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

Summary of recommendations

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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

This “summary of recommendations” document summarises the key points from the above documents. It can potentially be used as a checklist for ensuring participation changes are well-managed throughout a clinical trials unit (CTU) and its trials.

Please consult the above documents for more on the rationale for each recommendation and further explanation of how we recommend each point is carried out.

Contents

General considerations:[1]

- Encourage an understanding of complexity in participation changes, and use terminology and language to match
- Plan effectively
- Involve the right people
- Tailor the approach to the trial
- Take a cautious approach

Managing participation changes through CTU policies:[2]

- Consider referencing the PeRSEVERE principles if you agree these should guide how participation changes are managed in your CTU.
- Consider adopting a 'presumed ongoing consent' approach to trial data collection and/or other aspects of trial participation. 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

[1] PeRSEVERE Implementation Guidance part 1: general considerations

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

ways (subject to the conditions set out in the PeRSEVERE Principles and Explanation document).

- Confirm that data already collected until a participant says they want data collection to stop will be retained, and made available at the end of the trial for secondary research purposes.
- Alongside these points, remind staff that each participant's situation needs to be assessed on its own features, and the policy positions should not be applied in a blanket manner without further thought.

Standard Operating Procedures (SOPs) about participation changes:[2]

- SOPs should reinforce the message that trial participation changes can take many forms, and guide CTU staff on how to manage this complexity.
- SOPs can list the decisions to make and document for each trial, including:
    - Whether aspects of participation will be formally organised into tiers or levels for practical reasons.
    - What level of flexibility may be acceptable regarding what the protocol requires participants to do (e.g. in follow-up schedules).

    - Whether there are any alternative follow-up or data collection mechanisms or schedules.
    - How to manage loss of contact between participants and researchers.
    - Any trial-specific considerations affecting the general principle that data already collected is retained.
    - Any trial-specific aspects to which a ‘presumed ongoing consent’ approach might be applied (see above).
    - Trial-specific processes to help record and maintain information about participants’ contact details and preferences.
    - Any specific features of the trial that could make handling participation changes more difficult, for example in an international context.
- SOPs can list the key information to be communicated to potential trial participants about changing their participation.
- SOPs should outline the general steps to take when participants express a wish to stop, reduce or change their participation.
- SOPs should be clear about the need to complete enough statistical planning before a trial starts recruitment, including how the trial analysis will be done in ways that

give the best chance of a reliable result despite participation changes.

- 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 analysed.
- SOPs could also confirm that, in general, data *generated* prior to a participant's decision to stop data collection can still be collected.
- Where data collection is to fulfil a regulatory requirement, SOPs should state that collection of these sorts of data continues indefinitely (e.g. collection of some safety data in clinical trials of investigational medicinal products).
- 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.
- 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.

Research grant applications:[3]

- Consider how to ensure there is adequate resource to support all trial follow-up activity, including for participants whose participation changes during their time on trial, and those who 'complete' all aspects of participation.

Protocol development:[3,4]

- Protocols should retain standard confirmation that participants have the right to withdraw their consent at any time.
- Protocol content should be written with an understanding that participation changes can take many forms. Use language to convey this complexity.
- All members of the trial team can make important contributions to the protocol. For agreeing content about participation changes, there may be particularly important roles for statisticians and patient contributors.

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

[4] Please note that we refer to the protocol here as shorthand for all trial instructions; the same points can be covered in other, related documents if this is more convenient.

- Consider presenting content about broad sorts of participation change in different sections.
- Consider referencing the PeRSEVERE principles and related guidance in the protocol, if these guide your trial's approaches.
- Consider using the protocol to emphasise some of the positions given in the PeRSEVERE principles, about how participation changes should be managed in the trial.
- The protocol should explain what needs to happen when a participant says they want to stop or reduce their participation in the trial.
- The protocol should include instructions for trial staff in case they lose contact with participants.
- The protocol should be clear about any data collection that needs to continue in all cases.
- Options for reduced or alternative follow-up schedules or methods should be referenced, with instructions for how and when to broach them with participants.
- The protocol should contain any definitions of trial-specific participation changes that are anticipated.
- The protocol could include guidance about what should happen if a participant wants to *increase* their level of involvement after having previously reduced it (especially

if this is expected to happen relatively frequently, for any reason).

