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

Part 6: training and support

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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. Training of CTU staff

Alongside policies and standard operating procedures **[Part 2[1]]**, CTU staff can receive specific training on preparing for and managing participation changes. This will give them more confidence in managing what can sometimes be a challenging area, and is an important way to address PeRSEVERE principle **D6[2]**. Training can further increase the likelihood that staff will follow best practice in their day-to-day work.

Training for CTU staff could link with, or run alongside, standard Good Clinical Practice training. Training content on participation changes could include:

- The fundamental principles guiding participation changes and withdrawal of consent, including those in PeRSEVERE and the supporting ideas in Good Clinical Practice.
- Participants' 'right to withdraw consent' as presented in ethical guidance about clinical trials, and the need for individuals' rights to take precedence of those of science and society (as per Good Clinical Practice)
- The 'balance' to be struck between changing participation in line with participants' wishes **[O2[3]]** while ensuring processes aimed at establishing participants' wishes do not prevent participants stopping any aspects of participation that they want to stop.
- The need for everyone involved in trials (in any capacity) to understand the potential complexity around participation changes and to use language and terminology to match **[O1[4]]**.
- The value of collecting as much of the planned data as possible, particularly in relation to primary outcome data **[O3[5]]**.
- That the features of each trial need to be taken into account when considering participation changes, and the sorts of decisions that need to be made in trial design and protocol development **[Part 3[6]]**.

- Actions expected from CTU staff and others (e.g. trial site staff) when managing different types of participation change. This includes where participants express a wish to stop, change or reduce their participation, where intervention stops primarily due to decisions by people other than the participant, and where participants and trial staff lose contact with one another.

[1] PeRSEVERE Implementation Guidance part 2: policies and processes
[2] D6 Training and support
[3] O2 Participants decide how their participation changes
[4] O1 Participation can stop, reduce or change
[5] O3 The more data, the better
[6] PeRSEVERE Implementation Guidance part 3: trial funding, protocol development and statistical planning

- What a 'presumed ongoing consent'[7] approach is, when it can be appropriate to apply it, and what associated conditions need to be met in order to apply it **[O5[8]]**.
- Guidance on what to do in more complex cases, for example involving changes to participants' health or capacity to consent, or situations where participants' wishes about specific aspects of participation are not known.

Note that some of the points about training for trial sites mentioned below may also apply where the CTU is recruiting trial participants directly (i.e. where there are no trial sites).

Statistical staff (and potentially others within the trial team) should have training and opportunities to learn about evolving best practice in handling missing data in trial analyses, including defining and using estimands[9] **[R1[10]]**.

Other training can reinforce the PeRSEVERE principles. For example, data protection training will emphasise the importance of not collecting more data than required for a specific purpose **[D1[11]]**, and explain that exemptions to data subjects' rights given in UK and EU data protection law allow for research data to be retained once already collected **[O6[12]]**.

There should also be ways for staff to learn from one another, share good practice and ask questions about the best approach for general and specific issues in handling participation changes. Tools, templates and checklists can be developed to make it easier for staff to follow the Standard Operating Procedures and all other best practice guidance **[Part 2[13]]**.

2. Training and support for trial sites

a. How could training for trial site staff on managing participation changes be incorporated into existing training?

It is the responsibility of Principal Investigators at trial sites to ensure all trial site staff are adequately trained and qualified to perform their trial roles. It could nonetheless be helpful for CTUs to provide additional training about managing participation changes. This may not be necessary in future if site staff training routinely covers similar ideas to those in the PeRSEVERE principles. However, our experience is that this is currently variable.

It is, however, routine (and a legal requirement for clinical trials of investigational medicinal

[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] O5 Continuing data collection

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

[10] R1 Analysing studies with participation changes

[11] D1 Protecting study integrity by design

[12] O6 Retaining data

[13] PeRSEVERE Implementation Guidance part 2: policies and processes

products in the UK) for all staff to receive Good Clinical Practice training. This emphasises that participants' consent is an ongoing process and that participants can withdraw their consent at any time. Additional CTU-provided training on participation changes would ideally build on and complement that routine training, and could improve confidence among trial site staff (previously suggested to be important in managing participation changes in trials[14]).

b. Suggested content for trial site staff training about participation changes

Training materials about approaches to managing participation changes could include:

- The **main messages from the PeRSEVERE principles**, with rationale. The overarching principles that guide the overall approaches to managing participation changes might be emphasised in particular. The overall aim could be highlighted, namely to prepare for and manage participation changes in ways that uphold the interests of participants *and* the trials they take part in.
- Opportunities for trial site staff to **talk through any concerns, misunderstandings or disagreements** with the messages presented. This could help establish a shared understanding of what is expected when managing participation changes. This may be important, as previous evidence suggests that trial processes around managing participation changes can sometimes conflict with individuals' 'moral compass'.[15]
- Recognition that it can be **challenging to accommodate the needs of trial participants** (respecting any wishes to stop data collection, and taking time to establish what participants' wishes about data collection are), and **trials** (to continue collecting outcome data where possible), particularly as each trial's requirements may differ.
- The need for all involved in trials (in any capacity) to **understand the potential complexity in participation changes** and to use language and terminology to match **[O1[16]]**. This should be reflected in the data reported to CTUs about participation changes. It is important for CTUs to know exactly how participation has changed (including if participants' wishes about any aspects of participation are not known).
    - This could be reflected in training materials by separating content about different sorts of participation change (e.g. stopping intervention after clinical decisions, losing contact with participants, responding to participants' wishes).
- The **importance of collecting as much of the planned data as possible [O3[17]]**, with a particular focus on trial outcome data.

