it was deemed to be more relevant and useful. We therefore feel that this statement is fair.

Please see quote under “A role for investigator-initiated trials” - “We don’t have the evidence to change local practices but we definitely know some written guidelines don’t work. There are a number of unanswered questions for trials but we don’t know how to do them. We need clinical research [in disease areas] that has a different effect in Ethiopia, for example HIV and TB. These diseases are similar as to other places but we have had little success [controlling them] here. So why? Where are the mistakes? These sorts of investigations are easy, they would support awareness and fill gaps.” FGD - 3 PPT – 1-

Comment 38:
3. Paragraph 3 line 7, …a U.K ……research development …..do we need this
Response 38:
All references to DFID removed, as reviewers agree they are distracting and unnecessary.

Methods
Comment 39:
Study area omits most parts of the country focused on Gondar and Addis Ababa, why are other areas omitted or not involved
Response 39: (Same as response 34)
This is a small formative study, and as such, had limited scope. It was not our intention to provide a representative picture of all research in Ethiopia, but rather to represent local investigators experiences and perspectives. This is acknowledged in the “strengths and limitations” section. Health research is mainly carried out in the cities of Addis Ababa, Gondar and Jimma. We focussed on Addis Ababa and Gondar because as the reviewer points out, they have rich experiences in research. Therefore, we recruited from 2 of the 3 main cities conducting health research.
We describe some findings from a study at Jimma University in the discussion; this was a major global study, and Jimma was their sole case study from Ethiopia. As such we believe that only recruiting from Addis Ababa and Gondar is sufficient for the purposes of our study.

Comment 40:
Paragraph 3 line 5 no audio recorded why and what are the limitations related to this. It should clearly come out. This shades haziness on the description that we have in the article as it may be the feeling or assumed expression of the participants. The clinical trailists involved could understand the importance and consent for recording.
Response 40:
The majority of participants were uncomfortable with audio recording and said they would speak more openly, not being audio recorded. We have added the participants’ explanations for this in the methods section (Page 5, paragraph 2 “This was because they would be uncomfortable criticising partners or regulatory bodies while being recorded. One participant explained that this worry was a result of the legacy left by previous authoritarian regimes”.), and added the following sentence to the “Strengths and “limitations Sections” (page 11 final paragraph) – “Inability to audio record the discussions may have had some impact on the accuracy of notes taken. However, we felt it was more important to ensure open and frank dialogue, and the detailed notes were subsequently reviewed by participants to ensure accurate representation”.

Comment 41:
A role for investigator-initiated trials Line 1 ….and regretted the lack of local evidence to guide policy ….does this mean that policy is not supported by evidence or could have been supported by clinical trial Knowledge about research priority with regard to clinical trial is not shown in the study? Does it show that the country does not need clinical trial and does not have policy outlines or the investigators failed to pick it?

Response 41:
Sentence revised to clarify this – “All participants reported that too few clinical trials are conducted in Ethiopia, and felt this limited the ability for guidelines to be based on local evidence.”
Knowledge about disease research priorities was gathered from participants so research priorities do exist, and participants are aware of them. Since this study investigates participant perspectives of barriers and enablers to clinical trials, we did not think that context on research priority setting was necessary.

Human and material capacity
Comment 42:
The investigators blame the curriculum for not including clinical research and extra time is requested by participants so that clinical trials will be done. Do they have any comment from the institutions working on this as they have interview areas where medical schools are based? Does extra time guarantee clinical trial? Why was not it possible to conduct clinical trial as part of the routine work? More notes on this?
Response 42:
To prevent confusion, the authors do not blame the curriculum, the participants (some of whom were investigators) thought that not including more research in the medical curriculum was part of the problem.
Five participants had experience of research leadership in medical schools (as stated in the recruitment matrix in figure 2), and their comments are represented in the paper. To clarify these participant roles, figure 2 has been revised.

