Author's response to reviews

Title: Missing steps in a stair case: a qualitative study of the perspectives of key stakeholders on the use of adaptive designs in confirmatory trials

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Author's response to reviews: see over
Response to Reviewer 1’s comments

Table 1: I would have liked to know whether respondents were thinking more in an early phase setting or in a late phase setting. I suspect the challenges and gain may differ. Do the respondents’ comments apply equally?

**MD response:** We agree with the reviewer that this is important information for the reader to know. We acknowledge that some barriers are more prominent in the early phase than the confirmatory phase and vice versa. In fact, the trial phase itself was a factor contributing to the degree of conservatism towards the use of adaptive designs (see Section 3.3 on cross-disciplinary conservatism). Acknowledging the fact that some barriers may not be extrapolated between phases as described in our background, the interview guide was phrased to emphasise the confirmatory setting (see Additional file 1). During the interview analysis stage, we inferred that some issues such as the need for adequate data management structure, and the amount to work and time commitment were applicable to both early and late phase. However, we believe that respondents were primarily thinking about the late phase setting, although they were given an opportunity to talk about their early phase experiences and reflect by contrasting with late phase. In addition, some adaptive designs such as seamless 2/3 trials combine the learning and confirmatory phase together so you would expect barriers to equally apply in such cases. We have changed the section title from “Perceived potential barriers to the use of ADs” to “Perceived potential barriers to the use of ADs in confirmatory trials” to make this more obvious to the reader. We hope this will suffice without increasing the volume of the manuscript.

Table 2: I was not certain that I understood this table. What do the column and row labels mean.

**MD response:** Row and column labels represent the core roles of the participants. Ideally we would have liked to present Table 2 as a Venn diagram to represent overlapping roles. However, we considered this too complicated to display clearly due to the number of categories under consideration. We have now added an interpretation footnote below Table 2 to help the reader as follows “Interpretation: For instance (row 1), we interviewed 10 Statisticians with other overlapping roles: 6 had been co-applicants on research grants, 3 served on public funding boards or panels, 1 served as a CTU leader, 6 were IDMC and 5 TSC members, and so forth.”

Table 3: Not sure how the quotes relate to the thematic areas. Some undefined acronyms.

**MD response:** We selected key quotes to support some of the themes, but not all themes are reflected due to the size of the manuscript. We have underlined some of the important aspects to help the reader. Additional file 2 (originally Appendix B) provide support data on this. All acronyms in the Table have now been defined in the Table (AD, NHS, EU and US).
Response to Reviewer 2’s comments

Reviewer: 1) The text describing the potential barriers seems a bit on the long side, and becomes a bit difficult to read. The authors might consider whether the text could be condensed a bit, perhaps by focusing more on the high level findings.

MD response: We acknowledge the point raised and shared by others. We have edited the manuscript and reduced the length by 3 pages. We hope the revised version has improved.

Reviewer: On the opposite side of the spectrum, only 3 lines are devoted to facilitators recommended by respondents to address these barriers (though more information is provided in Table 5). It seems that this should be expanded a bit, since a discussion of how to remove these barriers is a critical component of this discussion.

MD response: We agree with the reviewer’s point. The length of this manuscript has been a challenge and we had to compromise on something. We took the decision to explain the barriers in detail in this manuscript and to provide much needed detail on facilitators in a follow-up manuscript centred on the surveys informed by this research. Hence here we decided to create a Table summarising facilitators and supported this with the discussion, and expanded further in the follow-up manuscript which is now ready for submission.

Reviewer: One additional minor concern is that it, if the information exists, it might be helpful to summarize the past experience of the survey respondents with respect to working on actual adaptive designs. For instance, it is unclear whether the participants have worked on adaptive designs in the past, have considered adaptive designs in the past but not used them due to the barriers discussed here, or have little past experience with clinical trials. A summary of this information would help to put the findings in a bit more context.

MD response: The reviewer raised a very good point. We have added the following sentence under “Description of participants” to reflect their previous AD experiences.

“Participants had diverse AD experiences: none (n=9), of which 6 expressed interest in ADs; planning only (n=6); planning and conduct, either in early or confirmatory phase or both (n=8); statistical regulatory assessment (n=4)”

In addition, we have now included participants’ previous AD experience together with supporting data “quotations” next to their roles.

We hope this will help readers to interpret our findings.
Response to Reviewer 3’s comments

Reviewer: 4) I have two reservations (4.1, 4.2) about the message which should be addressed with some somewhat repetitive editing throughout: abstract, introduction, main results, conclusions, and supplement 2 file

MD response: We have edited some sections, particularly main results and discussions, and tightened up the manuscript. Appendix B (Additional file 2) was meant to provide a detailed picture of support data, most of which was edited - so we still feel it is important to keep it that way.

