**Template study protocol content**

This document provides template study protocol content, including template wording and a suggested way to structure it, to implement the PeRSEVERE principles and guidance. This includes the detailed guidance specifically about protocol development (<https://persevereprinciples.org/protocol-development/>). We have also consulted existing guidance from SPIRIT, ICH and the UK Health Research Authority and others in developing this resource (see **References**).

Study teams can use this resource as a starting point for developing their own protocol content about managing participation changes. The content should be amended as required to address the specifics of each study and any identified study-specific risks and considerations relating to participation changes. Teams may decide that some of the more detailed content might be better in documents other than the study protocol (e.g. data management plans or statistical analysis plans), but this guidance can still be used for developing those.

We would welcome feedback on this resource. If you have any, please contact us at persevere@leeds.ac.uk.

If you use this resource in your study protocol, please acknowledge PeRSEVERE as the source in a suitable place (for example, in the protocol’s references). See <https://persevereprinciples.org/copyright/>.

Explanation of layout and formatting in this document:

* Content in this guidance is presented under headings that are expected to feature in a study protocol.
* At the start of most sections, there is a short explanation of what to include.
* Suggested text is then presented in indented italics.
* Text in square brackets is intended to be filled by study-specific details.

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**Suggested content for section about managing participation changes**

1. **Participation changes**

We recommend grouping all content about managing participation changes under a general ‘participation changes’ heading. This could be amended to something like ‘withdrawal and participation changes’, if it helps research staff find the content they need.

A suggested structure for this section is set out in the sections and subsections below.

* 1. **Introduction and definitions**

If you will use the PeRSEVERE principles in guiding all your protocol content about participation changes, consider referencing the principles or other PeRSEVERE outputs in this section of the protocol.

 ***Suggested text***

*Participants’ involvement may stop, reduce or change in various ways. The general term ‘participation change’ is used in this protocol to include all scenarios. See subsections below for more detail.*

*This study has been designed, and will be run, in line with the PeRSEVERE principles (persevereprinciples.org) to ensure that participation changes are managed in ways that protect participants’ interests and study integrity.*

* + 1. **General principles**

Confirm the general principles applying to all management of participation changes in the study. The example text below reflects the PeRSEVERE principles. These are expected to apply to most studies as they are, but amendments should be made as needed.

 ***Suggested text***

*Participants have the right to withdraw their consent at any time, without having to give a reason and without any negative effect on their usual care.*

*In practice, participants’ level of involvement can stop, reduce or change. It is primarily for participants to decide how their level of involvement will change. Exceptions to this are where someone else decides it is no longer in a participant’s interests to continue taking part in some part of the study, or where continued participation would no longer be feasible or no longer relevant to the study objectives.*

*Participants’ decisions about changing their level of involvement should be informed and freely-given. It is therefore important to provide information about their options and the advantages and disadvantages of these, for the participant and for the study. Study staff should help participants decide how they want their participation to change, and should make reasonable efforts to find ways to continue some follow-up, where participants are willing.*

*Interactions with participants must be conducted in a balanced way, providing sufficient information about different options, not pressuring participants to take further part in aspects of the study but also not assuming they want to stop all aspects.*

*Collecting as much as possible of a study’s planned data can help the study reach a reliable conclusion. This should be kept in mind by all study staff during the study.*

* + 1. **Types of participation change**

List out the expected or reasonably likely types of participation change in the study, and the implications of each for participants and for the study. Include any required actions that need to follow any of them. If stopping certain aspects of the study means other aspects would stop, make this clear – for example if stopping intervention would mean certain data collection would stop. A table might be a suitable way to present this information. A starting example is shown below.

Ensure the study statistician is involved in developing this section of the protocol so that it can be properly aligned with any study estimands[[1]](#footnote-1) and any other relevant statistical aspects.