Participants stated, that it was not possible to conduct clinical trials alongside routine work because “Individuals skilled in trials were often too busy with regular duties to be able to conduct research”. (Page 6, results, Human and material capacity paragraph 2). Extra time does not guarantee trials, but is one of the contributing factors. We have included in the results the multiple barriers and enablers, which operate alongside each other. For example, “Most senior trial staff were clinicians and while release from routine duties could be negotiated, they complained that healthcare tasks still had to be prioritised” (Page 6, results, Human and material capacity paragraph 2). This discussion is taken up in “prioritising research systems” when discussing greater resource allocation to research - “However, in a country with insufficient health workers to provide routine healthcare,[23] and many other competing priorities, this may be difficult.” (page 11, Prioritising research systems, 1st paragraph). We have also added the following sentences to the discussion in accordance with comment 31 from reviewer #3 - “Providing protected time for research and recognising research within careers would help motivate investigators to undertake trials through positive reinforcement, but this alone may not be sufficient without adequate salaries to offset lost revenue from private practice and consultancy work. “
(Results, page 10, Building a receptive research environment, paragraph 2)

Comment 43:
The term phobia as described here does not make sense better replaced by different wording or go back to the original document o check
Response 43:
The word “Phobia” (used in the section “Initiating an idea: Awareness, Confidence and Motivation”, Page 8) was the term used by a group of participants. This was confirmed when they reviewed their contributions. In order to accurately reflect participants’ perspectives, we believe it is right to use their words, rather than replace them with our interpretations or what we may consider “correct”, so as to not introduce our biases into the work. In this instance we believe participants’ use of the word “phobia” was used to convey fear or aversion.

Comment 44:
Regulatory and other administrative bottlenecks I am not convinced that the regulatory system does

not have guideline and creates major bottle neck. May be the team from Gondar could complain with regard to the team in Addis mostly they are expected to be part of the review team…is there anything like this which appeared during the interview?
Response 44:
Regulatory guidelines do exist (see Page 6, regulatory and other administrative bottlenecks, paragraph 1 “Respondents reported that complex and strict government regulations made it very difficult to investigate novel interventions and recruit vulnerable populations”). The problem identified by participants was that regulations were not clear, (Page 6, regulatory and other administrative bottlenecks, paragraph 2 “They emphasised that clarification of regulations and developing review capacity were essential to facilitate trial implementation and that more training in research ethics was needed”).

Several participants said regulatory delays were a major issue, and a concrete example from a process mapping exercise, where review took 12 months, was given (Page 7, Operational hurdles, Table 2). However this was for complex studies involving Investigational Products or vulnerable populations. Where the intervention was in non-vulnerable populations and interventions were previously approved, review times were generally not problematic. We have added details on this in the “Operational barriers” section in accordance with comment 29 from reviewer #3 (Page 7, results, Operational hurdles, paragraph 2). Another study also found regulatory review and laws to be very problematic and causing critical delays (Gaym A. Health research in Ethiopia--past, present and suggestions on the way forward. Ethiop Med J 2008;46(3):287-308.).

Both of the teams in Gondar and Addis Ababa independently mentioned that regulatory review was a problem, and neither appeared to be complaining about the other, nor appeared to have been part of the review process for the other.

The research system
Comment 45:
Paragraph 2 adverse regulatory and administrative systems: more negative and give s no credit for the work done in the country. It should modified and check in the light of the services the system has offered.
Response 45:
The observation is correct: paragraph 2, which reports a summary of the views of participants, does show a negative view of the research system. This is interpreted from participant narratives and is also backed up by a publication reviewing the Ethiopian Health Research System (see below). However this summary paragraph was intended to show how interconnected issues in the system are, and how deficiencies at one level cause barriers at another. It is not meant to suggest that there are no examples of good practice, or things are universally problematic.

We have added the following sentences to the section to clarify this (Page 9, Discussion, The research system, paragraphs 2 and 3)“The following description is intended to illustrate the interconnected nature of the barriers to trial research and how deficiencies at one level can have cascading negative effects”…..AND….. “A detailed review of the Ethiopian Health Research System also cites slow regulatory and ethical review, difficult administration systems, limited human resource allocation to research and few incentives as major impediments.[22] However it is important to emphasise that our description is not universal and individual examples of enabling practices are present. Nevertheless these results demonstrate the importance of taking a system-wide view to research development.”

We have added a sentence on the existing in-country experience available - “Fortunately in-country expertise exists in almost all major aspects of the health research system, which should greatly facilitate strengthening efforts.[22]” (Discussion, Research System, Paragraph 2, page 10). We have

also added several further positive advancements to the “Prioritising research systems section” (Page 11, Prioritising research systems section, paragraph 2), including information on the new Science and Technology Policy, the Ministry of Health policy, research culture in the New Public Universities and The Ethiopian Bioethics Initiative. We feel that this now provides a more balanced picture.

