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

Part 2: policies and processes

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. CTU Policies

a. Why can CTU policies be useful in managing participation changes?

Policy positions addressing some aspects of participation change management can inform process-level documents, ensure consistent approaches are taken across all trials and embed principles in practice. They can also help find a satisfactory resolution if something arises in practice that is not covered by specific process documents. CTUs can even choose to make policy documents public (more easily than, say, more detailed and changeable process documents), thereby improving transparency and accountability around approaches they take to managing participation changes.

b. Considerations for CTU policy positions about managing participation changes

If your CTU **uses all or many of the PeRSEVERE principles** to guide local practice, **consider referencing them directly** in policy documents. In any case, we recommend that policy documents cover what standard positions apply to management of trial participation changes, including how to achieve a 'balanced' approach **[Part 1[1]]**.

PeRSEVERE principle **O5[2]** suggests that, for participants whose participation is changing or reducing, **ongoing consent to continued data collection[3] can be presumed,** as long as certain conditions are met. This means that participants can say they do not want data collection to continue, but it will continue unless and until they do express such a wish, even if their participation reduces or changes in other ways (subject to the conditions set out in the PeRSEVERE Principles and Explanation document and below). CTUs may **consider setting this principle out at policy level**, if they want to adopt it, with trial processes and documents putting the policy into practice.

Policies could also state that this **same 'presumed ongoing consent' idea applies to other areas of trial consent** that meet the conditions described in PeRSEVERE. This means consent would be presumed to persist unless and until a participant explicitly says they want the activity concerned to stop. In other words, participants should 'reasonably expect' the activity to be continuing, in the circumstances.[4] Examples of where this might apply:

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[1] PeRSEVERE Implementation Guidance Part 1: general considerations

[2] O5 Continuing data collection

[3] Note the definition of 'data collection' from the PeRSEVERE Principles and Explanation document: "this means the act of adding relevant data onto study forms or systems, to make the data available for running and analysing each study. It does not refer to any separate tests or procedures used to generate the data in the first place."

[4] This is similar to the idea of 'reasonable expectations' used in the context of privacy and confidentiality: https://www.gov.uk/government/speeches/reasonable-expectations

- Consent for trial data to be linked with routine data sources (and consent for confidential information to be shared with routine data providers for the purpose of such linkage);
- Consent for medical notes to be accessed by trial staff for trial monitoring purposes;
- Consent for further contact from trial staff after participants end their participation where evidence suggests most participants would like to be contacted – in particular regarding receipt of trial results[5];
- Consent for storage and use of biological samples for research purposes;
- Consent for re-use and/or sharing of trial data for secondary research purposes (where CTUs' approach is to ask for participants' consent to this point).

Policies can confirm that **data already collected until a participant says they want data collection to stop is retained** (as per PeRSEVERE principle **O6**[6] and other guidance, for example from the UK Health Research Authority[7]). This can include data *generated* prior to that time **[O5]**, i.e. data that exists and that was created prior to the date, but which has not yet been added to trial forms or systems (with possible trial-specific exceptions; see recommendations about standard operating procedure content, below).

Principle **O6** also suggests that the **collected data should be included with other data made available at the end of the trial for secondary research** or re-analysis purposes, in line with international standards.[8]

Policies can outline **related, broader points** such as the idea that that trials will only collect data that is absolutely required for analysing or running the trial, or that participants' rights must always be communicated to them.

Policies could remind CTU staff that **each situation nonetheless needs to be assessed on its own features**, that the principles set out in the policy (and in PeRSEVERE) are only intended to be a guide and should not be applied in a blanket manner without further thought. This may mean that the principles are not followed in some cases, where doing something different is a better way to uphold participants' rights and interests.

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[5] South *et al.* (2021) Testing approaches to sharing trial results with participants: The Show RESPECT cluster randomised, factorial, mixed methods trial. *PLoS Med.* 18(10): e1003798. https://doi.org/10.1371/journal.pmed.1003798

[6] O6 Retaining data

[7] https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-detailed-guidance/data-subject-rights-and-research-exemptions/

[8] Taichman *et al.* (2017) Data sharing statements for clinical trials — a requirement of the international committee of medical journal editors. *N Engl J Med* 376, 2277-2279, https://doi.org/10.1056/NEJMe1705439

2. Standard operating procedures (SOPs)

a. What is the role of CTU SOPs in managing participation changes?

