Reviewer’s report

Title: Early warnings and repayment plans: novel trial management methods for monitoring and managing data return rates in a multi-centre phase III randomised controlled trial with paper case report forms

Version: 0 Date: 03 Dec 2018

Reviewer: Roberta Littleford

Reviewer’s report:

TRLS-D-18-00758


Manuscript Summary

The authors have identified an issue related to data collection timelines and its delay on analysis and dissemination of results.

The authors have assessed the return rates of visit specific paper case report forms to a central data entry centre from a multi-centre phase III Non-CTIMP randomised controlled trial from April 2015 to September 2016. To set return rate targets, the team, reviewed pre-study return rates, set site targets and implemented communication intervention/feedback and measured return metrics per site. The aim was to increase return rates, as well as develop an escalation process in the event that return rates failed to meet set targets.

While this is a limited study, it does address a possible management tool to assess return rates to trigger pre-defined target communication. Thereby enabling trial and data managers to concentrate their efforts on sites that require assistance.

The work is small-scale and exploratory, related to one multi-center Non-CTIMP with limited, participant visits over an 18 month review period. Although, the authors have identified the need for additional research to generate evidence based methods, which could include these elements in due course.

The following comments address both minor and major (generic) issues that the authors should address.

Major Comments:

The repayment plans described in the title are not currently evident in the manuscript. If repayment plans were part of the study design, these should be described in the methodology, and results. If this was a typographical error, this should be removed.

2. The authors should review the manuscript, checking grammar and style writing, tenses, single/plural issues thereby ensuring the standard required for publication.

3. Line 7. While this study is a NON_CTIMP, the authors should address Good Clinical Practice and introduce the concept in the Background and its relationship with data quality and validity. The authors should also address the responsibilities investigator to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4. Throughout the manuscript there are numerous; for examples, which makes for a jarred reading experience. Suggest the authors use; terms, including, embracing, comprising etc. In addition, these portray assumptions, with limited literature to support. Consider adding support, if available.

5. Line 3. The introduction of Table 1, is premature, prior to introducing concepts. Consider relocating to Methods section.

6. The authors do not specifically address the concepts of Data Quality Management (DQM) and Data Management Plans in relation to this study. While the authors address data management and quality they do not reference the quality management process, which is a formal process for managing the quality, validity and integrity of the research data captured throughout the study from the time it is collected, stored and transformed (processed) through analysis and publication. With the DMP describing data to be collected; how and where the data are captured and stored; process for reporting and handling corrections; confidentiality and data sharing etc. Both these concepts should be clearly defined and addressed and referenced within the manuscript.

Minor Comments

Abstract

Lines 40-42. Clarification required - "We also reported separately on forms that can and cannot be completed retrospectively" This is not clear, please revise.

Line 53. Grammar check required - "agreeing targets"
Main Paper

Lines 2-4. The introductory sentence is disjointed and should be rewritten to introduce the subject matter.

Line 4. Suggest that high data return rates are pertinent to all studies, not merely RCT. The authors can defined why of particular importance to RCTs; Non-CTMP and CTIMP.

Line 5 "a long delay' and Line 25 :" short data return” - can the authors quantify the term 'long' and 'short', or is it merely a mismatch between trial activity data acquisition and data availability in DMS.

Line 7 - Introduction of monitoring requires definition in relation to this manuscript. Is this a correct assumption?

Line 7-8. Introduction of the consent of monitoring. Require further explanation.

Line 9. Suggest amending the word 'capability' - the oversight committees have capability of making decisions, however, their decisions may not informed due absence of data.

Line 9. Consider singular and plural conditions in relation to return.

L17. …"helping prepare the database for trial analyses." This sentence should address the need for data lock prior to analysis.

Line 24. Suggest rewrite to: The central's team's ability to identify issues in a timely manner in relation to patient safety or protocol adherence is also reduced by slow data returns.

Line 25. a long delay' - can the authors quantify the term 'long', or is it merely a mismatch between data from activities performed not being recorded in the DMS.