Comment 46:
Building a receptive research environment Paragraph 3 …..the sentence which states……discouraged personal autonomy is not clear or needs to be better expressed
Response 46:
Agreed, and amended. (Please also see response 16)

Sentence changed to: “We also propose that previous regimes that actively discouraged autonomy, could have left a legacy that reduced the ability of individuals to act as agents in change”. (Page 10, Building a receptive research environment, paragraph 3)

Comment 47:
Prioritizing research systems
Mentions Jimma University for the best practice but ignored hearing from the investigators applauded
Response 47:
We agree that it would have been ideal if we had been able to also conduct this work at Jimma University. However, as formative research, this study had limited scope so we decided to focus our efforts on Addis Ababa and Gondar.
As stated previously, we believe that this selection and scope is justified and sufficient (please see response 34).
We have cited a highly detailed site report from Jimma University that includes the perspectives of researchers based there, so should readers wish to find more information on Jimma University, it is freely available.

Comment 48:
References In the references please add some policy documents and tools available le in the country
Response 48:

As part of our response to comment 45 from reviewer #4, we have added local policy documents from The Ethiopian Science and Technology Agency, The Ministry of Health and the Development Assistance Group Ethiopia (Page 11, Prioritising research systems, paragraph 2). This is in addition to the 2 international policy documents that are already included in the “Strengths and Limitations section”(page 11) – “This includes the key factors for an enabling research environment as identified by The Health Research System Analysis Initiative of WHO/RPC,[19] and recommendations for increasing investigator-initiated trial conduct by The European Science Foundation.[27]”

I have no competing interest or conflict of interest

VERSION 2 – REVIEW

REVIEWER	Gail Davey Brighton & Sussex Medical School Brighton UK I have 3 current research collaborations with one author (FE) and one with another (TL).
REVIEW RETURNED	24-Sep-2013

- The reviewer completed the checklist but made no further comments

REVIEWER	Datiko, Daniel University of Bergen
REVIEW RETURNED	15-Oct-2013

GENERAL COMMENTS	Comment 34: The study addresses one of the major deficiencies in research in the country and gives account to real problem and tries to find out the bottlenecks and possible solution. It has involved Addis Ababa and Gondar one of the areas with rich experience of conducting operational researches including clinical trials. However, it does not include major areas of the country specifically Jimma and did not interview potential sources form the ethical review board and the schools to check what is going on. More is said on the administrative part and training needs is not clearly shown. Response 34: This is a small formative study, and as such, had limited scope. It was not our intention to provide a representative picture of all research in Ethiopia, but rather to represent local investigators experiences and perspectives. This is acknowledged in the "strengths and limitations" section. Health research is mainly carried out in the cities of Addis Ababa, Gondar and Jimma. We focussed on Addis Ababa and Gondar because as the reviewer points out, they have rich experiences in research. Therefore, we recruited from 2 of the 3 main cities conducting health research. We describe some findings from a study at Jimma University in the discussion; this was a major global study, and Jimma was their sole case study from Ethiopia. As such we believe that only recruiting from Addis Ababa and Gondar is sufficient for the purposes of our study. Representatives from ethics review boards (n=3), senior research leaders from medical schools (n=5) and 1 ex government official, were included as participants. This is explained in the recruitment matrix (figure 2). As the other reviewers point out, this figure is not clear, so revisions have been made to this – please see comment 11 amendment. The response is given well. Comment 35: The strength of the study is it addresses key issue and highlights the need and potential enablers and barriers. I am afraid that the findings are over stated and may not reflect the existing situations. For example how many trails were applied and how many were rejected how long did it take and what were the problems is not checked. Response 35: Review times for specific studies and operational problems are