[14] Daykin *et al.* (2018) 'Recruitment, recruitment, recruitment' – the need for more focus on retention: a qualitative study of five trials. *Trials.* 19, 76. https://doi.org/10.1186/s13063-018-2467-0

[15] Ibid.

[16] O1 Participation can stop, reduce or change

[17] O3 The more data, the better

    - Training could cover what this idea means (and does not mean) in practice, with example scenarios and what the best action might be in each case (in terms of participants' rights and trials' integrity).
    - Training may include a hierarchy of data importance within a trial, though this should not inadvertently imply that data below the top level is unimportant.
    - It is likely preferable to express the importance of trial data to participants 'positively', i.e. in terms of the benefits of collecting as much as possible of the planned data. However, it could be useful for trial site staff to understand the possible negative effects missing data can have on trial results.[18]

- The idea that trial **data collection continues until the participant says they want it to stop**, the conditions that need to apply to make this approach valid, and the role of trial site staff in applying the approach **[O5[19] and Part 2[20]]**.
- Confirmation that, if a participant does say they want data collection to stop, **data already collected is retained [O6[21]]** and data *generated* prior to that point can also still be collected **[O5]** (with some trial-specific exceptions **[Part 2]**).

Training materials about informed consent and participant communication could include:

- **Information to convey during initial consent about participation changes [D3[22], D4[23]]**, including the following points:
    - How participants can express a wish to change participation later on;
    - Limitations on participants being able to stop or undo aspects of participation;
    - Details of any activities that would carry on until the participant says they want them to stop **[O5]**, including how to express such a wish (e.g. what sort of thing would be taken as confirmation that they want those elements to stop);
    - It may not be helpful to give details up front about specific ways that participation could be reduced. However, it could help to convey that there may be other options if the participant is later struggling to continue participating in all aspects of the trial **[Part 4[24]]**.

[18] 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
[19] O5 Continuing data collection
[20] PeRSEVERE Implementation Guidance part 2: policies and processes
[21] O6 Retaining data
[22] D3 Participant information about stopping participation
[23] D4 Participant information about losing contact
[24] PeRSEVERE Implementation Guidance part 4: patient information, participant communication and consent

- Encouragement to have **dialogue wherever needed** about participation changes, both with participants **[D5[25]]** and with CTUs (to discuss individual cases or to seek advice).
    - Training on this point could include trial-specific expectations about what would constitute 'reasonable efforts' to check participants' ongoing willingness to take part. This could link with trial-specific processes or expectations around checking participants' ongoing capacity to consent.
    - Trial site staff can be encouraged to use their own judgement about what constitutes reasonable efforts to check ongoing willingness. This may depend on their relationship with each particular participant. The nature of the involvement may also be relevant, for example the amount of commitment or risk required from participants, or whether any 'implied consent' might apply.
- Emphasis on **communication with participants being balanced and positive**, i.e. there is no 'wrong choice' for participants about their level of involvement in the trial. Communication should also be **realistic,** recognising that it is completely understandable that participants sometimes cannot complete all parts of a trial. Participants should also understand that in some cases there are limitations on what types of participation or contributions will actually help the trial meet its objectives.
- Advice about how to talk to participants about topics where staff may worry about the **risk of appearing to put pressure on participants.** This includes, for example, about the benefit of collecting more of the planned trial data **[O3[26]]**, 'presumed ongoing consent' approaches, asking participants if they would be happy to give a reason for changing their participation, or what would happen if trial staff and participants lose contact with each other.

Training materials about managing specific participation change situations could include:

- Confirmation that trial staff should **assess each individual situation** for its specific features and sensitivities, and prioritise participants' rights. This includes stopping all trial activities where assumptions supporting participants' ongoing consent may be unreliable or where participants may not reasonably expect activities to be continuing.
- Emphasising that when a **participant says they want to stop or reduce their participation, it does not mean they need to stop all involvement**. There can be benefits to participants of further involvement in the trial. They may also wish to continue contributing if it is possible. It is therefore important to establish what each participant wants to do when they say they want to stop or reduce their participation.
- Emphasising that the **nature and extent of participation changes should be participants' decision [O2[27]]**. Decisions by others to stop aspects of participation – in particular stopping trial intervention – should only apply to those specific aspects.