Reviewer: 4.1 My limited collaborations in qualitative research lead me to believe that achieving focus group "consensus" requires further stages of interviewing. Here "consensus" does not mean every participant agrees with each other, rather that qualitative scientists reviewers achieved consensus in review and do not expect any surprises if further focus groups are conducted. Perhaps "closure" better captures the concept.

MD response: The reviewer has a good point. It should be noted that these interviews were not meant to generalise the findings or draw consensus, but to inform the design of follow-up surveys which are then used to generalise the findings. We felt that 1 to 1 interviews were necessary for participants to talk about their experiences, perceptions and attitudes without due influence or hesitation. We completely avoided the term “consensus” to describe our methods and results. However, there is scope to consider a consensus approach to some aspects following the results from our follow-up surveys which we have now obtained.

Reviewer: 4.2 The authors have identified an appropriate but dauntingly diverse pool of Stakeholders. I think the authors need to provide stronger caution about the importance of diversity in future considerations, and as a source of uncertainty in the conclusions.

MD response: The reviewer raised an interesting point. The main reason we considered this diverse pool of participants was to try to alleviate the shortcomings of previous research, which could have overlooked some of the barriers or concerns. For instance, given what we know now from this study and the follow-up surveys, this diversity enabled us to unpick concerns about robustness of adaptive designs in decision making and acceptability to change practice among policymakers and decision-makers, and clinical investigators. Hence, we strongly the diversity in our participant pool as a major strength given what we know now from follow-up surveys.

Reviewer: Does the design meet qualitative principles and standards? 5.1) Was there fidelity to qualitative process?

MD response: This is a good point. Yes, fidelity was considered as part of the qualitative process. The length of the manuscript limited us to expand further on this. However, we acknowledged its importance to the readers and highlighted that internal pilot interviews were conducted to test aspects such as the appropriateness of the interview guide, interview duration, and value to generated information (see section 2.3 Selection of Participants). In addition, an experienced qualitative researcher validated a sample of the interview scripts during analysis regarding the coding of themes (see section on Strength and limitations of the study). Mapping of the themes was also discussed independently with JB and Alicia O’Cathain who are qualitative experts as stated.

Reviewer: 5.2) Use of the term "internal pilot" seems not deserved, relative to the published literature.

MD response: We initially excluded this, but the Editors requested additional information during our initial submission. Given the length of the paper and comments from other reviewers, we have now completely removed this information in order to reduce the size of the manuscript.

Reviewer: 5.3) I have concerns about the sample size being inadequate
**MD response:** There is no consensus regarding the optimal sample size for such qualitative studies. We have tried to provide the rationale behind the sample size of up to 10 interviews per homogeneous subgroup based on available literature. In addition, time and practical constraints were other important considerations (see Section 2.2 Sample size).

**Reviewer:** 5.4) I am concerned about lack of completion of the focusing process.

**MD response:** Please see my response to a related comment on 4.1 above

**Reviewer:** 5.5) Although mentioned in the supplement, the text has no mention of influenza epidemic in possible applications. Seems like a winner.

**MD response:** We absolutely agree with the reviewer. This information is already in the manuscript. Please see page 10 under section “3.2.2 Perceived therapeutic areas of opportunity to use ADs”. Unfortunately, the length of the paper limited us from expanding further on this – in addition, we classified influenza under respiratory diseases.

**Reviewer:** 7) I am concerned about opinions in the supplement becoming citable. For example, there is a claim by implicit assumption of some participants that fully blinded analysis (e.g. of internal pilots) is the only choice and has no risks. Both claims are controversial, with no consensus in the literature. Many authors instead advocate arms-length blinding to avoid risks of analysis bias. Need for “caveat emptor” text is clear.

**MD response:** We acknowledge the concern raised by the reviewer. It is important to differentiate preferences from facts. We avoided portraying such assumptions in this manuscript. For example, section 3.2.3 “Perceived types of ADs with potential in confirmatory setting” makes it clear that sample size estimation can be done either in a blinded or unblinded manner without giving preference. We also pointed out that preference varies considerably among researchers and policymakers. Although some interviewees showed preferences for fully blinded analysis (such as sample size), our follow-up surveys showed that there is a sizeable proportion of adaptive designs implemented in an unblinded manner. I have added a caveat emptor to Additional file 2 (originally appendix B) “Please note that participant’s preferences and views on certain aspects may not represents facts”

**Reviewer:** 8) "quote" should be "quotation"

**MD response:** We thank the reviewer for the correction. Done!