	mentioned in the “operational barriers” section. The “regulatory and other administrative problems” section also deals with this in detail. A breakdown of trial registration in Ethiopia is given in the methods (figure 1). The purpose of the study was to represent participants’ perspectives and experiences, and to reflect on these, not to provide a comprehensive regulatory overview. We therefore feel that we sufficiently addressed this area and any further details are beyond the scope of this study. This should appear as limitation of the study. Introduction Comment 36: 1. More note about the local clinical trials capacity and what we know so far in terms of their contribution to policy Response 36: We agree that this needs to be more explicit. We have added an extra point to table 1 (page 4) providing references discussing the role of local clinical trials in contributing to policy. • More likely to influence policy [13] and sustainably link research to action [14] Add more notes on this section. I do belive that there is some clinical trial capacity though not organized. Comment 37: 2. Paragraph one: line 5 often not relevant to LMICs : is over stated as the main clinical practices we have is based on international experience and some LMICs Response 37: Within the Introduction, this point is general, not specific to Ethiopia. Within the results, we do not argue that the main clinical practices in Ethiopia are not based on international experience. Rather, the international evidence cannot be contextually tailored and as such is not always relevant. Locally derived evidence that adapts international guidelines would be preferred as it was deemed to be more relevant and useful. We therefore feel that this statement is fair. Please see quote under “A role for investigator-initiated trials” - “We don’t have the evidence to change local practices but we definitely know some written guidelines don’t work. There are a number of unanswered questions for trials but we don’t know how to do them. We need clinical research [in disease areas] that has a different effect in Ethiopia, for example HIV and TB. These diseases are similar as to other places but we have had little success [controlling them] here. So why? Where are the mistakes? These sorts of investigations are easy, they would support awareness and fill gaps.” FGD - 3 PPT – 1- This could be better described that the respondant does not know thn there is no evidence used to influence policy. Comment 38: 3. Paragraph 3 line 7, …a U.K ……research development …..do we need this Response 38: All references to DFID removed, as reviewers agree they are distracting and unnecessary. Good. Methods Comment 39:

	Study area omits most parts of the country focused on Gondar and Addis Ababa, why are other areas omitted or not involved Response 39: (Same as response 34) This is a small formative study, and as such, had limited scope. It was not our intention to provide a representative picture of all research in Ethiopia, but rather to represent local investigators experiences and perspectives. This is acknowledged in the "strengths and limitations" section. Health research is mainly carried out in the cities of Addis Ababa, Gondar and Jimma. We focussed on Addis Ababa and Gondar because as the reviewer points out, they have rich experiences in research. Therefore, we recruited from 2 of the 3 main cities conducting health research. We describe some findings from a study at Jimma University in the discussion; this was a major global study, and Jimma was their sole case study from Ethiopia. As such we believe that only recruiting from Addis Ababa and Gondar is sufficient for the purposes of our study. agreed. Comment 40: Paragraph 3 line 5 no audio recorded why and what are the limitations related to this. It should clearly come out. This shades haziness on the description that we have in the article as it may be the feeling or assumed expression of the participants. The clinical trailists involved could understand the importance and consent for recording. Response 40: The majority of participants were uncomfortable with audio recording and said they would speak more openly, not being audio recorded. We have added the participants' explanations for this in the methods section (Page 5, paragraph 2 "This was because they would be uncomfortable criticising partners or regulatory bodies while being recorded. One participant explained that this worry was a result of the legacy left by previous authoritarian regimes".), and added the following sentence to the "Strengths and "limitations Sections" (page 11 final paragraph) – "Inability to audio record the discussions may have had some impact on the accuracy of notes taken. However, we felt it was more important to ensure open and frank dialogue, and the detailed notes were subsequently reviewed by participants to ensure accurate representation". Please include how you ensured that the idea of the respondants is included well and not missed. Comment 41: A role for investigator-initiated trials Line 1 ….and regretted the lack of local evidence to guide policy ….does this mean that policy is not supported by evidence or could have been supported by clinical trial Knowledge about research priority with regard to clinical trial is not shown in the study? Does it show that the country does not need clinical trial and does not have policy outlines or the investigators failed to pick it? Response 41: Sentence revised to clarify this – "All participants reported that too few clinical trials are conducted in Ethiopia, and felt this limited the ability for guidelines to be based on local evidence." Knowledge about disease research priorities was gathered from participants so research priorities do exist, and participants are aware of them. Since this study investigates participant perspectives of barriers and enablers to clinical trials, we did not think that context on research priority setting was necessary. agreed.

