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

Part 3: trial funding, protocol development and statistical planning

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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. Research Grant Applications

Consider up front how to ensure there is adequate resource to support all trial follow-up activity **[D1[1]].** This should include follow-up activity for participants whose participation changes during their time on trial, and those who 'complete' all aspects of participation.

Planned costs should include supporting any alternative follow-up arrangements that could allow participants to continue taking part but with less commitment (see Protocol Development, below). Such alternative arrangements should be designed with the help of patient contributors, who can help ensure the planned trial is as burden-free as possible for its participants.

Decisions made in grant development should be informed by available data on trials with similar designs, similar interventions, similar participant populations or conducted in similar settings. This will give an indication of the expected frequency and nature of participation changes in the new trial. Data about prior trials should also inform any sample size 'inflation' done to ensure there would still be sufficient statistical power after any participation changes.

More research may be needed on the cost implications of different sorts of follow-up schedules and methods.

Any specific mechanisms to try to regain contact with, or collect further data about, participants who have lost contact with trial staff **[O4[2]]** should also be fully costed.

Costing should also include adequate funds to support all activity intended to help manage participation changes, including work on any relevant computer systems or to deliver training.

Resourcing requirements can be a barrier to sharing trial results with the trial's participants.[3] If the nature of the trial means it might require more resource to share results with participants who stop or reduce their participation, consider this in the trial costing.

2. Protocol Development

a. What should you consider when writing clinical trial protocol content about managing participation changes?

It is important to be proactive in considering how each trial will prepare for and manage participation changes. A main component of this preparedness is in the trial design and clear, comprehensive protocol content **[D2[4]]**. Please note that we refer to the protocol here as

[1] D1 Protecting study integrity by design
[2] O4 Losing contact
[3] Long *et al.* (2019) Health researchers' experiences, perceptions and barriers related to sharing study results with participants. *Health Res Policy Sys.* 17, 25. https://doi.org/10.1186/s12961-019-0422-5
[4] D2 Protocol content

shorthand for all trial instructions; the same points can be covered in other, related documents if this is more convenient.

It is unlikely to be possible to foresee and prepare for all eventualities. Prospective risk assessment enables assessment of uncertainties and monitoring allows trial teams to see how well their processes are working **[Part 5[5]]**. Trial monitoring processes can ultimately lead to protocol amendments if it is agreed that existing processes could be improved.

When designing the trial follow-up procedures, consider how to reduce the burden for participants, trial sites and all others running the trial. Consider also allowing flexibility in the timing, mode and frequency of follow-up so that participants can continue contributing with less commitment, if that suits them.

These considerations need to be balanced with the need for the trial to adequately meet its scientific objectives, and with feasibility. For example, trial follow-up cannot be so flexible that it is difficult for trial staff to manage. The potential benefits of more flexible approaches need to outweigh the costs and risks. Consider documenting the decisions made in designing the trial follow-up methods (e.g. in the trial protocol), including where it is agreed best *not* to allow much or any flexibility in follow-up methods. This way, these decisions can be revisited during the trial as required **[Part 5]**.

Other process documents, such as data management plans or work instructions, can go into more detail about how CTU staff should respond to notifications about participation changes as they occur in the trial. This can include checks that the protocol instructions about managing participation changes are being followed correctly, and what advice to give trial site staff if they contact the CTU for more support in managing any specific cases. These process documents should be informed by trial risk assessments **[Part 5]** and can be important in staff training **[Part 6[6]]**.

b. Specific recommendations for protocol content

It is already standard practice for trial protocols to **confirm that participants have the right to withdraw their consent** at any time, without having to give a reason and without detriment. This is unchanged by PeRSEVERE and should therefore still be included.

All protocol content should be written with an understanding that **participation changes can take many forms [O1[7]]**. Use language that conveys this complexity. Some suggestions for terminology to use are included in the PeRSEVERE Principles and Explanation document. Consider use of 'participation changes' as a general term to cover all types of change.

The procedures regarding participation changes should be written with the involvement of the **trial's statistician(s)** to ensure they are suitable to the planned analysis (including any

[5] PeRSEVERE Implementation Guidance part 5: risk assessment and monitoring
[6] PeRSEVERE Implementation Guidance part 6: training and support
[7] O1 Participation can stop, reduce or change

defined estimands[8]). **Patient contributors** should be involved to ensure the procedures are suitable and appropriate for the trial's participants.

Consider **presenting content about the broad sorts of participation change in different sections**, to encourage these to be considered and managed separately. As others have suggested,[9,10] it is usually advisable to present information about intervention stopping separately to other types of participation change because, unless the participant wants to change other aspects of their participation, these other aspects continue **[O2]**. Content about changes in participants' capacity to consent, and the implications for how participation should change, could again be separate.

