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

Part 1: general considerations

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PeRSEVERE collaborative group*

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

PeRSEVERE

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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. General considerations

a. Encourage an understanding of complexity in participation changes, and use terminology and language to match

PeRSEVERE principle **O1**[1] says that all those running or taking part in clinical trials should know that participation changes are not a matter of participants being in or out, participating or withdrawn. Instead, they can involve participation stopping, reducing or changing. This idea underpins many of the other principles.

Terminology and language used to talk about participation changes in any context should match this more nuanced conception. For example, although a term like "withdrawn" can be a useful shorthand to indicate a participant's involvement in a trial has changed, on its own it does not explain *how* participation has changed. Other terms like 'lost to follow-up' do not have a single, agreed definition, and this can lead to misunderstanding.

In our Principles and Explanation document, we suggest using language that describes participation ending or changing as explicitly as possible, aiming to therefore mean the same thing to everyone. This applies to all written or verbal communication about participation changes, including policy and process documents, trial protocols, information for patients and participants, and trial reports.

Explicit terminology can sometimes require more words to express, so sometimes does need to be balanced with the need for brevity. For example, it is possible to use shorthand for a given type of participation change, as long as this is clearly defined.

b. Plan effectively

In our PeRSEVERE Principles and Explanation document, we emphasise the need for good preparation to ensure participation changes can be managed as well as possible. Sometimes it will not be possible to carry out some of our suggestions without having prepared to do them in advance. This might be because they could not feasibly be done in a reactive way, or because they could not be done fairly without having been clear about the approach in advance with prospective trial participants.

Throughout this guidance, we mention what suitable planning may look like for each trial, and how to deal with uncertainty **[Part 5**[2]**]**.

We suggest there is also value in organisation-level preparation. For example, agreeing an organisational position about some aspects of participation changes could give more clarity about what to do in specific situations, should they occur **[Part 2**[3]**]**.

[1] O1 Participation can stop, reduce or change
[2] PeRSEVERE Implementation Guidance Part 5: risk assessment and monitoring
[3] PeRSEVERE Implementation Guidance Part 2: policies and processes

c. Involve the right people

Involving the right people in designing and running each trial helps ensure good decisions are made about managing participation changes. We suggest there may be a particularly important role for patient contributors (to ensure all actions taken and processes implemented are fair, appropriate and uphold trial participants' rights). We also highlight the role of statisticians, methodologists and trialists (to ensure that all actions and processes support the trial objectives and uphold trial integrity).

Other trial staff – including Chief and Principal Investigators, trial and data managers, and research nurses and practitioners – can help ensure plans for managing participation changes are comprehensive, feasible and clearly communicated.

It can be helpful for all these individuals to have a shared understanding – as far as possible – of best practice in managing participation changes in trials. This includes general best practice (as set out in PeRSEVERE) and the specific considerations applying in each trial.

d. Tailor the approach to the trial

Each trial is different and has its own specific setting, risks and requirements. We have aimed to make the PeRSEVERE principles and all our accompanying guidance general enough to apply to a wide range of different trials. However, each trial team should make sure their approaches to preparing for and managing participation changes are suitable for their trial. We accept that in some cases this will mean our guidance may not be the right approach.

For example, the processes around participation changes might look considerably different in a trial with various outcome measures and various aspects to participation versus a more streamlined, 'large, simple trial'.[4] Trials running internationally may be constrained in ways that do not apply to UK-only trials.

Nonetheless, we suggest the overall idea behind PeRSEVERE should always apply, namely adequately preparing for and managing participation changes in ways that do the best by participants and the trials they take part in.

e. Take a cautious approach

Many of the PeRSEVERE principles are about aiming to achieve a balanced approach to handling participation changes. When a participant says they want to stop or reduce their participation, it is right to establish exactly how they want their participation to change. For

[4] Altman (2015) ISIS and the emergence of large, simple trials. *The Lancet.* 386(9994), 15-21. https://doi.org/10.1016/S0140-6736(15)61450-7

the good of both the participant and the trial, their participation should not change other than in line with their wishes (with some caveats **[O2[5]]**).

However, processes to establish participants' wishes cannot get in the way of a participant stopping their involvement without having to discuss with anyone, if that is what they want. In this context, retaining a cautious approach to managing participation changes means designing trial processes that aim to achieve this balance. For example, a form for participants to clarify how they want their participation to change can be offered to participants, but not forced on them.

Some of the PeRSEVERE principles allude to the idea that, in some limited cases where participation has changed, previously given consent may persist (especially principles **O2, O4[6]** and **O5[7]**). Although we have suggested how this can be put into practice in a safe and acceptable way, these pointers should only be taken as general guidance. Everyone running trials should bear in mind that assumptions affecting participants' rights can only be used when they are reliable and justified, and only when applied transparently and fairly for participants.

Other factors to consider in applying the PeRSEVERE principles in a cautious way include changes to participants' health or capacity to consent (it is therefore important to have reliable processes to check for such changes as needed). The guiding ethical principle should remain, as per Good Clinical Practice, that the rights, safety, and wellbeing of participants are the most important considerations and should prevail over interests of science and society.

[5] O2 Participants decide how their participation changes
[6] O4 Losing contact
[7] O5 Continuing data collection