	Human and material capacity Comment 42: The investigators blame the curriculum for not including clinical research and extra time is requested by participants so that clinical trials will be done. Do they have any comment from the institutions working on this as they have interview areas where medical schools are based? Does extra time guarantee clinical trial? Why was not it possible to conduct clinical trial as part of the routine work? More notes on this? Response 42: To prevent confusion, the authors do not blame the curriculum, the participants (some of whom were investigators) thought that not including more research in the medical curriculum was part of the problem. Five participants had experience of research leadership in medical schools (as stated in the recruitment matrix in figure 2), and their comments are represented in the paper. To clarify these participant roles, figure 2 has been revised. Participants stated, that it was not possible to conduct clinical trials alongside routine work because “Individuals skilled in trials were often too busy with regular duties to be able to conduct research”. (Page 6, results, Human and material capacity paragraph 2). Extra time does not guarantee trials, but is one of the contributing factors. We have included in the results the multiple barriers and enablers, which operate alongside each other. For example, “Most senior trial staff were clinicians and while release from routine duties could be negotiated, they complained that healthcare tasks still had to be prioritised” (Page 6, results, Human and material capacity paragraph 2). This discussion is taken up in “prioritising research systems” when discussing greater resource allocation to research - “However, in a country with insufficient health workers to provide routine healthcare,[23] and many other competing priorities, this may be difficult.” (page 11, Prioritising research systems, 1st paragraph). We have also added the following sentences to the discussion in accordance with comment 31 from reviewer #3 - “Providing protected time for research and recognising research within careers would help motivate investigators to undertake trials through positive reinforcement, but this alone may not be sufficient without adequate salaries to offset lost revenue from private practice and consultancy work. “ (Results, page 10, Building a receptive research environment, paragraph 2) Good> I know the curriculum included what is expected to be and the practice may be different. For example students are thought about research too early and when they need it they do not have the capacity or the course. Comment 43: The term phobia as described here does not make sense better replaced by different wording or go back to the original document o check Response 43: The word “Phobia” (used in the section “Initiating an idea: Awareness, Confidence and Motivation”, Page 8) was the term used by a group of participants. This was confirmed when they reviewed their contributions. In order to accurately reflect participants’ perspectives, we believe it is right to use their words, rather than replace them with our interpretations or what we may consider “correct”, so as to not introduce our biases into the work. In this instance we believe participants’ use of the word “phobia” was used to convey fear or aversion.

	You may need to add some notes as how the person described it. Can you have a look at the sentences before and after in the data. Comment 44: Regulatory and other administrative bottlenecks I am not convinced that the regulatory system does not have guideline and creates major bottle neck. May be the team from Gondar could complain with regard to the team in Addis mostly they are expected to be part of the review team…is there anything like this which appeared during the interview? Response 44: Regulatory guidelines do exist (see Page 6, regulatory and other administrative bottlenecks, paragraph 1 “Respondents reported that complex and strict government regulations made it very difficult to investigate novel interventions and recruit vulnerable populations”). The problem identified by participants was that regulations were not clear, (Page 6, regulatory and other administrative bottlenecks, paragraph 2 “They emphasised that clarification of regulations and developing review capacity were essential to facilitate trial implementation and that more training in research ethics was needed”). Several participants said regulatory delays were a major issue, and a concrete example from a process mapping exercise, where review took 12 months, was given (Page 7, Operational hurdles, Table 2). However this was for complex studies involving Investigational Products or vulnerable populations. Where the intervention was in non-vulnerable populations and interventions were previously approved, review times were generally not problematic. We have added details on this in the “Operational barriers” section in accordance with comment 29 from reviewer #3 (Page 7, results, Operational hurdles, paragraph 2). Another study also found regulatory review and laws to be very problematic and causing critical delays (Gaym A. Health research in Ethiopia--past, present and suggestions on the way forward. Ethiop Med J 2008;46(3):287-308.). Both of the teams in Gondar and Addis Ababa independently mentioned that regulatory review was a problem, and neither appeared to be complaining about the other, nor appeared to have been part of the review process for the other. There is lack of clarity in terms understanding the rules or there is a problem of adherence to the written rules. Poor adherence to the set guidelines are the main ones as to my knowledge. Please add more on this. The research system Comment 45: Paragraph 2 adverse regulatory and administrative systems: more negative and give s no credit for the work done in the country. It should modified and check in the light of the services the system has offered. Response 45: The observation is correct: paragraph 2, which reports a summary of the views of participants, does show a negative view of the research system. This is interpreted from participant narratives and is also backed up by a publication reviewing the Ethiopian Health Research System (see below). However this summary paragraph was intended to show how interconnected issues in the system are, and how deficiencies at one level cause barriers at another. It is not meant to suggest that there are no examples of good practice, or things are universally problematic.

