PeRSEVERE implementation guidance: a practical guide to managing participation changes in clinical trials and other research

Part 5: risk assessment and monitoring

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PeRSEVERE collaborative group*

From the PeRSEVERE project: PRincipleS for handling end of participation EVEnts in clinical trials REsearch

*** For a full contributor list, see https://perseverepriciples.org/about-persevere/.**

This guidance document is part of the PeRSEVERE project (PrincipleS for handling end of participation EVEnts in clinical trials REsearch). The full set of guidance available is:

- 1: General considerations
- 2: Policies and processes
- 3. Trial funding, protocol development and statistical planning
- 4. Patient information, participant communication and consent
- **5. Risk assessment and monitoring**
- 6. Training and support
- 7. Data collection about participation changes
- 8. Analysis and reporting

The suggestions in these guidance documents are more detailed than the general recommendations in the PeRSEVERE Principles and Explanation guidance (https://perseverepriciples.org/the-persevere-principles/). We still expect individual trial teams to make their own judgements, based on their knowledge of their trial, their research area, and the patients they work with. We recognise there will sometimes be good reasons to deviate from our recommendations.

Although we encourage use of this guidance in other settings, it has been written primarily for Registered CTUs within the UKCRC Network. This is reflected in the terminology used (e.g. 'CTUs') and some assumptions about trial settings. We aim to accommodate different arrangements of CTUs, sponsors and participants. This includes trials where CTUs have no direct contact with participants (i.e. because participants are only in contact with 'trial sites'), trials where CTUs have some participant contact, and trials where there are no trial sites (i.e. where the CTU works only directly with participants). We have aimed to accommodate all trial designs, not just randomised controlled trials.

We use 'trial staff' as a general term to mean all those working on behalf of a trial, in any capacity. We use more specific terms where needed (e.g. 'CTU staff', 'trial site staff', 'clinical staff' etc). We use 'trial team' to mean those responsible for designing and managing the trial.

Key to notes and symbols used

- Links to specific PeRSEVERE principles are denoted by the relevant reference code in square brackets, e.g. **[O5]** with a link to the relevant principle's 'title' in a footnote.
- Symbols used in these guidance documents:

Indicates an area where more research is needed

Indicates a link to a different PeRSEVERE implementation guidance document

Contents

1. Risk assessment

Conducting a risk assessment prior to starting a trial is considered best practice and is included in recent revisions of ICH Good Clinical Practice guidance.[1] When in the context of planning for participation changes, risk assessment means considering the likelihood that the number or type of participation changes could impact negatively on the trial's objectives or on participants' rights or wellbeing.

It might be that aspects of a trial's population, design or setup make certain sorts of participation change more likely. Factors to consider could include the length of follow-up, possible changes in participants' health, media coverage about the trial intervention, or availability of treatments outside of the trial. Understanding the risks (which may be high, low or unknown in terms of likelihood and impact) means trial conduct and analysis can be risk-proportionate. It also gives an opportunity to review aspects of the trial design in light of the assessed risks, such as whether potential burden on participants can be further reduced.

From a practical point of view, it may be useful to provide those performing each trial's risk assessment with a list of prompts. This can help them think through risks applying to their trial, though it is important for the prompt list not to discourage trial staff from considering risks not present in the list. Prompts might include the likelihood of many participants stopping intervention early (for any reason), many participants saying they want other aspects of their participation to stop, many participants losing contact with the trial staff or many losing capacity to consent during the trial.

Trial staff might be prompted to consider risks associated with the participation change processes themselves, and how these could be mitigated. For example, if there are plans to try to regain contact with, or collect further data about, participants who are no longer in contact with trial staff, might these activities be seen as intrusive or unexpected? Where intervention delivery and outcome data collection are closely linked (e.g. the intervention delivery and outcome measure collection take place at the same clinic visits), could efforts to improve visit attendance affect the generalisability of the trial results?

2. Central monitoring using aggregate data

Information about participation changes should be regularly reviewed by trial oversight groups during each trial. The frequency of review will depend on the trial and its risks. However, it should be frequent enough to allow any corrective actions to be taken (and have time to be effective) in response to any issues raised through the review.

Some considerations for reporting participation change data for monitoring purposes:

- The terminology used should convey the complexity in participation changes **[O1[2]]**.