[25] D5 Encouraging dialogue
[26] O3 The more data, the better
[27] O2 Participants decide how their participation changes

- The need to explore whether a **change in trial site** could help the participant continue contributing to the trial, if they want to. This could include where the participant will be moving home or where the travel to the current site is proving to be a challenge).
- Guidance and expectations for **establishing what a participant wants to do** when they say they want to stop or reduce their participation. This includes helping them understand their choices and the pros and cons of different options, and ways to facilitate participants' decision-making (e.g. to remind them of their choices).
    - Where an optional form is used for participants to make clear how they want their participation to change, trial staff could get guidance on how they can help participants complete this **[Part 4[28]]**.

- Information about **possible flexibilities in each trial's follow-up procedures**. This could include an understanding of participation 'tiers' **[Part 3[29]]** and advice about when to broach these with participants **[Part 4]**.

- Reminders to **communicate clearly with participants if aspects of participation stop when it was not participants' choice** (or if the trial design means participants can no longer take part in some or all of the trial), providing clear reasons for the change and giving participants opportunities to ask questions **[Part 4]**.

- **Expectations around record-keeping** for all types of participation change. This includes keeping a clear record of participants' wishes about participation changes, and any discussions had about these, in medical notes or other source records.
    - Sites should also use their own records of participant wishes to ensure those wishes are carried out, for example with regard to further data collection for the trial, or receiving further contact about the trial.
- What is practically expected of trial staff in cases where they are **unable to contact research participants [O4[30]]**, including handling potential sensitivities and taking a cautious approach to attempting re-contact.
- Advice about how to ask participants if they might be happy to provide any **information about why they want to change their participation**.
    - Training for trial staff can provide an understanding of what sort of information is useful, why it can help the trial, and what level of detail is adequate.
    - Training can emphasise a balance between the acceptability (in most cases) of trial staff asking participants for their motivations and participants' right to refuse to provide any information.

[28] PeRSEVERE Implementation Guidance part 4: patient information, participant communication and consent

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

[30] O4 Losing contact

- Advice about how to ask participants **if they are willing to provide trial outcome data** when they stop or reduce their participation (if it would help the trial's objectives[31]);
- Confirmation that stopping participation **does not automatically remove participants' rights to receive relevant information** that they might want or need **[O7[32]]**.
    - Training could clarify what is expected from trial staff in finding out participants' preferences for further contact when they stop or reduce their participation, and maintaining contact after this point.
- It may be useful to present **common scenarios** that may arise and what would be expected from trial staff in these scenarios.
- Any other trial-specific practical steps to take when managing participation changes.

An equally important part of the PeRSEVERE principle **D6[33]** is adequate support for trial sites. The PeRSEVERE principles aim to ensure that participants' interests and trial integrity are both upheld as far as possible. This can be challenging in practice, particularly for those who engage directly with trial participants and discuss participation changes with them.

"Support" can take various forms, including clear instructions, adequate resources to do the required work, or availability of timely advice about the best action to take in each case. It might also be considered supportive for the tone and content of any training materials to acknowledge the potential challenges in handling participation changes.

Tools and templates can help standardise practice and reduce uncertainty about what is required. These could include:

- A **checklist or "crib sheet"** for trial staff to use when **managing different sorts of participation change**, including to sensitively guide discussions with participants.
- Templates for trial staff to use **when attempting to regain contact** with participants who they have lost contact with. This could help standardise the approach to minimise the risk that re-contact attempts seem intrusive or insensitive.
- Templates to **check participants' preferences for further contact** about the trial after they stop participating.
- Template **'source data sheets'** in case they could help to obtain further, relevant information about trial participants from NHS organisations who are not participating in the trial. This approach may be useful when participants and trial staff have lost contact with one another. These source data sheets could be completed by the non-trial sites and provided back to trial sites, where they could be used to complete trial

[31] 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

[32] O7 Information after stopping participation

[33] D6 Training and support

data collection forms. Such contact with non-trial sites may need to rely on participant consent in some cases **[Part 4[34]]**.

Trial forms used to record data about participation changes – either for the main trial data collection **[Part 8[35]]** or participant-completed **[Part 5[36]]** – could guide interactions between trial staff and participants at the time of participation changing.

3. Other training

Training and guidance covering similar points as mentioned above could be developed for other stakeholders involved in trials, for example Chief Investigators, oversight committee members, sponsor representatives or patient contributors. This could focus on their particular roles and what is expected of them in preparing for and managing participation changes.

Patient contributors can play a particularly important role in ensuring proposed methods for handling participation changes are suitable **[Part 1[37]]**. Guidance for contributors could refer to specific elements they might advise on, such as ensuring trials are as burden-free as possible from participants from the outset, advising on ways participants could continue participating with less commitment **[D1[38]]** and on what should happen if trial staff and participants lose contact with one another **[O4[39]]**.

[34] PeRSEVERE Implementation Guidance part 4: patient information, participant communication and consent
[35] PeRSEVERE Implementation Guidance part 8: analysis and reporting
[36] PeRSEVERE Implementation Guidance part 5: risk assessment and monitoring
[37] PeRSEVERE Implementation Guidance part 1: general considerations
[38] D1 Protecting study integrity by design
[39] O4 Losing contact