	We have added the following sentences to the section to clarify this (Page 9, Discussion, The research system, paragraphs 2 and 3)"The following description is intended to illustrate the interconnected nature of the barriers to trial research and how deficiencies at one level can have cascading negative effects".....AND..... "A detailed review of the Ethiopian Health Research System also cites slow regulatory and ethical review, difficult administration systems, limited human resource allocation to research and few incentives as major impediments.[22] However it is important to emphasise that our description is not universal and individual examples of enabling practices are present. Nevertheless these results demonstrate the importance of taking a system-wide view to research development." We have added a sentence on the existing in-country experience available - "Fortunately in-country expertise exists in almost all major aspects of the health research system, which should greatly facilitate strengthening efforts.[22]" (Discussion, Research System, Paragraph 2, page 10). We have also added several further positive advancements to the "Prioritising research systems section" (Page 11, Prioritising research systems section, paragraph 2), including information on the new Science and Technology Policy, the Ministry of Health policy, research culture in the New Public Universities and The Ethiopian Bioethics Initiative. We feel that this now provides a more balanced picture. Agreed. Comment 46: Building a receptive research environment Paragraph 3 .....the sentence which states……discouraged personal autonomy is not clear or needs to be better expressed Response 46: Agreed, and amended. (Please also see response 16) Sentence changed to: "We also propose that previous regimes that actively discouraged autonomy, could have left a legacy that reduced the ability of individuals to act as agents in change". (Page 10, Building a receptive research environment, paragraph 3) Comment 47: Prioritizing research systems Mentions Jimma University for the best practice but ignored hearing from the investigators applauded Response 47: We agree that it would have been ideal if we had been able to also conduct this work at Jimma University. However, as formative research, this study had limited scope so we decided to focus our efforts on Addis Ababa and Gondar. As stated previously, we believe that this selection and scope is justified and sufficient (please see response 34). We have cited a highly detailed site report from Jimma University that includes the perspectives of researchers based there, so should readers wish to find more information on Jimma University, it is freely available. Comment 48: References In the references please add some policy documents and tools available le in the country

	Response 48: As part of our response to comment 45 from reviewer #4, we have added local policy documents from The Ethiopian Science and Technology Agency, The Ministry of Health and the Development Assistance Group Ethiopia (Page 11, Prioritising research systems, paragraph 2). This is in addition to the 2 international policy documents that are already included in the "Strengths and Limitations section"(page 11) – "This includes the key factors for an enabling research environment as identified by The Health Research System Analysis Initiative of WHO/RPC,[19] and recommendations for increasing investigator-initiated trial conduct by The European Science Foundation.[27]" Agreed.

VERSION 2 – AUTHOR RESPONSE

Reviewer Name Datiko, Daniel
Institution and Country University of Bergen
Please state any competing interests or state 'None declared': None

Comment 35:
The strength of the study is it addresses key issue and highlights the need and potential enablers and barriers. I am afraid that the findings are over stated and may not reflect the existing situations. For example how many trails were applied and how many were rejected how long did it take and what were the problems is not checked.
Response 35:
Review times for specific studies and operational problems are mentioned in the "operational barriers" section. The "regulatory and other administrative problems" section also deals with this in detail. A breakdown of trial registration in Ethiopia is given in the methods (figure 1).
The purpose of the study was to represent participants' perspectives and experiences, and to reflect on these, not to provide a comprehensive regulatory overview. We therefore feel that we sufficiently addressed this area and any further details are beyond the scope of this study.

Comment 35b
This should appear as limitation of the study.
Response 35b
We do not feel that this constitutes a limitation of the study, since the goal of the study was to represent participants' perspectives and experiences, which we feel we have achieved.

However we agree that this is an important discussion point so we have added the following to the Discussion; The research system; paragraph 2, line 2: The research system; paragraph 2, line 2: "However it is important to emphasise that our description is not universal and individual examples of enabling practices and trial capacity exist. Furthermore no information was available to us on the number of trial applications, rejections and turnaround times and although little local evidence-based practice was reported, this was not confirmed by the authorities and examples of local trials influencing policy are found in the literature (Yassin et al., 2013). Nevertheless these results demonstrate the importance of taking a system-wide view to research development."