CTU SOPs put policy positions into practice and instruct staff on how to prepare for and manage participation changes in their trials. Tools and templates associated with each relevant SOP can help staff put the SOP requirements into practice.

b. Considerations for SOP content about participation changes

SOPs should reinforce the message that **participation changes can take a variety of forms [O1[9]]**. Acknowledge that there may be 'levels' of participation, with participants taking part in all, some, few or no aspects of the trial depending on how their participation has changed. Participation can also change without reducing, e.g. change in nature (such as a change in mode of follow-up) or *increase* (after having previously reduced). Use language and terminology accordingly, recognising the complexity and communicating how participation has changed in each case. The general expectation should be that the nature and extent of participation changes is based on informed and freely-given decisions by participants **[O2[10]]**.

Some aspects of managing participation changes will necessarily need to depend on the nature of the trial, its design, interventions and population. **SOPs can list the decisions that need to be made for each trial and documented in the protocol (or other trial document)**. These might include:

- Whether aspects of participation will be formally **organised into tiers** for practical reasons **[Part 3[11]]**.
- **What level of flexibility may be acceptable,** from a trial integrity point of view, regarding what the protocol requires participants to do (e.g. in follow-up schedules; **[D1[12]]**). Alternatively, it may be important to specify any limitations on how participation could change. Trial teams should decide to what extent any flexibility (or lack thereof) needs to be communicated to participants and/or trial site staff.
- Whether there may be any **alternative follow-up or data collection mechanisms or schedules [D1]**, available to offer to participants who are struggling to stick to the default mechanism/schedule.

[9] O1 Participation can stop, reduce or change
[10] O2 Participants decide how their participation changes
[11] PeRSEVERE Implementation Guidance Part 3: trial funding, protocol development and statistical planning
[12] D1 Protecting study integrity by design

    - Examples may include follow-up by a different mode (e.g. phone calls instead of in-person visits) or data collection from a different source (e.g. using routinely-collected healthcare data instead of trial-specific data collection).
    - The alternative follow-up options may not need to be communicated to participants up front, and it may even be unhelpful to do this **[Part 4[13]]**. Alternative arrangements should focus on collection of data required for the primary outcome measure and any other key outcome measures.
    - Teams should consider whether these alternatives, if they are less burdensome for all involved, should in fact be the default follow-up method for the trial.
    - If it is agreed that alternative follow-up options are not needed or useful, this decision could also be documented and explained within the trial master file. This might be the right approach where alternatives are not feasible, or where they might impair rather than help the trial achieve its research objectives.

- Trial teams should decide how they will **manage loss of contact** between participants and trial staff **[O4[14]]**. This includes trial-specific instructions for trying to re-gain contact and when to stop trying. Teams should consider whether any methods to try to re-gain contact or collect further data may be considered intrusive by participants and should therefore only be done with participants' consent. The general aim should be to reduce as far as possible the potential effects of loss of contact on the robustness of each trial's results. The likelihood of many participants losing contact with the trial should be assessed in the pre-trial risk assessment **[Part 5[15]]**.

- Teams should consider if there are any **trial-specific considerations affecting the general principle that data already collected is retained [O6[16]]**. This may include where it is considered fair to give participants a period to change their mind about providing data (as is done in some qualitative, interview-based research). Complexities around informed consent may also apply, e.g. use of a deferred consent model, or issues to do with loss of capacity to consent.
- Whether there may be any **trial-specific aspects to which a 'presumed ongoing consent' approach to consent could be applied [O5[17]]**, i.e. where participants can say they want those aspects to stop, but the activities will otherwise continue unless and until participants do say that. Any such consent approaches must meet the conditions set out in the PeRSEVERE Principles and Explanation document:
    - The participation aspects affected must be low impact on participants (in terms of safety, time or emotional burden or anything else) and must be necessary;

