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

Part 8: analysis and reporting

Version 1.0 September 2023

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. Trial analysis

Trial analysis should be conducted in ways that give the best chance that the trial will still have reliable results despite any participation changes that have occurred **[R1[1]]**. This is facilitated by careful statistical planning **[Part 3[2]]** and collection of useful data **[Part 7[3]]**. Any deviations from the analysis plan should be declared in the final trial report.[4]

2. End of trial reporting

The CONSORT statement[5] (with any subsequent updates and extensions) should be followed to ensure a complete report of

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[1] R1 Analysing studies with participation changes

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

[3] PeRSEVERE Implementation Guidance part 7: data collection about participation changes

[4] Kahan *et al.* (2020) Public availability and adherence to prespecified statistical analysis approaches was low in published randomized trials. J Clin Epidemiol 128:29–34. https://doi.org/10.1016/j.jclinepi.2020.07.015

[5] CONSORT (Consolidated Standards of Reporting Trials): https://www.consort-statement.org/

each clinical trial. This includes the reporting of a 'participant flow', showing for each treatment group 'the number of participants who were randomly assigned, received intended treatment and were analysed for the primary outcome', and 'for each group, losses and exclusions after randomisation, together with reasons'. Others have encouraged reporting of proportions as well as just numbers.[6]

Some additional considerations on top of the minimum standard defined by CONSORT are explained below.[7] If it is not possible to include this level of detail in the main trial report, further information could be made available as supplementary material.

[6] 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

[7] Some of the suggestions are derived from Akl *et al*. (2015) Reporting missing participant data in randomised trials: systematic survey of the methodological literature and a proposed guide. *BMJ Open*. 5:e008431. https://doi.org/10.1136/bmjopen-2015-008431

When reporting the 'participant flow,' **use clear terminology** to describe the participation changes **[O1[8]]**. This could either be explicit, self-explanatory terms that are likely to mean the same thing to everyone (the PeRSEVERE 'Principles and Explanation' document contains some suggestions). If shorthand terminology like 'withdrawn' or 'lost to follow-up' are used then these need to be clearly defined and consistent with the trial protocol **[Part 3[9]]**. Other suggestions for best practice are available in the published literature.[10]

Participation in trials is often made up of various elements and can therefore change in various ways **[O1[11]]**. It is unlikely to be necessary to report every detail of how participation has changed, but **enough detail should be reported to allow**

[8] O1 Participation can stop, reduce or change

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

[10] Kahale *et al.* (2019) A guidance was developed to identify participants with missing outcome data in randomized controlled trials. *J Clin Epi*. 115, 55-63. https://doi.org/10.1016/j.jclinepi.2019.07.003

[11] O1 Participation can stop, reduce or change

correct and complete understanding and interpretation of the trial results.

At the least, it is likely to be useful to **separate the major categories of participation change**, i.e. intervention stopping primarily due to clinical decisions, participation changes arising from participants' expressed wishes, cases of loss of contact between trial staff and participants, participation changes due to loss of capacity to consent, and death.

Modifications to the CONSORT flow diagram – for example, use of dotted and solid lines – could help **distinguish between participation changes that led to no further trial follow-up from those where the participant continued** to provide data for the trial.

Consider how to **ensure that reported information on 'reasons' for 'losses and exclusions after randomisation' can be as useful as possible**.

- It may be useful to provide known information on a) whose choice the participation change was (participant or someone else), b) what the broad motivation was (e.g.

primarily clinical decision, participant finding follow-up visits burdensome, or no longer able to attend due to worsening health) and c) any relevant indirect factors (e.g. could not continue in trial follow-up due to moving house).

- The amount of reported detail should balance the need to be informative with the need to avoid revealing sensitive or confidential details about any participants.
- Where missing data have occurred for reasons other than participation changes (e.g. outcome data not collected for technical reasons) then this should be made clear.
- Present reasons for participation changes and missing data by treatment group.

In some cases, information about the **timing of participation changes** might be important to include, for example if many participants in one treatment group stopped or changed their participation soon after randomisation.

Other suggestions have been made regarding reporting around missing data in trials (regardless of whether the missing data arises from participation changes). For example:

- Considering inclusion of a comparison of baseline characteristics for participants in each trial arm with (any) missing data and those without missing data[12] (though some point out that this can only be indicative as trials are not likely to be powered to make formal comparisons of these groups[13]);
- Making clear the number of participants in each trial arm with missing outcome data, and presenting this separately per outcome if need be.[14]

Trial reporting should describe the trial results in terms of any pre-specified estimands. Reports should make clear the methods for handling missing data in the trial analysis, any assumptions underpinning the choice of methods, and the

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[12] Dumville *et al.* (2006) Reporting attrition in randomised controlled trials. *BMJ.* 22;332(7547):969-71. https://doi.org/10.1136/bmj.332.7547.969.

[13] 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

[14] Akl *et al*. (2015) Reporting missing participant data in randomised trials: systematic survey of the methodological literature and a proposed guide. *BMJ Open* 5:e008431. https://doi.org/10.1136/bmjopen-2015-008431

methods and results of any missing data sensitivity analyses[15]. It has also been suggested by others that the possible impact of missing data on the trial's conclusions should be included in the report's discussion section.[16]

[15] 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

[16] Ibid.