Author's response to reviews

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

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We thank the two reviewers for their helpful comments. Response to each comment is provided below:

Reviewer: Charlie Goldsmith:

1. However, there are now some examples added as appendices. This means that there are now two lists of short forms and indeed many short forms are NOT listed in either of them: CRB, AE, CFQ, EQ5D, CV, DMA, HTA, ISF, CTIMP, QALY, LREC, R&D, RSA, TMF, IP, DSUR, DMP, PDR, SDV, HoS.
   # All abbreviations are now included within one single list.

2. The R(eference)s have URLs that are NOT dated for date of last access: 5, 6, 13.
   # URLs have been updated and dates of last access added

3. The appendix pages are not numbered to these items will need to searched to find them: Replace [regime] with [regimen].
   # All appendices have been updated

4. Appendix 1, ?first page uses a different date format to the rest of the pages. Each of A2 seems to use a different date at the bottom of each page.
   # dates have been updated or deleted if not relevant

   # All appendices have been updated
6. Suggest including a date format on all signoff sheets such as yyyy-mm-dd or another one that has a date format included.

# The date format has been changed

7. There is at least one more [and/] that should be deleted.

# This has been deleted

8. Data seems to be treated as a singular word in various places where [is] should be [are].

# [is] has been replaced by [are] where appropriate. However, for the following [is] should be used as we are referring to the single document: “Document defining Source data is located within the TMF. Each site signs a paper copy detailing the location of source data at site. This is received at the CTRC and stored in the TMF”

Reviewer: Oana Brosteanu

The authors have answered to all points addressed.

However, some concerns remain.

- Major Compulsory Revisions

  1. Risk assessment:

     The authors have added a short description of the risk assessment procedure, and state that they purposely do not explain the scoring system, since risk assessment is not in the main focus of the paper. I understand this point, but my concern is that the risk assessment template, which is meant as an example, will nevertheless be used by future readers. Thus, in my opinion it is necessary to explain in more detail how to use it. In particular, the following aspects should be covered:

     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?

     # The total score for the trial is already included on the first page along with the mean score and overall % score. In addition, the following text has been included within the manuscript to address the point above regarding what to do when a trial has overall a low risk but some categories are very high.

     The total, mean, and overall percentage risk scores are calculated for the trial (using formulae described in Appendix 2) to provide an overall guide and trial risk classification. However, individual risk scores should also be examined closely (using the risk management matrix and key in appendix 2) to ensure that
appropriate strategies are in place for monitoring hazards with particularly high risk scores. The allocation of scores can be subjective and alternative approaches to risk assessment, which do not require the calculation of a numerical score, may be appropriate.

- Minor Essential Revisions
2. In the diagrams in Figure 4, the y-axis is labeled, but the respective scale is still missing.

# Scale has now been included and figures improved slightly