If you accept the PeRSEVERE principles in guiding all your protocol content about participation changes, **consider referencing the Principles and Explanation document, or other PeRSEVERE outputs**.

Given that the protocol is the primary instructional document for how the trial will be run, consider using it to **emphasise some of the positions given in the PeRSEVERE principles**, including that:

- The nature and extent of participation changes should be an informed and freely-given decision by the participant **[O2[11]]**.
- If any elements of participation stop because of decisions made by others to protect participants (e.g. stopping trial intervention), these decisions should only apply to aspects of participation relevant to the decision, and not beyond these **[O2]**. When decisions like these are made on behalf of the participant, they should be communicated and explained to the participant. The participant should have the chance to ask questions of an appropriate person so that they can understand aspects of their participation had to stop.
    - These same points may apply if the trial design means that sometimes aspects of participation cannot continue even where the participant is willing (for example, in some early phase trials where stopping trial intervention means there will be no further trial follow-up).
    - If the protocol gives specific rules about when trial intervention should stop, it may be useful to be explicit about what follow-up activity would be expected after that, in the absence of a participant's decision that they want that other trial activity to stop as well.

[8] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf
[9] Lynggaard *et al.* (2022) Principles and recommendations for incorporating estimands into clinical study protocol templates. *Trials.* 23, 685. https://doi.org/10.1186/s13063-022-06515-2
[10] Wittes (2009) Missing Inaction: Preventing Missing Outcome Data in Randomized Clinical Trials, *J Biopharm Stat*. 19:6, 957-968. https://doi.org/10.1080/10543400903239825
[11] O2 Participants decide how their participation changes

- Collecting as much as possible of a trial's planned data can help the trial reach a reliable conclusion. This should be kept in mind by all trial staff during the trial **[O3[12]]**.
- Loss of contact between trial staff and participants is not the same as an explicit wish to stop or reduce participation **[O4[13]].**
- Data collection (and any other aspects of participation where a 'presumed ongoing consent' approach applies[14]) will continue until a participant says they want it to stop **[O5[15]].** The protocol could explain the conditions that need to apply when using this approach **[Part 3[16]]**. It could give expectations around reviewing each specific case to check the appropriateness of the presumed ongoing consent, considering aspects like changes in the participant's health or capacity to consent.
- Data *generated* until a participant says they want data collection to stop can still be collected for the trial **[O5]**. This may not apply in the same way if the data collection itself has confidentiality considerations, for example if it involves people outside the care team accessing medical notes to transfer data to trial forms. In this case, a 'presumed ongoing consent' approach could theoretically apply, but may not easily be done fairly and transparently **[Part 2[17]]** .
- Data collected until such a point a participant says they want data collection to stop is retained until the end of the trial archiving period and used in trial analysis **[O6[18]]**.
    - PeRSEVERE principle **O6** states that this data can be made available to others outside the trial team for secondary research purposes; the protocol can state the trial position on this, including how it interacts with participants' consent (for example, a 'presumed ongoing consent' approach may be appropriate).
    - The protocol could give a general instruction to follow in case of any requests (e.g. from participants) for trial data to be deleted. This may involve contacting the CTU as soon as possible to review and discuss details of the case.
- Information about how trial results will be shared with participants should make clear that results will also be made available to participants who stopped or reduced their participation, if they would like to receive those results **[O7[19]]**.

[12] O3 The more data, the better
[13] O4 Losing contact
[14] 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)
[15] O5 Continuing data collection
[16] PeRSEVERE Implementation Guidance part 3: trial funding, protocol development and statistical planning
[17] PeRSEVERE Implementation Guidance part 2: policies and processes
[18] O6 Retaining data
[19] O7 Information after stopping participation

- Instructions can be given on how these participants' contact details and preferences will be elicited and maintained, including to check whether these may have changed at the time participants stop or reduce their participation.
- Participants could be offered a way, such as an online portal, to maintain their own records about their contact details and preferences. Alternatively, centralised services such as NHS Digitrials could be used to help manage participant communication.[20]

The protocol should explain **what needs to happen when a participant says they want to stop or reduce their participation** in the trial. This may include:

- How to establish exactly what a participant wants to do when they say they want their participation to change, including their preferences for further contact about the trial.
- Expectations around how the participant's wishes should be documented for trial purposes (e.g. in the medical notes and on trial-specific forms).
- If it would help the trial's objectives, consider collecting trial outcome data at the time of a participation change, particularly where participants say they want no further data collected after this time.[21] Care should be taken when communicating with participants about this **[Part 4[22]]**.
- While participants have the right to stop taking part in the trial without having to give a reason, it is acceptable for trial staff to try to establish the participant's motivations. The protocol can give advice about how to broach this with participants, gauging when it may not be appropriate to ask, and what sort of information is and is not useful to the trial.
- Any activity required to check participants' safety during the time when they stop or reduce their participation, particularly in relation to stopping trial intervention. This could include a final safety assessment with the trial doctor, additional data collection by trial site staff or from routinely collected healthcare data, or specific advice to pass to the participant's usual care teams.
- If there are plans to share any particular information or communications with participants when they stop or reduce their participation (or while they are deciding what to do)**,** this could be explained in the protocol **[Part 4]**.