Introduction
Comment 36:
1. More note about the local clinical trials capacity and what we know so far in terms of their contribution to policy

Response 36:
We agree that this needs to be more explicit. We have added an extra point to table 1 (page 4) providing references discussing the role of local clinical trials in contributing to policy.
• More likely to influence policy [13] and sustainably link research to action [14]

Comment 36b
Add more notes on this section. I do belive that there is some clinical trial capacity though not organized.
Response 36b
We do not think this should be discussed further in the introduction section as it is deliberately general. However, we agree this should be discussed further, specifically relating to Ethiopia, in the discussion. Isolated examples of trial capacity do exist. This is reflected in the results, but perhaps needs to be more emphasised in the discussion, with examples of the successful local trials influencing policy. Upon searching the literature for examples, we found reviewer #4's work to be a particularly suitable current example.

In response we have added the following to the Discussion;
1. The research system; paragraph 2, line 2: "However it is important to emphasise that our description is not universal and individual examples of enabling practices and trial capacity exist. Furthermore no information was available to us on the number of trial applications, rejections and turnaround times and although little local evidence-based practice was reported, this was not confirmed by the authorities and examples of local trials influencing policy are found in the literature (Yassin et al., 2013). Nevertheless these results demonstrate the importance of taking a system-wide view to research development."
2. Prioritising research systems; second paragraph; second sentence: The importance of research and developing research capacities is now central to the Ministry of Health strategy, and local trial data (Datiko and Lindtjorn, 2009) has influenced policy. (Ethiopian Ministry of Health, 2011) Recommendations for fostering a research culture in the New Public Universities have been developed (Melis et al., 2008) and Jimma University….."

Comment 37:
2. Paragraph one: line 5 often not relevant to LMICs : is over stated as the main clinical practices we have is based on international experience and some LMICs
Response 37:
Within the Introduction, this point is general, not specific to Ethiopia. Within the results, we do not argue that the main clinical practices in Ethiopia are not based on international experience. Rather, the international evidence cannot be contextually tailored and as such is not always relevant. Locally derived evidence that adapts international guidelines would be preferred as it was deemed to be more relevant and useful. We therefore feel that this statement is fair.
Please see quote under "A role for investigator-initiated trials" - "We don't have the evidence to change local practices but we definitely know some written guidelines don't work. There are a number of unanswered questions for trials but we don't know how to do them. We need clinical research [in disease areas] that has a different effect in Ethiopia, for example HIV and TB. These diseases are similar as to other places but we have had little success [controlling them] here. So why? Where are the mistakes? These sorts of investigations are easy, they would support awareness and fill gaps." FGD - 3 PPT – 1-

Comment 37b
This could be better described that the respondant does not know thn there is no evidence used to influence policy.
Response 37b

We feel that the above response sufficiently addresses this in the results section. However more emphasis may be needed in the discussion. Therefore we have added the following sentence to the Discussion; The research system; paragraph 2, line 2: “However it is important to emphasise that our description is not universal and individual examples of enabling practices and trial capacity exist. Furthermore no information was available to us on the number of trial applications, rejections and turnaround times and although little local evidence-based practice was reported, this was not confirmed by the authorities and examples of local trials influencing policy are found in the literature (Yassin et al., 2013). Nevertheless these results demonstrate the importance of taking a system-wide view to research development.”

Comment 40:
Paragraph 3 line 5 no audio recorded why and what are the limitations related to this. It should clearly come out. This shades haziness on the description that we have in the article as it may be the feeling or assumed expression of the participants. The clinical trailists involved could understand the importance and consent for recording.
Response 40:
The majority of participants were uncomfortable with audio recording and said they would speak more openly, not being audio recorded. We have added the participants’ explanations for this in the methods section (Page 5, paragraph 2 “This was because they would be uncomfortable criticising partners or regulatory bodies while being recorded. One participant explained that this worry was a result of the legacy left by previous authoritarian regimes”.), and added the following sentence to the “Strengths and “limitations Sections” (page 11 final paragraph) – “Inability to audio record the discussions may have had some impact on the accuracy of notes taken. However, we felt it was more important to ensure open and frank dialogue, and the detailed notes were subsequently reviewed by participants to ensure accurate representation”.

