Author's response to reviews

Title: Risk proportionate clinical trial monitoring: an example approach from a non-commercial trials unit

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Author's response to reviews: see over
Dear Editor

Thank you for the opportunity to resubmit this manuscript.

My co-authors and I would like to thank the three reviewers and editorial team for helpful comments which have been addressed in the revised manuscript with detailed responses (in red) to each comment included below.

Please also see the suggested alternative format for the abstract in response to reviewer 3 which may provide a better summary of this manuscript compared to the standard abstract format.

I look forward to hearing from you.

Yours sincerely

Catrin Tudur Smith
Reviewer 1: Charlie Goldsmith

1. There should be a list of all short forms in one place. Many of them are not standard usage.

A separate list of abbreviations has been included in the revised manuscript.

2. Dates should be standardized and not assumed as to format.

One date was amended in appendix 3. No further dates could be detected.

3. The focus is too much the UK when the issues are just a relevant around the world.

As the Clinical Trials Research Centre, and the majority of trials which are coordinated through the centre, is based in the UK, the focus of this paper is on the UK. Many of the principles outlined within the paper are more widely applicable but as stated in the discussion it would be difficult to standardise the approach to monitoring to fit all trials across the world. Nevertheless, the methods described do draw upon the latest methodological research undertaken by international organisations such as the Clinical Trials Transformation Initiative, and the paper does briefly mention the FDA viewpoint. But, as the aim of the paper is to simply present one approach, albeit from a UK perspective, it would be difficult, and inappropriate to try and generalise issues so that they reflect the ‘world’ perspective.

4. References are not in line with Trials format to list up to 30 authors before use of et al.

References have been reformatted as requested.

5. Many uses of [and/or] when [and/] is redundant

This has been amended throughout the manuscript.
Reviewer 2: Oana Brosteanu

Major Compulsory Revisions
This is an interesting manuscript for those working in the field of non-commercial clinical trials. Since a few years, we experience a paradigm shift with respect to quality management of clinical trials, in favour of a risk-based approach tailored to the needs of the respective trial. However, most of the published recommendations remain on a general level and do not provide specific details how to implement risk proportionate approaches. Therefore, we are in need for practical examples, and I encourage the publication of this manuscript. However, in my opinion the following revisions should be incorporated:

1. The authors mention the risk-assessment they perform for each trial (page 6), and provide an example as a supplement. A description of the risk-assessment procedure is missing in the manuscript and should be added. At least the following aspects should be covered:
   a. Who is involved in risk-assessment?
   b. How are the risk categories identified?
   c. What are the provisions if a trial has overall a low risk, but there is one or more risk category with a high (>10) or even very high (>=20) score? Why on the first page of the risk-assessment only the mean score is mentioned and not the maximum score?

   A brief description of the risk assessment process has been added to the paper. However, we purposely haven’t provided too much detail on the risk assessment itself, including the scoring system, as the risk assessment is used to guide the monitoring plan and discussion about the merits of different approaches to risk assessment is beyond the scope of this paper.

2. In Section 3 (page 7) the authors briefly mention the monitoring plan they develop based on prior risk-assessment, and provide an example as a further supplement. Here again, a more detailed description on the contents of the monitoring plan would be helpful for the readers, since the example provided is not in all parts self-explaining.

   The aim of the paper itself is to describe the sections that should be considered within the monitoring plan with the example monitoring plan provided as an illustrative example. The text on page 7 (section 3) has been amended to clarify this.

3. In section 3.2.1.1. (page 9) the authors mention that in general copies of completed informed consent forms are faxed to the CTRC. The authors should comment on data protection issues pertinent to this procedure. Are full names faxed?

   Full names (as signatures) are included in the faxed documents. A sentence has been added to section 3.2.1.1 to highlight the data protection issues.

- Minor Essential Revisions
4. The sentence “The purpose of this paper…” (Abstract - Purpose) should be rephrased. It remains unclear to what “relevant to standard clinical practice”
refers.

Sentence revised as requested.

5. In Figure 4, in all three diagrams the scale for the y-axis is missing.

The scale for the y-axis does appear in the pdf version that was created on submission.