The protocol should provide **instructions for trial staff in case they lose contact with participants**. These should be suitable to the trial and appropriate to the patient population. It may be sensible not to be too prescriptive, instead allowing trial site staff to use their own judgement for each specific participant. However, general guidance could include:

[20] https://digital.nhs.uk/services/nhs-digitrials

[21] 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

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

- A minimum (or maximum) number of attempts to contact the participant before stopping and considering them to be uncontactable (or uncontactable for now);
- Recommendations about how to attempt to get back in contact. This may include use of more than one contact method across the attempts where possible, if participants may be less likely to respond to certain methods (for example, some people may not answer the phone if they do not recognise the number). Each participant's circumstances should be taken into account when planning these recontact attempts. For example, if it was known that a participant's health was deteriorating at the last trial contact, or if they had already spoken about potentially leaving the country;
- Actions to take on establishing that a participant is now out of contact with the trial (following unsuccessful attempts to get in contact according to the protocol instructions). This could include notifying the CTU, or sending the participant a written confirmation of their change in status, if their contact details are still considered likely to be correct **[Part 4[23]]**;

- Expectations for trying to regain contact nearer the end of the trial (only where this could be helpful to the trial's objectives). Again, information known about each participant's circumstances should be taken into account when deciding what to do;
- Expectations for action to take in the situation where a participant gets back in contact after a while out of contact. This could include whether the participant needs to be asked to formally restate their consent to participate (e.g. in writing) or whether their consent can be implied. This may depend on the specific circumstances in each case, so guidance could instead cover how to decide what to do. In any case, trial staff must be satisfied that the participant is happy to restart trial activities and understands what doing that would mean for them. Staff should document the interaction they had with the participant about this;
- Any processes for contacting other people or sources to regain contact and/or collect further trial data. This might include contact with GPs, family or carers, or accessing routine data sources, either centralised (e.g. NHS England) or localised (e.g. individual NHS organisations that are not participating in the trial).
    - The protocol should be clear about how participants' consent impacts on these activities. This includes if there are any requirements for specific, prior consent to allow these activities where they might otherwise be considered intrusive. It also includes where 'presumed ongoing consent' approaches may apply to allow the activities to continue if certain conditions are met (see above).
    - Take care in any case to reduce the chance that these processes could be considered intrusive. Patient contributors may be able to advise on this aspect in particular.

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

- Successfully obtaining data from non-trial sites (e.g. where data would be provided to trial sites, which then provide it to the CTU) can be challenging. Those other sites are not specifically resourced to do any of the work required to provide the data. Some may be unsure of the rules around collecting and sharing data in this way, or about whether it might constitute trial activity that should only happen at trial sites. Further work to explore and resolve these challenges could be useful.

The protocol should be clear about any **data collection that needs to continue in all cases**, for regulatory or other reasons (for example, collection of certain information about intervention safety in clinical trials of investigational medicinal products, required for adherence to the UK Medicines for Human Use [Clinical Trials] Regulations 2004[24]).

Options for **reduced or alternative follow-up schedules or methods** should be referenced, with instructions for how and when to broach them with participants.

- This may include **organising elements of participation into 'tiers'**. While participation should change in line with participants' wishes **[O2[25]]**, in some trials where participation comprises multiple elements, there may be many ways that participation could change, in theory. Using participation tiers or layers can avoid overwhelming participants with choices and make things practically easier for those running the trial. Deviations from the tiers may still be possible if participants want their participation to change in a different way. An example might be to specify levels of participation such as:
    - 1) participating in all aspects;
    - 2) stopped trial intervention only, continuing all other aspects;
    - 3) stopped trial-specific clinic visits (with or without continuing questionnaire completion) but happy for data to be used from routine healthcare visits;
    - 4) stopped trial-specific clinic visits and no longer wants data to be used from routine healthcare visits, but other 'passive' elements of participation continue (in line with a 'presumed ongoing consent' approach **[Part 2[26]** and **O5[27]]**);
    - 5) all aspects of participation stop but data collected already is retained;
    - 6) all aspects of participation stop and data collected already is not retained (only in very unusual circumstances **[O6[28]]**);
    - Preferences for further contact about the trial, including receiving trial results, might not need to be tied to any particular levels of participation and could be managed independently.

