Author's response to reviews

Title: A Tutorial on Pilot Studies: The What, Why and How

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Author's response to reviews: see over
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Anastasios Koutsos, PhD.  
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Dear Dr Koutsos

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A Tutorial on Pilot Studies: The What, Why and How  
Lehana Thabane, Jinhui Ma, Rong Chu, Ji Cheng, Afisi Ismaila, Lorena P Rios,  
Reid C Robson, Marroon Thabane, Lora Giangregorio and Charles H Goldsmith

Thank you your email of October 28, 2009 with reviewers’ comments on our paper. We found the comments very helpful and thank the reviewers for their thorough and insightful reviews. We have revised the manuscript in accordance with these comments. Please find attached a revised of the manuscript and responses to specific suggestions raised by the reviewers. We have highlighted all the major changes that we have made in the manuscript.

We hope we have adequately addressed the reviewers’ comments and the manuscript is in an acceptable form.

Please note that we have added Dr Lora Giangregorio to the authorship. Her name was left out as an oversight

We look forward to hear from you.

Sincerely,

Lehana Thabane, PhD  
Associate Professor, Department of Clinical Epidemiology and Biostatistics,  
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Responses to Reviewers’ Comments

We are grateful to the reviewers for very constructive comments and suggestions. We feel that the comments have greatly improved the presentation and message of the paper. Below are our responses to the specific suggestions and issues raised by the reviewers.

Reviewer 1
1. An interesting and worthwhile paper. I have a few relatively minor comments and observations.
RESPONSE: We thank the reviewer for a positive view of the paper.

2. Although the authors refer to pilot studies in general reading the paper makes it clear that they really mean quantitative pilot studies. Not conducting three face-to-face pilot interviews before embarking on a full-scale qualitative study of 34 interviews. Perhaps this should be acknowledge somewhere, or at least reflected upon.
RESPONSE: We thank the reviewer for the suggestion. We have narrowed our definition of pilot studies to quantitative studies, in particular to trials. We have added some description regarding qualitative pilot studies in the discussion.

3. Page 4: The last sentence of the paragraph finishing at the top of the page can be shortened as the reference 5 to 8 are not necessary and don’t add to the paper. I suggest stop the sentence after “.. conducting a larger scale study.” AND remove the four references altogether.
RESPONSE: We thank the reviewer for the suggestion, but feel that the cited references support our statement of examples of clinical areas where pilot studies have been conducted.

4. Under section 2 Van Teijlingen is misspelt twice, it is also wrong in reference 11.
RESPONSE: We apologize for these typos and have corrected them.

5. Page 3: Explain to audience, who might not be epidemiologists, clinical researchers or quantitative researchers what a phase I, II and III study is.
RESPONSE: Suggestion adopted.

6. On page 6 the authors begin their section 4 with the sentence “The biggest challenge with pilot studies is that many of them never get published...” In the first paragraph is not a single reference, which is a missed opportunity, especially since the publication by van Teijlingen & Hundley (2001) which is your reference 11 has a section called: ‘Why are pilot studies not reported?’
RESPONSE: We have cited van Teijlingen & Hundley (2001) to support the statement.
7. Grammar: The authors use et al a few times this should be et al. (as al. is an abbreviation).
RESPONSE: We have corrected the typo.

Reviewer 2
This is not really research, but should prove a useful article for others to consult. 
Compulsory revisions
1) The authors should refer to the paper by Lancaster (2004) which covers some of the same ground
RESPONSE: Suggestion adopted.

2) I think they should distinguish between Phase II and feasibility studies. A Phase II study is a precursor to a Phase III trial, a feasibility study could be a qualitative study to evaluate whether patients would be willing to be in a clinical trial
RESPONSE: We have now clarified the relationships between feasibility studies and phase I, II and III studies.

3) I think they could make more of the British MRC guidance on complex interventions (MRC, 2008), (Craig et al 2008). This explicitly recommends the use of feasibility studies prior to Phase III clinical trials, but stresses the iterative nature of the processes, in contrast to the linear development from Phase I, through II to III in pharmacological trials.
RESPONSE: We have adopted the suggestion and cited the suggested references.

4) The sample size calculation in the 3rd paragraph on page 9 is unclear and should be revised. They should use proper notation and not ‘computer language’ (eg *SQRT)
RESPONSE: We have adopted the suggestion.

Minor essential revisions
5) On page 10, the percentages for determining success in the PROTECT Trial are unusually precise and unjustified (eg why should 91.7% receive every scheduled dose in a blinded manner. If only 90.5% did would this be a failure?)
RESPONSE: We have taken these numbers from the cited reference and cannot comment on their precision or justification. The idea was to provide an example in which a priori rule for deciding on feasibility is provided.

6) P14. In the consent form I suggest the authors actually state a definition of a proof-of-concept study
RESPONSE: Suggestion is adopted.