[1] ICH Guideline for Good Clinical Practice: https://www.ich.org/page/efficacy-guidelines

[2] O1 Participation can stop, reduce or change

- Presented data should separate different types of participation change. This might include participants stopping intervention only, stopping further follow-up but allowing use of data from routine follow-up, stopping all data collection, or having lost contact with trial staff. The exact categories may depend on the trial. They may also align with the 'tiers' of participation **[Part 3[3]].**

- Prioritise data about issues that could affect completeness or validity of the primary outcome measure(s).
- Reviewed data should summarise information on reasons for participation changes, when available **[Part 7[4]],** including where the reason is unknown.[5]

- In any trials with more than one intervention group, data should also be presented and reviewed by treatment group. It may be more appropriate for this information to be restricted to the Independent Data Monitoring Committee (particularly for randomised trials), rather than being accessed by members of the trial team.
- Data should be reviewed by trial site and based on any other important subdivisions for a given trial, e.g. by country in international trials.
- Information about baseline characteristics should be included with any of these statistics as required.[6] This can show any differences in characteristics between groups of participants who have missing outcome data and those who do not.

As always, data reports generated during an ongoing trial should be interpreted with some caution, as data collection and cleaning will be ongoing.

The above list (as per the rest of this guidance) mostly focuses on participation changes. Missing data may occur for other reasons, such as participants not attending some trial visits (without fully stopping their participation) or administrative or technical reasons. Summarised information about the occurrence of missing data (with any cause) should be reviewed on a regular basis throughout the trial.

3. Individual-level monitoring

Depending on the trial risk assessment, it may be useful to plan monitoring activity around individual participation changes. This could take place during on-site monitoring visits. It could involve review of participants' medical notes to check that participation has changed in line with participants' wishes. Monitoring could help verify that trial sites have followed best

[3] PeRSEVERE Implementation Guidance part 3: trial funding, protocol development and statistical planning
[4] PeRSEVERE Implementation Guidance part 7: data collection about participation changes
[5] Marie Curie Research: Missing data in palliative and end of life care trials. https://www.mariecurie.org.uk/globalassets/media/documents/research/Missing-Guidance-Report-final-June-2022.pdf
[6] Ibid.

practice regarding managing participation changes (including record-keeping, and all other relevant aspects as set out through the PeRSEVERE project).

The impact of participants' changing consent on trial staff's access to participants' medical notes needs to be considered. This access to confidential information is based on participants' consent, which may not automatically remain in place if participants withdraw their consent to take part in some or all aspects of a trial. It may be suitable to apply a 'presumed ongoing consent' approach to this aspect of participation.[7]

Central monitoring processes should also help identify where a participant's wishes have not been followed. For example, if a participant expresses a wish for no further data collection about them for the trial, processes in place at the CTU should immediately identify if the trial site provides trial data (in error) after that time.

4. Responding to monitoring findings

The most appropriate action to take in response to monitoring findings depends on what issues are found. It could include more training or feedback for trial sites or CTU staff, or amendments to the protocol, statistical analysis plan or data collection forms.

If monitoring shows that the originally expected frequency of participation changes is different to the observed frequency, action may be required to amend the protocol or analysis plan content about handling participation changes, or even to amend the trial's sample size.

Trial statisticians can advise on prospective thresholds to indicate where the frequency of participation changes might be high enough to impact on trial integrity. Site-level thresholds can be used to target site-specific monitoring, e.g. via a 'triggered monitoring' approach.[8]

5. Monitoring plans

The monitoring plans for each trial need to be specific to that trial. However, template documents (including monitoring plans and oversight committee charters) can include prompts to ensure all relevant points mentioned here are at least considered.

More guidance on clinical trial monitoring is available via the UKCRC Registered Clinical Trials Unit Network website.[9]

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[7] This means participants' consent to a particular trial activity is presumed to be ongoing if the participant has not said they want that activity to stop, as long as certain conditions are met. For more details, see PeRSEVERE principle O5 (continuing data collection) and PeRSEVERE Implementation Guidance part 2: policies and processes)

[8] Stenning *et al.* (2018) Triggered or routine site monitoring visits for randomised controlled trials: results of TEMPER, a prospective, matched-pair study. *Clin Trials.* 15(6):600-609. https://doi.org/10.1177/1740774518793379

[9] https://ukcrc-ctu.org.uk/guidance-for-ctus/