[24] https://www.legislation.gov.uk/uksi/2004/1031/contents/made
[25] O2 Participants decide how their participation changes
[26] PeRSEVERE Implementation Guidance Part 2: policies and processes
[27] O5 Continuing data collection
[28] O6 Retaining data

- It may not be helpful to mention any of the reduced or alternative options in the initial pre-consent patient information **[Part 4[29]]**.
- The 'tiering' approach may include defining a minimum dataset that would still inform the main trial objective(s) for any participants whose participation changes, with a particular focus on the primary trial outcome measure and other key outcome measures.
- Another example of possible 'flexibility' in trial follow-up is to plan to allow participants to skip a planned trial visit where this might make it easier for them to keep contributing, and where otherwise they might want or need to stop attending all further trial visits. This could only be suitable if it still resulted in collection of adequate trial outcome data, and if it was feasible for all trial staff to manage.

The protocol should contain any **definitions of trial-specific participation changes that are anticipated** (or 'intercurrent events', to use the terminology from the addendum to ICH guideline E9 [R1][30]). This includes any specific action required by trial staff in response to those change types and what data collection would continue (in the absence of a participant's decision that they want data collection to stop). These instructions should be written with any defined estimands in mind **[D2[31]][32]**. Statistical planning (in the protocol or Statistical Analysis Plan) should make clear if any types of participation change have trial-specific implications for the planned analysis, for example in terms of defining the outcome measures.

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). This could include how to establish and document the participant's wishes, how to communicate these wishes to the CTU and how to make sure the participant's wishes are carried out.

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 in relation to participation changes. This can help ensure they are given adequate support to manage participation changes for the good of both the participants and the trial **[D6[33]].**

The trial protocol should contain at least a high-level explanation of how missing data will be handled in trial analyses, in line with any defined estimands. Further details can be given in the statistical analysis plan.

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

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

[31] D2 Protocol content

[32] Lynggaard *et al.* (2022) Principles and recommendations for incorporating estimands into clinical study protocol templates. *Trials.* 23, 685. https://doi.org/10.1186/s13063-022-06515-2

[33] D6 Training and support

3. Statistical analysis plans

There is already a substantial amount of guidance and best practice available regarding development of statistical analysis plans (SAPs). This includes guidelines for SAP content in general[34] and for early phase clinical trials in particular[35]. Guidance on SAP content emphasises the need for:

- Adequate planning prior to beginning any trial data collection;[36]
- Where appropriate, defining trial estimands[37], i.e. specifically what values the trial is looking to estimate (given the near inevitability of some participation changes or 'intercurrent events');[38]
- Robust planning for how missing data will be handled in the trial analysis, in alignment with any trial estimands, underlying assumptions and proposed missingness mechanisms;[39]
- Sensitivity analysis targeting the same estimands should be performed to assess the robustness of the statistical assumptions made in the main analysis.

As with other trial documents, we suggest that the language and terminology used in SAPs reflects the complexity of participation changes **[O1[40]].** The SAP could also be clear about which types of participation change are most relevant to the trial analysis.

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 **[D1[41]]** 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).

[34] Gamble *et al.* (2017) Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. *JAMA.* 318(23):2337–2343. https://doi.org/10.1001/jama.2017.18556
[35] Homer *et al.* (2022) Early phase clinical trials extension to guidelines for the content of statistical analysis plans. ***BMJ.*** 376:e068177. https://doi.org/10.1136/bmj-2021-068177
[36] Kahan *et al.* (202) How to design a pre-specified statistical analysis approach to limit p-hacking in clinical trials: the Pre-SPEC framework. *BMC Med.* 18, 253. https://doi.org/10.1186/s12916-020-01706-7
[37] https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf
[38] Kang *et al.* (2022) Incorporating estimands into clinical trial statistical analysis plans. *Clin Trials*. 19(3):285-291. https://doi.org/10.1177/17407745221080463
[39] 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
[40] O1 Participation can stop, reduce or change
[41] D1 Protecting study integrity by design

Given the available guidance elsewhere, we will not go into further detail about statistical planning here and instead would refer the reader to those other sources (see examples in footnotes.[42,43,44]

[42] Mallinckrodt *et al* (2017) Choosing estimands in clinical trials with missing data. Pharm Stat. 16(1):29–36. https://doi.org/10.1002/pst.1765

[43] Cro *et al.* (2020) A four-step strategy for handling missing outcome data in randomised trials affected by a pandemic. BMC Med Res Methodol. 20(1):1–12. https://doi.org/10.21203/rs.3.rs-32455/v1%0ALicense:

[44] Cro S *et al.* (2020) Sensitivity analysis for clinical trials with missing continuous outcome data using controlled multiple imputation: a practical guide. Stat Med. sim.8569. https://onlinelibrary.wiley.com/doi/abs/10.1002/sim.8569