- Participating trial sites might be encouraged to contact the CTU to discuss the best action to take if any particularly complex or challenging situations arise.

Statistical analysis plans (SAPs):[5]

- Given the breadth of existing guidance around content of SAPs, we have not given detailed recommendations within the PeRSEVERE guidance.
- However, we suggest that, as with other trial documents, the language and terminology used in SAPs reflects the complexity of participation changes.
- If it has been agreed that participants who want to stop taking part can continue to contribute with less commitment via alternative follow-up schedules or methods, then the SAP could cover any implications for how the study outcome data will be analysed (i.e. if some data was collected in different ways).

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

Patient information sheets:[6]

- Information sheets should be written with an understanding that participation changes can take many forms. Use language to convey this complexity.
- Participants must be made aware that they have the right to stop taking part in the study at any time, without having to give a reason and without effects on the standard of care they receive.
- They can also be made aware that it can help the quality of research studies if as much as possible of the planned data is collected.
- They can also be told why it can help the study when they give reasons for stopping their participation, if they are happy to do so (or want to).
- It should be made clear that the nature and extent of participation changes are primarily the participant's choice.
- Potential participants should get information about generally what would happen if they decided to stop or reduce their participation later on.

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

- Where applicable, it should be clear that if a participant struggles to continue participating, it may be possible for them to continue participating but with less commitment.
- It may be useful to confirm that doctors will monitor participants' safety and recommend they stop trial intervention early, if it is no longer in participants' best interests to continue receiving it.
- Potential participants should get clear information about what will happen if they lose contact with the trial staff during the trial.
- Mention any limitations on participants' rights to stop or 'undo' aspects of participation.
- It should be made clear if data collection, or any other aspects of trial participation, would continue until the participant clearly says they want it to stop.
- It should be clear that stopping or changing participation will not mean that participants cannot receive the results of the trial or other information.
- Pre-trial information should include anything else relevant to the process of stopping participation in the study, or the implications of stopping on things like incentives, or access to the trial treatment(s), particularly where these could constitute negative consequences of a decision to stop participating.

Consent:[6]

- Some aspects of managing participation changes might need to rely on consent from participants, for example where there are implications of participants' confidentiality, or where planned trial processes might otherwise be considered intrusive or burdensome.
- In some cases it may be necessary to seek others' consent, for example if there are plans to collect details of a participant's family or carer as part of managing participation changes.
- We suggest that sometimes it is not helpful or necessary to rely on consent for certain aspects of managing participation changes. Specifically, we recommend participants are not asked to consent to allow 'presumed ongoing consent' approaches (see above) or to be asked for reasons for participation changes.

Other participant communications:[7]

- In Implementation Guidance Part 4, we provide further guidance on possible communications after initial consent, in particular to inform participants' decisions about changing their participation, and to provide key information after participants stop or reduce their participation.
- In the same Part, we outline some potential methods – not commonly used at the moment – that might support freely-given and informed decisions by participants about changing their participation. There are potential risks and benefits associated with each of these. Our suggestions are:
    - Participants could be offered an optional form to confirm how they would like their participation to change.
    - Participants could be given the chance to discuss their participation with someone independent of the usual trial staff.
    - Participants could be offered a route to stopping their participation without having to speak to anyone.

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

Risk assessment and monitoring:[8]

- We recommend that routine trial risk assessments include considerations about participation changes. In PeRSEVERE Implementation Guidance Part 5, we provide further detail in about what could be considered.
- In the same guidance document, we provide detailed recommendations around a) central monitoring of participation changes, b) monitoring of individual participation changes, c) responding to monitoring findings and d) monitoring planning.

