Reviewer's report

Title: Implementing monitoring triggers and matching of triggered and control sites in the TEMPER study: A description and evaluation of a triggered monitoring management system

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Reviewer: Joe Eustace

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Implementing monitoring triggers and matching of triggered and control sites in the TEMPER study: A description and evaluation of a triggered monitoring management system Carlos Diaz-Montana, MSc; William J Cragg; Rahela Choudhury; Nicola Joffe; Matthew R Sydes; Sally P Stenning Trials

This report serves a dual purpose, it details a triggered site monitoring approach to trial monitoring -relevant to trialists potentially interested in adopting such an approach- and it describes how this approach was used to pair-match sites within the TEMPER trial, which is of independent methodological importance. The report is well written and timely, especially so, given the persistent uncertainties around risk based monitoring despite it mandated use in ICH GCP E6[R2].

I have several minor comments, none of which I consider critical but which may enhance what the reader can take from the paper.

1. Across the 3 studies 23 Trigger Meetings were held at between "3-6 month intervals". Was the frequency of meetings pre-determined or what factors influenced its frequency (baseline risk assessment/results of prior site visits/available resources etc)?

2. What was the extent of the monitoring that took place at the selected sites (100% source data verification or otherwise)

3. The selection of appropriate Triggers play a critical role in the described approach. As different triggers fired between 0 and 79% of occasions, it would be interesting to add the frequency of firing to Table 1 or to categorize this frequency e.g. common/uncommon/rare. Providing the additional trigger parameters, of Trigger Weight and Frequency might also be of interest to the reader.
4. The authors indicate that the trial specific triggers were based on existing trial practises and in their discussion describe the potential future development and evaluation processes for triggers. However any additional insight, based on their experience within TEMPER, that the authors can provide to the reader as to factors that may or should determine the selection of triggers would be of use to trailists adopting their approach.

5. I found the description of the inequality rule L72-L79 confusing, in part because I wasn't initially sure of what was meant by the sample and population and found L73 -74 particularly opaque, also I am not sure that "<>" has an standard definition as compared for example to "vs.". This may be easier to follow when in the published version, Figure 2 will be in proximity to this description. However, this might be clearer if L72 was clarified, for example "…relationship between a given trigger threshold and the quotient of the sample meeting this threshold over the relevant total number of assessments of that trigger."

6. Which triggers if any were assigned a weight of 0 for the study, and did their performance justify the future use of these triggers with a more influential weight.

7. In calculating the score how was repeated occurrences of the same trigger during the same assessment captured e.g. if 2 medications errors had occurred since last assessment in the same trial.

8. Can the authors comment on the choice of variables used for the matching process in pairing triggered with non-triggered sites. Is there any validation of the predictive power of the used variables with regard to trial performance or protocol compliance over time.

9. The number of sites chosen for monitoring per trigger meeting was 1.83, was the number of sites chosen during any one Trigger Meeting dependant on the absolute site score or what determined this.

10. To what extent did sites within a trial vary in their scores over time. Did such temporal trends influence triggering.

11. As the 'penalty' was fixed per trial (L164], it does influence the ordering of site scores at a given Trigger Meeting or the selection of the matched site - as the ordering of potential matching sites by their scores would be the same for [distance +site score] as for [distance +(site score * 'penalty' factor)], given that the penalty factor is a constant. The purpose of penalty factor would therefore appear to be exclusively to compensate for across-trial heterogeneity and to facilitate the combining of data from the 3 different trials
used in the study. However the description of how the penalty factor was derived in L161-164 is quite vague and appears subjective. How effectively it standardises the results from across the 3 trials and allows for a fair aggregation of the trial specific data is unclear. Given the difficulty in validating the effectiveness of the 'penalty' it would seem preferable to present trial specific data for each of the 3 trials in Table 2 as well as the aggregate data derived from the use of the penalty as is currently shown.

12. L233 "Trigger scores informed rather than mandated the selection of triggered sites"
What additional factors were taken into account in deciding this and what percentage of cases was the triggered site determined by team decision rather than by the trigger-score approach. Was there a difference in the matched monitoring findings between triggered sites and those in which the selection was manually informed?

13. L335 Conclusion, the statement (L335) ....."Temper -MS implemented an approach of standardizing current practise triggers…", is misleading, Trigger formats and triggering processes were standardized but the triggers themselves varied considerably between studies which, as mentioned in the future direction, remains an important challenge to the proposed approach.

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