Lines 8, 24-28 - Concept of monitoring. The authors are requested to introduce the concept of monitoring

Line 27. Suggest amending "on-site -monitoring and increased use.. " to

Line 28 "The usefulness of these is largely dependent on having" to "The usefulness of these are largely dependent upon having"…the authors are requested to review the whole manuscript and edit singular/plural grammatical issues

Line 29. Concept of good quality date - authors require to define good quality data. What does it look like, how is it assessed?

Line 32. The authors require to outline what is novel about their methods in relation to current knowledge of the subject matter.
Line 34. Is there a reference to support this assumption?

Line 39. Grammar check required - "time to data being available"

Line 45. The authors should consider why pCRF are not completely replaced by EDCS; relevant to many investigator trial, cost/time/validation methods/systems etc.

Lines 53 -54. Review grammar in relation to "i.e. thresholds to colour acceptable centres green…

Line 56. Consider amending "slipping" to deteriorating, falling, declining etc.

Line 88. Grammar correction required. "by, at most, one full-time data". There is only one, so most is not applicable.

Line 90. Clarification in relation to "sent." Sent by email, post. If post, were they copies with the original at site?

The authors should consider a flow diagram depicting the CRF requirements per visits/study timeline, and the interaction with CTU. Indicating best case and worst case scenario timelines.

Line 98-99. Grammar check required. "we expect" to we would expect

Line 103. Clarification related to percentages listed; "was around 92%, and had generally been between 85% and 90%". How can it be greater than the maximum of 90%.

Line 106. How and who decided that 80% return rate was an amber flag for a centre requiring support to increase data return?

Line 109. Clarification required. "in each report". Please clarify the meaning of this sentence.

Line 111. As the TMG only met every 6 months, there was potentially only 3 opportunities for metrics to be assessed during the 18 month CRF review period. Therefore, four centres (11%) had <80% DRR in more than 1 meeting? Please clarify the importance of this statement.

.Line 112. Grammar check required. Please consider rewriting the sentence amending the concept of "better quality" to improved, and to outline how completeness is different from quality? Suggest defining the metrics used to assess quality and provide relevant results/discussions in the appropriate sections.

Line 114. Suggest outlining previous processes and how the new processes were determined as novel. In the discussion the authors will have to address

Line 115. Developed a more comprehensive process for handling DRR than had been used previously. Outline what the process was before how the new processes were novel. In the discussion a comparison is required outlining the improvement metrics in relation to
resource/capacity of DM investment into the new processes. The authors should also discuss future professing via automatic reminders to sites.

Line 119. Grammar check required. "Our first aim was to be able to better visualise…"

Line 126. The authors should expand on the concept of "The tool underwent testing prior to use". How and what was done - validation process should be outlined.

Line 127 -129. In contract to data integrity and GCP expectations - the process outlined to assess data appears to be open to potential errors. The authors should address the validation processes used to ensure no errors during copying and pasting. In addition, the authors should address this as a current limitation and outline potential technology advances that can be employed going forward.

Line 135 - 138. Interesting granularity between green and red. It would be advantageous for the reader to understanding what each would indicate if a continued trend and what migrating and escalation processes would be required to rectify intervention points.

Line 150-151. While this is a correct assumption. The study design could also have had an impact. As the study and clinic visits could align, depending upon the organizational skills of the study team, CRN or trial specific RN, issues with staff change over, the patient outcome questionnaires may not have been readily amiable at the time of the patient visits. This should be addressed as a possible causal impact.

Related Figure 3. CRF return rate for patient -reported outcomes. This requires to be addressed by the authors in relation to the low number of completion at some sites. What remedial actions were instigated to improve this data?

Line 169. …"hypothesised that this approach might be better received by centres". The methodology of 'novel trial management methods for monitoring" did not include discussions with trial centres?

Line 173.. …" some room for negotiation, as long as the plan would result in improved DRR 174 over time" how was this managed as this would not be known prior to negotiation…this was prospective.