6. The authors remark that the “trial monitoring report should not be confused with the reports … [for] the IDSMC”. A brief description of the contents of the IDSMC report should be added for less experienced readers.

A sentence has been added to the manuscript.

- Discretionary Revisions

7. In Figure 1, I would prefer a flow diagram (with a loop) to the circle depicted.

Figure 1 has been changed to a flow diagram as suggested

8. An example for a monitoring report would be helpful.

Unfortunately as the example trial is still ongoing we are not able to include an example monitoring report but would be able to on request at a later date.

Reviewer 3: Lehana Thabane

Abstract:
- Results and Conclusion section needs to provide clear description of the results. For example, it is unclear from the abstract what method was used in the example and why.

As this manuscript describes an approach with illustrative example there are no ‘results’ or ‘conclusions’. Completion of the abstract according to the standard structure is quite difficult and we suggest an alternative format for the abstract as follows:

Abstract:
Some level of monitoring is usually required during a clinical trial to protect the rights and safety of trial participants and to safeguard the quality and reliability of trial results. Although there is increasing support for the use of risk proportionate approaches to achieve these aims, the variety of methods and lack of an empirical evidence base can present challenges for clinical trial practitioners.

This paper describes the risk proportionate approach to monitoring that is utilised by a non-commercial clinical trials unit which coordinates a range of clinical trials across a variety of clinical areas with different associated risks. An example risk assessment and corresponding monitoring plan for a low risk
(type A in the MHRA classification system) paediatric trial is provided for illustration.

We present ideas for developing a monitoring plan for a clinical trial of an investigational medicinal product based on our experience. Alternative approaches may be relevant or preferable in other settings based on inherent risk.

• What are the take-home messages about which method is appropriate and under what conditions

The take home message would be that monitoring activities and methods should be chosen to be proportionate to the risks of an individual trial. We have provided examples of possible approaches but do not attempt to make specific recommendations about which method is appropriate and under what conditions as this would very much depend on the inherent risks of the individual trial. Furthermore, there is a lack of empirical evidence available on which to base such recommendations. A sentence has been added to the abstract to highlight this.

Background:
• The purpose of the paper addressed in the last sentence of this section needs to include descriptions of all available methods with relevant empirical data to support their applications.

The last sentence has been amended slightly although a description of all available methods has been omitted as these are already detailed throughout the rest of the manuscript. As noted above there are, unfortunately, no real supporting empirical data available.

• Also include the pros and cons of all available methods.

This paper presents possible methods that could be applied within a risk-proportionate approach to monitoring. The paper does not attempt to make comparisons or recommendations and an assessment of the pros and cons is beyond the scope of this paper although we agree that this would be worthwhile to do in a future research project. A sentence has been added to the conclusions to note this.

Rest of the Paper:
• How many trials have used these particular methods of monitoring?

All trials conducted through the CTRC adopt the approach described in this paper. A sentence has been added to section 2 to clarify.

• What lessons can be generalized to similar settings?

Any of the approaches described could be generalized to similar settings. As highlighted throughout the paper, the most important step is to identify risks and plan monitoring activities to mitigate those risks.
• What makes unique about his unit and what make it a good example to share. How is the unit fit to be a model template?

Section 2 of the paper describes the key characteristics of the Clinical Trials Research centre and aims to set the scene so that the reader can relate to their own setting. The Unit is one of 48 UK registered CTUs and this has been highlighted in the revised manuscript. Whether the unit is fit to be a model template should be left to the reader to decide.

• What are the inherent costs of the various methods being discussed?

As above, this is beyond the scope of this paper and would require further research to assess and compare costs of different methods.

• The first method (central monitoring) provides detailed descriptions of activities, but analogous descriptions are not provided under the second method (on-site monitoring). This makes it difficult to compare the two methods. More detailed description is needed for on-site monitoring.

As noted above this paper is not a comparison of methods but a description of methods that can often complement each other within a risk proportionate approach.

Conclusions:
• How does the experience of the unit compare to the CTTI project recommendations?

Text has been updated.

• What lessons can be shared based on the Unit's experiences of monitoring different trials? It would be best to make empirical recommendations.

This is recognised but not possible at this time.