[13] PeRSEVERE Implementation Guidance Part 4: patient information, participant communication and consent
[14] O4 Losing contact
[15] PeRSEVERE Implementation Guidance Part 5: risk assessment and monitoring
[16] O6 Retaining data
[17] O5 Continuing data collection

    - The consent approach must be made clear to participants in advance;
    - It must be clear for participants how to say that they want the activity to stop;
    - Trial staff must make reasonable efforts to find out participants' wishes about the different aspects of participation, when participants say they want to stop or reduce their participation;
    - If there is a suitable mechanism, participants should be reminded of what trial activity is still ongoing (if any) after they change their participation;
    - Any trial activity continuing on the basis of this approach must still be in line with the consent previously given;
    - Each case should nonetheless be reviewed on its own rather than applying a blanket rule. This includes allowing a route for the activity to stop if there is any doubt about the appropriateness of continuing (e.g. because of changes in a participant's health, personal circumstances or capacity to consent).

- Any trial-specific processes in place to help **record and maintain information about participants' contact details and preferences** for contact about the trial (e.g. for trial updates and the overall trial results). This includes checking if participants' preferences change when they stop or reduce their participation **[see Part 4[18]]**.

    - Trial teams should decide their approach to sharing information about the trial (such as the trial's results) with participants' relatives or carers in the event the participant loses capacity to consent or dies while the trial is ongoing. The best approach will depend on the trial and should be decided with the help of the trial's patient contributors.

- Whether any **specific features of the trial** might make handling participation changes more difficult. For example, in international trials different rules around clinical research or data protection may apply. There may be other specific issues highlighted through the trial risk assessment **[see Part 5[19]].**

SOPs can list the **key information to be communicated to potential trial participants** in every case **[Part 4]**, for example:

- Participants' **right to withdraw their consent** at any time, without having to give a reason (unless they want to) and without their standard of care being affected;
- **Recommended action for participants to take** if they decide they want to stop or reduce their participation;
- **Limitations on stopping or undoing any aspects of participation**;

[18] PeRSEVERE Implementation Guidance Part 4: patient information, participant communication and consent

[19] PeRSEVERE Implementation Guidance part 5: risk assessment and monitoring

- Any aspects of participation that **would continue until the participant explicitly says they want it to stop** (see above for more on 'presumed ongoing consent' approaches);
- Where appropriate, the possibility of **aspects of participation being stopped by someone else**;
- The value to the trial of **collecting as much of the planned data as possible [O3[20]]**.

SOP content should outline the **general steps to take when participants express a wish to stop, reduce or change their participation**. These may include:

- An expectation for CTU staff to discuss with trial site staff (where applicable) to establish exactly how the participant wants their participation to change, and their preferences for further contact about the trial. This process may include reminding trial site staff about what options are available to the participant.
    - Available options could routinely include consideration of whether transferring the participants' care to a different trial site could allow the participant to continue taking part in the trial, if they want to and subject to the participant's and other site's agreement to the transfer.
- What level of evidence would be expected to be available – for example, in participants' medical notes – to document a participant's wish to stop *all* aspects of participation (including 'active' and 'passive' aspects).
- Ensuring a clear record of the participant's wishes are conveyed to the CTU.
- Ensuring the participants' wishes are recorded in the trial database and reported in line with the CONSORT statement[21] and PeRSEVERE principle **R2**.[22]
- Ensuring all steps are taken to carry out participants' wishes. For example, if the participant does not want to complete any more trial questionnaires, preventing all further requests for questionnaires to be completed.
- If any aspects of participation are affected by 'presumed ongoing consent' approaches mentioned above, ensuring these are implemented in a consistent and fair manner and not applied in a blanket fashion.
- Carrying out any participant communications planned around the time of participation ending, such as an end of participation information sheet **[Part 4[23]]**.

