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

Part 7: data collection about participation changes

Version 1.0 September 2023

PeRSEVERE collaborative group*

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

PeRSEVERE

*** 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. What does 'good quality' data about participation changes look like, and why is it useful?

Data collected by trial teams about participation changes should be good enough to usefully inform trial management, monitoring and analysis **[M1[1], M2[2], R1[3]]**, and to be able to clearly report what participation changes took place during the trial **[R2[4]]**.

Good quality data also underpins several other PeRSEVERE principles. Accurate data is important in keeping a record (and being able to carry out) participants' wishes in relation to their participation **[O2[5]]** or further contact about the trial they took part in **[O7[6]]**.

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[1] M1 Informative data collection about participation changes
[2] M2 Monitoring
[3] R1 Analysing studies with participation changes
[4] R2 Consistent and complete reporting
[5] O2 Participants decide how their participation changes
[6] O7 Information after stopping participation

Therefore, although the level of detail implied in this guidance may be more than is required for analysis purposes, detailed data is useful to support the other purposes. Having access to granular detail also gives trial statisticians choices about what data they use in trial analyses.

Specific recommendations for data collection about participation changes are given below**.** As well as data about participation changes, it is important to consider what other data items might be needed for handling missing data in trial analyses (for example, to interpret the missing data mechanisms[7] or ensure data about all 'intercurrent events' of interest will be collected[8]).

[7] Hussain *et al.* (2022) Development of guidelines to reduce, handle and report missing data in palliative care trials: A multi-stakeholder modified nominal group technique. *Palliative Medicine*. 2022;36(1):59-70. https://doi.org/10.1177/02692163211065597

[8] Lynggaard *et al.* (2022) Principles and recommendations for incorporating estimands into clinical study protocol templates. *Trials.* 23, 685. https://doi.org/10.1186/s13063-022-06515-2

2. Specific recommendations for data collection about participation changes

Data collection forms should recognise the variety of possible participation changes, and **use suitably specific terminology and language**, including in specific questions and the names of forms **[O1[9]]**. Avoid non-specific terms like 'withdrawal' or 'loss to follow-up' unless a specific definition is provided. Those reporting participation changes to CTUs (on data collection forms or otherwise) should be encouraged to be clear about exactly how participation has changed. The suggested terminology given in the PeRSEVERE Principles and Explanation document may help.

The trial **statistician should be as involved as needed** in data collection design, including to ensure the data being collected is suitable for any defined estimands. Experienced **data managers** should help ensure the data collection forms are well designed and will collect good quality data that meets the needs of the trial protocol.

[9] O1 Participation can stop, reduce or change

Given that participation in trials can stop, reduce or change **[O1[10]]**, it is possible that a participant's participation could change more than once. Data collection forms **may therefore need to be completed at more than one timepoint.** Form design should accommodate this.

Data about different types of participation change could be collected separately (e.g. on separate forms or in distinct sections) to reinforce the differences between these, namely:

- Stopping trial intervention: this happens to all trial participants at some point (except where intervention continues until the end of the whole trial). Details of stopping – whatever the circumstances – should therefore be recorded for all participants. Stopping intervention may not be the participant's choice, and this sort of decision made by someone other than the participant is more common with stopping intervention than with other sorts of participation change. Stopping intervention should not usually mean other aspects of participation need to stop. Presenting the intervention stopping separately may help reinforce this point.

[10] O1 Participation can stop, reduce or change

- The ICH E9 guideline addendum explains the importance of distinguishing between intervention stopping and participation changes that can lead to missing data: ‘the former represents an intercurrent event, to be addressed in the precise specification of the trial objective through the estimands [and] the latter [give] rise to missing data to be addressed in the statistical analysis’.[11]

- Cases where participants and trial staff have lost contact with one another (according to the rules or definitions given about this in the trial protocol **[Part 3[12]]**).

- Other participation changes, which could be split into those resulting from an expressed wish by the participant themselves, and those resulting from a decision by someone else (e.g. because of a change in the participant’s capacity to consent, or where further participation is not possible for reasons to do with the trial design).

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[11] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf

[12] PeRSEVERE Implementation Guidance part 3: trial funding, protocol development and statistical planning

Data collection forms should request information about each participation aspect (e.g. trial intervention receipt, trial follow-up appointments attendance, trial questionnaire completion, biological sample storage etc) and **record whether or not each one has changed.** The types of possible participation change will depend on the trial, and should be considered (and, where necessary, defined) during trial setup.