Training of CTU staff:[9]

- In PeRSEVERE Implementation Guidance Part 6, we give detailed recommendations for how to ensure CTU staff are trained and supported to manage trial participation changes for the good of participants and trials.

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

[9] PeRSEVERE Implementation Guidance part 6: training and support

Training and support for trial sites:[9]

- We suggest that more detailed training for trial site staff about managing participation changes would be a good addition to existing training that staff already routinely receive.
- We make recommendations for training content:
    - The main messages from the PeRSEVERE project, with rationale.
    - Opportunities for trial site staff to talk through any concerns, misunderstandings or disagreements with these main messages.
    - Recognition that it can be challenging to accommodate the needs of trial participants and the trials they take part in.
    - 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.
    - The importance of collecting as much of the planned data as possible, with a particular focus on trial outcome data.
    - 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.

- Confirmation that, if a participant does say they want data collection to stop, data already collected is retained and data generated prior to that point can also still be collected in most cases.
- Information to convey during initial consent about participation changes.
- Encouragement to have dialogue wherever needed about participation changes, both with participants and with CTUs (to discuss individual cases or to seek advice).
- 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.
- Advice about how to talk to participants about topics where staff may worry about the risk of appearing to put pressure on participants.
- Confirmation that trial staff should assess each individual situation for its specific circumstances and sensitivities, and prioritise participants’ rights.

- Emphasising that when a participant says they want to stop or reduce their participation, it does not mean they need to stop all involvement.
- Emphasising that the nature and extent of participation changes should be participants' decision.
- The need to explore whether a change in trial site could help the participant continue contributing to the trial, if they want to.
- Guidance and expectations for establishing what a participant wants to do when they say they want to stop or reduce their participation.
- Information about possible flexibilities in each trial's follow-up procedures.
- Reminders to communicate clearly with participants if aspects of participation stop when it was not participants' choice.
- Expectations around record-keeping for all types of participation change.
- What is practically expected of trial staff in cases where they are unable to contact research participants.

    - Advice about how to ask participants if they might be happy to provide any information about why they want to change their participation.
    - 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);
    - Confirmation that stopping participation does not automatically remove participants' rights to receive relevant information that they might want or need.
    - It may be useful to present common scenarios that may arise and what would be expected from trial staff in these scenarios.
- We make further suggestions for how trial site staff could be better supported to manage participation changes. We provide examples of tools and templates that could help with this, such as checklists for managing different sorts of participation change, templates to use when attempting to regain contact with participants or to check participants' preferences for further contact.

Data collection about participation changes:[10]

- 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.
- Trial statisticians and data managers have a particularly important role in data collection design.
- Data collection forms about participation changes may 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.
- 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.
- Reasonable efforts should be made to find out exactly how participants want their participation to change. However, sometimes it could be that participants' wishes

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

are not known about one or more aspects of their participation. Data collection forms should enable recording of this missing information, where applicable.

- Data collection should record the dates relating to the participation change.
- 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.
- 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 about whether the participation change had anything to do with changes in the participant’s health, or information about the participant’s health or prognosis at the time of the participation change.
- 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, or about other possible actions required in response to the participation change.

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

Trial analysis:[11]

- 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. This is facilitated by careful statistical planning and collection of useful data (as above). Any deviations from the analysis plan should be declared in the final trial report.

End of trial reporting:[11]

- In PeRSEVERE Implementation Guidance Part 8, we recommend approaches to ensure clear reporting of information about participation changes in addition to the minimum standard defined by the CONSORT statement.[12]

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[11] PeRSEVERE Implementation Guidance part 8: analysis and reporting

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

- When reporting the ‘participant flow,’ use clear terminology to describe the participation changes.
- It is unlikely to be necessary to report every detail of how participation has changed, but enough detail should be reported to allow 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.
- Modifications to the CONSORT flow diagram 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.
- 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.
- We refer to best practice recommendations elsewhere about reporting on ‘missing data’ in trials, and reporting analysis methods.