Comment 40b
Please include how you ensured that the idea of the respondants is included well and not missed.
Response 40b
We ensured that we accurately presented respondents ideas, and that we did not miss any issues, by returning copies of the transcripts to participants and asking them to confirm the accuracy of our written representation of their accounts. We feel this is sufficiently explained in the sentence: Strengths and limitations Sections” (page 11 final paragraph) – “Inability to audio record the discussions may have had some impact on the accuracy of notes taken. However, we felt it was more important to ensure open and frank dialogue, and the detailed notes were subsequently reviewed by participants to ensure accurate representation”.

Furthermore, Author FE is an Ethiopian clinical researcher with extensive experience. He has reviewed and contributed to findings and believe them to be an accurate representation of the situation. Since author details are already included, we feel this is sufficient.

Comment 43:
The term phobia as described here does not make sense better replaced by different wording or go back to the original document o check
Response 43:
The word “Phobia” (used in the section “Initiating an idea: Awareness, Confidence and Motivation”, Page 8) was the term used by a group of participants. This was confirmed when they reviewed their contributions. In order to accurately reflect participants’ perspectives, we believe it is right to use their

words, rather than replace them with our interpretations or what we may consider “correct”, so as to not introduce our biases into the work. In this instance we believe participants’ use of the word “phobia” was used to convey fear or aversion.

Comment 43b
You may need to add some notes as how the person described it. Can you have a look at the sentences before and after in the data.
Response 43b
The sentence before and after the use of the term “phobia” is already included in the Results section: Initiating an idea, quote under paragraph 2 - “We need to develop and support a research culture by capacity building to develop skills and resources, not big capacity building like an operating room, but small scale like small grants for beginner researchers to do research and get practice - this would take away the phobia of writing proposals and publications. When the phobia has gone there will be floods of research. We need to open our eyes and see what can be done. For instance people don’t know how to write a proposal. In people’s academic studies this sort of stuff is not given priority. Even small research will be an eye opener and the phobia will be gone.” FGD - 3 PPT - 2, Clinician and junior investigator

All authors consider the participant’s use of the term to be correct and as intended. Therefore we feel that it would be inappropriate to change it.

Comment 44:
Regulatory and other administrative bottlenecks I am not convinced that the regulatory system does not have guideline and creates major bottle neck. May be the team from Gondar could complain with regard to the team in Addis mostly they are expected to be part of the review team…is there anything like this which appeared during the interview?
Response 44:
Regulatory guidelines do exist (see Page 6, regulatory and other administrative bottlenecks, paragraph 1 “Respondents reported that complex and strict government regulations made it very difficult to investigate novel interventions and recruit vulnerable populations”). The problem identified by participants was that regulations were not clear, (Page 6, regulatory and other administrative bottlenecks, paragraph 2 “They emphasised that clarification of regulations and developing review capacity were essential to facilitate trial implementation and that more training in research ethics was needed”).

Several participants said regulatory delays were a major issue, and a concrete example from a process mapping exercise, where review took 12 months, was given (Page 7, Operational hurdles, Table 2). However this was for complex studies involving Investigational Products or vulnerable populations. Where the intervention was in non-vulnerable populations and interventions were previously approved, review times were generally not problematic. We have added details on this in the “Operational barriers” section in accordance with comment 29 from reviewer #3 (Page 7, results, Operational hurdles, paragraph 2). Another study also found regulatory review and laws to be very problematic and causing critical delays (Gaym A. Health research in Ethiopia--past, present and suggestions on the way forward. Ethiop Med J 2008;46(3):287-308.).

Both of the teams in Gondar and Addis Ababa independently mentioned that regulatory review was a problem, and neither appeared to be complaining about the other, nor appeared to have been part of the review process for the other.

Comment 44b
There is lack of clarity in terms understanding the rules or there is a problem of adherence to the written rules. Poor adherence to the set guidelines are the main ones as to my knowledge. Please

add more on this.

Response 44b

We have reviewed the data and feel that we have reported all data on both sides of the arguments in the Regulatory and administrative bottleneck sections. Please see paragraph 1 line 1 (lack of rule clarity), and paragraph 2 line 2 (poor adherence to rules) in this section. These arguments came from 2 different groups of sources: researchers and ethics board members. We do not think that it is possible to privilege one opinion over the other. Therefore, it is not possible from the data collected to be able to say which of the opinions expressed is correct, or more correct, than the other.

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