[20] O3 The more data, the better
[21] Schulz *et al.* (2010) CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMC Med*. 8, 18 https://doi.org/10.1186/1741-7015-8-18
[22] R2 Consistent and complete reporting
[23] PeRSEVERE Implementation Guidance part 4: patient information, participant communication and consent

- Any expectations around monitoring of participation changes, both at trial-wide level and review of individual cases **[M2[24]].**

SOPs should be clear about the need to complete enough statistical analysis planning before the trial begins recruitment. In particular, this includes **how the analysis will be done in ways that give the best chance of a reliable result despite participation changes** meaning that not all the study data has been collected as planned **[R1[25] and Part 3[26]]**.

SOPs should state the general position that **data already collected at the time a participant says they want data collection to stop is retained** and used in the trial analysis **[O6[27]]**. This data can also be made available with other trial data for further research at the end of the trial, as long as this remains in line with those participants' consent (whatever the consent arrangements are for the given trial).

- SOPs could also explain any general exemptions to the data retention principle, for example if a participant's original informed consent is called into question.
- Standard processes could include how to consider individual cases where it is requested or proposed that trial data be deleted. For example, who would need to be informed of such cases, and who would ultimately decide what should happen to the data, including the relevant Data Protection Officer[s] if required by local policies.
- If there is an expectation that retained data will be de-identified or otherwise have its identifiability reduced, steps for doing this could be explained.

SOPs could confirm that, in general, **data *generated* prior to a participant's decision to stop data collection can still be collected [O5[28]]**. However, trial teams should check how this applies to their trial. For example, if data exists but only in confidential medical notes that would need to be accessed by trial staff based on participant consent, then this may not be so straightforward.

- In that case, trial teams could in theory decide to apply a 'presumed ongoing consent' approach (see above), meaning that that accessing of confidential medical notes would continue until participants say they want it to stop. This could only be for the purpose of collecting data generated until the point the participant said they wanted data collection to stop. However, in this scenario, it might be challenging to meet the conditions for 'presumed ongoing consent' to be done in a fair and transparent way, as mentioned in the PeRSEVERE Principles and Explanation document.

[24] M2 Monitoring
[25] R1 Analysing studies with participation changes
[26] PeRSEVERE Implementation Guidance part 3: trial funding, protocol development and statistical planning
[27] O6 Retaining data
[28] O5 Continuing data collection

Where data collection is to fulfil a regulatory requirement, SOPs should state that **collection of these sorts of data continues indefinitely [O5]**. In particular, collection of some safety data in clinical trials of investigational medicinal products may need to continue in order to adhere to the UK Medicines for Human Use (Clinical Trials) Regulations 2004.[29] It is possible that there may be trial-specific decisions to make about this as well.

SOP content regarding the emergence of new information about trial interventions' safety should include the requirement to **decide whether the new information may need to be shared with all participants, including those who have stopped participating in the trial**. Where it is agreed to make such contact with those who have stopped, SOPs could set out the process to go through to share this information. This could include specific approval from a Research Ethics Committee (REC) to share the information, particularly if this would involve contacting participants who had said they did not want any further contact about the trial.

SOPs about sharing trial results with participants (and any other routine participant communications) should be clear that **stopping participation does not automatically exclude participants from receiving such information [O7[30]]**. Instructions should be given for recording participants' contact preferences, including changes to these during the trial.

3. Other governance

A Data Protection Impact Assessment (DPIA) is required to be completed for high-risk data processing under the UK General Data Protection Regulation.[31] In line with guidance from the UK Health Research Authority,[32] the DPIA can be conducted at the level of the Quality Management System (i.e. the policies and processes governing how all trials in the trials unit are run) rather than done per trial.

The DPIA can document key points relating to management of participation changes. This includes the approach of collecting only the data that is required for each trial (and no more than that). The DPIA could also mention the implementation of, and justification for, limitations on trial participants' rights as 'data subjects' (in particular, the limitation on their right to have data about them deleted once it has been collected in the trial).

[29] https://www.legislation.gov.uk/uksi/2004/1031/contents/made
[30] O7 Information after stopping participation
[31] https://www.legislation.gov.uk/eur/2016/679/contents
[32] https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/what-law-says/data-privacy-impact-assessments/