Author’s response to reviews

Title: What are the main inefficiencies in trial conduct: a survey of UKCRC registered clinical trials units in the UK

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Response to referees

Referee 1

• I find the manuscript very interesting. It identifies important aspects that make it difficult to successfully carry out clinical trials that can be extrapolated to areas other than those involving CTUs. Optimizing the resources that are invested in clinical research is a subject of great importance from both economic and ethical points of view.

Response: We thank the referee for these positive comments

• I have no suggestions for improving the content of the manuscript. However, I do think that some punctuation errors should be corrected (eg page 12, line 260), and some abbreviations
should be clarified as well: "DM", "CI" (page 10, lines 224 and 226); "IT", "CLRN" (Figure 1), and "PIL" (Figure 2).

Response: These corrections and clarifications have been added

Referee 2

• This article is the result of a survey carried out in 2013 to identify inefficiencies during what the investigators consider the two key processes in a clinical trial development: 1) From the award of the grant to the first participant inclusion and 2) from the first participant to the final report of results. Respondents were asked to list, in their opinion, the three top inefficiencies in both processes. There was also a free space where they could explain why they thought those were important, if desired. Thus, it is presumed that the survey did not have closed-ended questions and the answers must be subject to the authors' interpretation and classification. This approach is more subject to biases than if the survey had contained closed-ended questions. Therefore, it leads to a subjective interpretation and the analysis will be more likely to have inaccuracies.

Response: The reviewer is correct that we did not use closed-ended questions. This was because closed-ended questions would have inevitable been based around our own views of the relevant inefficiencies, and we wanted to elicit unprompted responses from a range of disciplines within CTUs. Closed-ended questions would have risked ‘prompting’ or ‘leading’ respondents. Also, closed-ended questions would have been subject to interpretation in a variety of ways by different respondents; hence subjectivity is a potential issue for both types of questions. Therefore we disagree that our use of free text responses would be likely to lead to more ‘inaccuracies’ than closed-ended questions.

• Within the 45 units registered in 2013, only 25 answered the survey and, from them, there were only 43 respondents. In the discussion held by the authors, they consider this response rate lower than expected. It cannot be drawn from the results if the distribution of those 43 respondents was more or less homogeneous among units or some units contributed more than others. In the latter case, the inefficiencies of those units would be overestimated in the survey.

Response: In fact 43 responses were submitted. Five were received from one unit, four from another, two units submitted three responses and five submitted eight responses. The remainder submitted one response per unit. This information has now been added to the text. Whilst a small number of units were particularly active in submitting responses, nevertheless we achieved a broadly representative response based on geographic distribution and type of unit. Our focus was to ensure a broad representation of disciplines as this may be a bigger driver of what is perceived as an inefficiency than individual units.

• Most of the article includes the original texts of the respondents. Therefore, the reader is able to interpret the responses in a different way to the one carried out by the authors. For example, inefficiencies regarding the CRF design are included in the two key processes mentioned above. However, the CRF design is expected to be finished when the first participant
is included and, from this reviewer's point of view, it shouldn't be registered as "inefficiency" from the inclusion of the first participant to the final report of results, as the authors did.

Response: Our paper describes a survey, and hence the two categories of inefficiencies are reported within the category respondents placed them. This is not our interpretation. CRF design was reported by respondents as an inefficiency both for grant to first participant, and for first participant to results. We disagree that CRF design should not be regarded as an inefficiency for first participant to results. Poor initial CRF design may only become apparent when the first participant is recruited, and changes made at this late stage can be a major inefficiency in trial conduct.

• Other responses could also be related to processes of a research in general more than in relation to the unit in which the respondent was included, for example the biases in the publication.

Response: Unfortunately we do not understand this comment.

• In other cases, the responses were unclear, as the authors said in the discussion. Moreover, it is also discussed if the units perform research with medical drugs or not, which can also have a big influence in the inefficiencies described in the survey. I agree with the authors that, from a regulatory and administrative point of view, a clinical trial carried out with medical drugs is not the same as an observational study.

Response: The referee has misunderstood, as our survey was only about inefficiencies in the conduct of multicentre randomised trials, and did not include observational studies. We do comment that not all units conduct clinical trials of investigational medicinal products, but the context of this comment is to put in perspective the numbers of respondents reporting inefficiencies in working with pharma and around supply of the drugs. We have changed the wording to make clearer that if they do not conduct drug trials that do conduct other types of clinical trials (medical devices and complex interventions).

• Therefore, this issue can influence the responses. From 2013 until now a new clinical trial regulation has been implemented (EU 536/2014) and many regulatory authorities have implemented changes in their policy of research studies to improve efficiency and reduce the time of approval. At this time, due to the remarkable legislative changes, the study performed in 2013 could be obsolete and inefficiencies could be different. Taking into account the responses in this article, the authors could use this study as a pilot study and design a new one with close-ended questions not subject to interpretation and including the latest regulatory developments.

Response: Whilst we agree that inefficiencies may change overtime, many of the inefficiencies reported by respondents to our survey are unlikely to have been solved by changes in clinical trial regulation. We agree it might be useful to repeat the survey, but as discussed above would still advocate open-ended responses.