Reasonable efforts should be made to find out exactly how participants want their participation to change **[O5[13]]**. However, **sometimes it could be that participants' wishes are not known** about one or more aspects of their participation. **Data collection forms should enable recording of this missing information**, where applicable. This helps avoid trial staff making any assumptions about participants' wishes. However, trial staff should consider any information they *do* have that might indicate what a participant wants to do (e.g. things the participant previously said). Based on the 'wishes not known' status, the trial team can decide – working with trial site staff and using what is known about the participant's circumstances – whether it is appropriate to continue the relevant trial activity

[13] O5 Continuing data collection

under a ‘presumed ongoing consent’ approach[14], where the conditions mentioned in principle **O5** are met.

Data collection should record the **dates relating to the participation change**. Specific dates to request may depend on the type of participation change and the trial’s planned analysis, so the trial statistician should be consulted about the choice of date. It could be that more than one date is needed. In any case, data collection forms should be clear about exactly what date is sought (not just ‘date’ or ‘date of withdrawal’). Possible dates to collect may include:

- The date of the participant’s last clinic visit;
- The date of last intervention received;
- The date of the last active involvement of any kind in the trial (or date of last contact with the participant where contact has been lost);

[14] 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)

- The date the participant expressed their wish to stop participating;
- The date someone else made a decision that participation should change or stop (if the participation change was not the participant's choice);
- The date it was agreed to consider the participant to have lost contact with the trial.

Data collection forms should be designed to help **understand why the participation change has happened**. There may often be more than one 'reason' to record.

- Where the change follows an active decision by the participant or someone else (e.g. their doctor), the forms should try to ascertain the main motivations behind these decisions, with clarity about who made the decision.
- There may also be indirect factors to note, for example changes in the participant's circumstances meaning they can no longer take part (even if they want to).
- In other cases, participation may stop because of reasons to do with the protocol requirements or trial design.

- It should always be clear *who* has provided the information about motivations or reasons for the participation changes (i.e. participant, trial staff).[15]

- It may be useful to develop a standardised list of reasons for participation changes, in order to improve data quality (i.e. as an improvement on free-text responses). This list could be available for use across trials, and made trial-specific (and even updated as a trial progresses).

    - Good Clinical Practice standards confirm that participants can end their participation without *having* to give a reason, but does not say that participants *may not* give a reason or *may not be asked.* ICH Good Clinical Practice guidance even says that 'the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the [participant's] rights'.[16] However, trial staff may feel uncomfortable asking. A list-based tool to elicit

[15] 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

[16] ICH Guideline for Good Clinical Practice: https://www.ema.europa.eu/en/documents/scientific-guideline/iche-6-r2-guideline-good-clinical-practice-step-5_en.pdf

participants' reasons for stopping may help with this. The approach may also increase participants' willingness to provide reasons, if it involves just ticking boxes from a list rather than providing lots of personal details.

- Guidance alongside the questions on the data collection form could help trial staff gauge how much detail is needed for trial purposes. Enough detail should be requested for the trial's purposes, but no more than this, as participants' motivations for changing their participation may be personal and sensitive.
- Consider whether there might be ways for participants to provide information on their motivations in ways that mean trial staff they interact directly with would not see it, in case this could encourage honest and open reporting.

As well as requesting 'reasons' for the participation change, **more specific questions could help trial statisticians handle missing outcome data** when they perform the trial analysis. This could include questions to find out whether (in the clinicians' and/or participant's view) the participation change

had anything to do with changes in the participant's health. It may be useful to ask about the participants' health (or prognosis) at the time of the participation change compared to participants with otherwise similar characteristics.

Data collection should include **participants' preferences for further contact** about the trial (including receiving the trial results).

Data collection forms could be a suitable place to **remind those completing them about key aspects in handling participation changes.** For example, the form about trial intervention stopping could mention that other aspects of participation continue after that point unless the participant wants them to stop **[O2[17]]**. Data collection forms could remind trial staff of the need for good record-keeping around participation changes (for example, retaining a clear record of the participant's wishes in their medical notes). Forms can also request confirmation that key trial-specific actions required by the trial protocol have been followed.

[17] O2 Participants decide how their participation changes

Where relevant, data collection forms could **remind those completing them of other possible required actions**, such as completing a Serious Adverse Event (SAE) form if the participation change met the criteria of an SAE.

Implications of **each participation change on further data collection** should be considered**,** including the potential for *increases* in participation that previously stopped or reduced.

- Systems and processes should be in place to ensure all participation changes are implemented. For example, if a participant says they want to stop trial questionnaires, any automated requests for these should stop. Where trial site staff enter data directly into the trial database (i.e. via 'remote data entry'), CTU staff could control database access prevent further data entry if no further data should be entered.
- If the trial protocol has allowed for participation to be organised into 'tiers' **[Part 3[18]]**, or includes provision for specific 'alternative' follow-up methods, the data collection

[18] PeRSEVERE Implementation Guidance part 3: trial funding, protocol development and statistical planning

and data management processes should be designed with these in mind.