7) I would be interested to know the authors opinion of randomization. Should pilot studies be randomised and if so why?
RESPONSE: We believe one of the goals of a pilot study could be to assess the feasibility of randomization procedures – ie whether people consent to being randomized; whether the investigators are able to implement the randomization for a multi-site study, etc. Further, if the main study involves randomization, it would desirable to design a pilot in a manner similar to the main study so that we can get a realistic picture about the feasibility of the main study including randomization aspects. We have added our suggestion on the role of randomization in pilot studies in the form of question and answer.

Reviewer 3
Major compulsory revisions
1. However, the article rather makes me more confused, mainly because it is not clear to me what they mean by a pilot study.
RESPONSE: We have tried to simplify and focus our definition of a pilot in the context of quantitative studies, particularly, trials. We hope this change clarifies the situation.

2. According to the definition in the abstract, all studies, apart from phase III and phase IV seem to be pilot studies. So phase I and phase II studies are special cases of pilot studies? But then there is a lot in the article that I do not understand, because it deviates from what is usually considered to be appropriate for phase I and II.
In my view, phase II and I trials are not pilot studies. They do not (yet) have the aim to investigate the feasibility of large studies (in fact they may be large themselves). They do not fulfill the criteria in table 1. Their aim is to identify a safe and possibly efficacious treatment. How this treatment then has to be tested in a larger trial is another matter.
In any case the authors should clarify the difference (if any) between pilot, phase I and phase II studies.
RESPONSE: We have clarified the relationship between pilot studies of phase III studies and phase I and II trials/studies.

3. The authors explicitly discuss the relationship between proof of concept (poc) studies and pilot studies. I am not sure why, because (in their view) a poc study simply is a special case of pilot study.
RESPONSE: We have now focused our definition of a pilot study for phase II trials. Within this framework, PoC studies – which are usually, phase I/II trials, may not fit our restricted definition of a pilot. We have appropriately revised the text in body of the manuscript and in Table 3 to reflect this change.

4. The authors even consider studies that evaluate marker data in cohorts as pilot studies. So they not only discuss clinical trials, but also observational studies? However, further in the article they create the impression that they are
Talking about trials only, for example, they propose the CONSORT format for reporting. In fact, throughout the paper I have the impression that the authors discuss trials, but I may be wrong.

Minor revisions (in no way exhaustive or conclusive, because I am not sure what the authors consider a pilot study and they would depend on that):

1. I do not think that dose finding studies get no attention in the literature.

**RESPONSE: We have clarified the connection between pilot studies of Phase III studies – which is the main focus of our definition of a pilot – and phases I and II studies.**

2. I cannot see how there can be confusion between a pilot study and a study with an adaptive design. There can be doubt as to how to choose between them, to decide what is the best approach in a particular situation, but once the decision is taken, it is obvious what is what. Whether or not a study is a pilot, depends on its objectives. Whether or not an adaptive method is used is a strategy to reach that objective and is of a completely different nature. Both a pilot and a non-pilot could be adaptive.

**RESPONSE: We thank the reviewer for the thoughtful reflection of the issues. We have tried to clarify the connection between piloting and use of adaptive designs.**

3. On page 11, the authors claim that data from the pilot can be combined with data from the main study. In general, this is definitely not the case. For example, multiple testing issues may arise or other opportunistic actions may create bias: the investigator may be tempted to include the results of the pilot only when they are ‘suitable’. If any pooling is considered, this should be planned beforehand and the protocol should describe in advance how and discuss the statistical consequences and methods.

**RESPONSE: We agree with the reviewer that caution is needed in situations where data from pilot studies are to be combined with those from the main study. We have provided additional comments to caution readers further about the potential for bias.**

4. On page 16, the authors state that the primary outcome of the main study should be defined in the pilot. But is it not the case that pilots may be conducted with the aim to find out what is a suitable (practical or surrogate) endpoint?

**RESPONSE: True. In that case, it is important to clearly state that part of the goals of the pilot is to determine which outcome to use (ie clinical or surrogate). We have added this point in the discussion of the issue.**

5. I would be interested in the opinion of the authors about randomization and blinding in pilot studies. Should randomization (if it is done) not be clearly described in the report?

**RESPONSE: See our response to item 7 of Reviewer 2**

The authors could provide a useful contribution when they first could provide a
clear, logical and consistent framework to classify studies. A framework that is an extension of existing frameworks, such as the Phase I-IV classification. Maybe they could provide an organogram of the different types and subtypes of studies (or maybe just trials)? I would advice them to choose a rather narrow definition of pilot trials. If it is too wide, it is difficult to provide guidance.

RESPONSE: We have narrowed our definition of pilot studies to quantitative studies, in particular, trials. We have also clarified the relationship between pilot studies of phase III trials and Phase I and II trials.