Line 176-188. Escalation Process. Was it ever implemented, if so how successful was it? Did the sites know there would be escalation if they did not reach the pre-defined targets? How were sites informed of their targets?

Line 190-191. Evaluation. The authors should either consider removing this and document analysis with the results, or provide a description of the evaluation, methods chosen.

Line 194-195. Rationale for stopping the analysis. The authors should consider providing additional details. Did this have a limitation to data collection/analysis etc?
Line 197-198. The authors should present potential reasons why it reached a peak at this point; related to study design, due to DM measures being implemented, was there a lag time and this was the impact zone, etc.?

Line 203. Clarification required - the new process. What was the new process, the title states novel trail management methods - what were they? The authors should address how communication with sites the need to address an issue is novel.

Table 1 outlines multiple metrics, but they are not addressed independently in the results section. How each/or a combination changed over time or in response to 'collaborative' telephone reminder.

Neither the results nor the discussion addresses the concept of data quality measures. The authors should address the quality of data prior to managing CRF targets, was quality maintained, reduced or improved as a result of setting and delivering to target?

Lines 245-247. "Centres might not be contacted about corrective actions, for example, if they have already notified the CTU team that they currently have resourcing issues." The authors require to address this. In site agreements for RCT and a requirement for GCP (RCT) it is a legal responsibility the there is adequate recourses available. In addition, HRA, Statement of Activates are sign-off to ensure there is site resource/capacity. As part of trial management these issues need to be addressed, not dismissed.

Lines 238-240. Are the authors suggesting that the new staff on the trial were the stopping rule for evaluation? Independent decision to change the processes. What were those processes and who decided that this was appropriate at that stage of the study? With reference to Figure 1b. Could the authors describe the impact on the new preferences and the number of centres who fell below the 80% target?

Line 263. Grammar check required - "This would require storing of each report snapshot within the report" Please clarify.

Line 288. Clarification required - "higher levels of the escalation plan". Earlier in the manuscript the authors note that the escalation plan was not required. The authors are requested to clarify, if and to what degree the escalation plan was used.

Line 292. "there are no significant incentives to help ensure completeness of follow-up data" - breach to GCP and research governance framework. The authors should address the legal and best practice guidelines representing the foundation of data integrity and address the issues in the manuscript.

Line 293-296. The authors should address the issue of secondary outcomes in TRISST and the likely hood they will be analysed and published.

Line 335. The authors are requested to delete sentence related to publication and add the emphasis of further research required.
Line 312. The authors should address the idea that CRF is over a tear overdue. Unlikely to receive data, staff changes, access to patient notes, etc. This timeline is unacceptable, and is a trial management failing.

The authors should consider per site, central data entry issues. The level of responsibility and relevance for site staff.

While the DRR and timelines are specific for this trial what inferences, if any, can be made regarding CTIMPs in relation to reporting AEs/SAEs?

Its generalizability to studies with additional; visits, assessments per protocol and medicinal intervention are not addressed, especially in relation to the need for in-time safety reporting.

The authors are requested to address the limitation of the current studies in relation to these elements.

Figures 1a-c.

Figure 1c. With reference to the addition of a timelines in relation to patient visits and CRF completion, this would highlight a decrease in the percentage of CRFs for the stage of the study. Not sure what benefit the cumulative recruitment line gives to understanding. To present context a percentage of expected vs actual CRFs would perhaps be more informative.

Figure 3. CRF return rate for patient-reported outcomes. This requires to be addressed by the authors in relation to the low number of completion at some sites. What remedial actions were instigated to improve this data?

Level of interest
Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

Quality of figures
All images and figures within the manuscript should be genuine i.e. without evidence of manipulation. No specific feature within an image may be enhanced, obscured, moved, removed, or introduced. If you have concerns about the veracity of the figures you should choose the first option below.

Statistical review
Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.

**Declaration of competing interests**

Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal

Were you mentored through this peer review?

No