The focus of this section is on the different aspects of participation and how they could change over time. The section below covering different participation change ‘scenarios’ is about the circumstances of each participation change rather than the extent of each change. However, often the extent and the circumstances of a participation change need to be considered together. Care should therefore be taken to make sure these sections are complementary but that they do not overlap more than necessary.

‘Intercurrent events’[[2]](#footnote-2) and other events relevant to study analysis could also be included in this table, even if they might not be considered ‘participation changes’, as such. This could include missed intervention or missed follow-up appointments (rather than permanently stopping either of these), receipt of additional intervention, treatment switching or co-enrolment in a different study.

Ensure any optional consent points from the original consent process are included in this information so that it is clear what should happen when they will stop.

 ***Suggested text***

| ***Type of participation change*** | ***Actions required at the time of participation change*** | ***Expected further study activity*** |
| --- | --- | --- |
| *Reducing or modifying study intervention* ***[refer to other section of protocol for details on possible modifications]*** | ***[For example, safety-related tests required or specific data collection]****If the change in intervention has occurred due to an adverse event, please submit* ***[safety reports as required]****.* | *All other study activities continue unless the participant says they want them to stop.* *Safety-related data collection/follow-up must continue while intervention continues.* |
| *Restarting intervention after a pause* ***[refer to other section of other protocol]*** | ***[For example, safety-related tests required or specific data collection]*** | *N/a* |
| *Stopping study intervention* | ***[For example, safety-related tests required or specific data collection]****If stopping intervention has occurred due to an adverse event, please submit* ***[safety reports as required]****.****[Mention if there are specific reasons for stopping intervention that would need to be reported, for example to inform study estimands.]*** | *Further treatment is at the discretion of treating clinician(s).* ***[Mention any specific requirements (for data collection or anything else) if participant will receive certain intervention instead, e.g. other interventions available in the study.]****All other study activities continue unless the participant says they want them to stop.* |
| *Stopping participant-reported outcome completion* | ***[E.g. ask if participant might be willing to reduce completion to only primary outcome data collection rather than stopping altogether]****The study coordinating centre must be notified as soon as possible so that questionnaire requests can be stopped.* | *All other study activities continue unless the participant says they want them to stop.* |
| *Reducing or changing mode of scheduled follow-up* ***[refer to other section of protocol for details on possible modifications]*** | ***[E.g. recording follow-up arrangements and communicating them to the study coordinating centre]*** | ***[State if it will not be possible for the participant to continue receiving intervention with reduced or alternative follow-up]*** |
| *Stopping all scheduled follow-up* | ***[E.g. ask if participant is willing for data from routine assessments to be used for the study, if they would be relevant]*** | ***[If relying on ‘presumed ongoing consent’ – see below]*** *Data collection from routine assessments will continue to be used for the study unless the participant says they want this to stop.****[If relying on updated consent at the point of the participation change]*** *Data collection from routine assessments will continue if they participant confirms their ongoing consent to this.* |
| *Stopping all further data collection* | *As far as possible, get confirmation from the participant that this is what they want. Ensure details of this interaction with the participant are recorded in their medical notes.**The study coordinating centre must be notified as soon as possible so that questionnaire requests can be stopped.* | *All further data collection stops, including participant-reported outcome measures.**Data about events that occurred before the participant stated their wish for no further data collection can still be collected* ***[amend as required if this is not true, e.g. because data collection has confidentiality considerations].*** |
| *Destruction of data collected so far* | *Participants’ rights to have their data destroyed are limited.* ***[Refer to further section below for action to take in case of requests]*** | *N/a* |
| *Loss of contact between researchers and participants* | ***[See section below]*** | ***[See section below]*** |
| *Participants dying during the study period* | *Notify the study coordinating centre within* ***[timeline]****.* | ***[Often not applicable, but mention or link to planned involvement of family members or carers e.g. to share study results with them]*** |
| ***[Add additional lines as required]*** |  |  |

If a ‘presumed ongoing consent’ approach applies to any of the types of participation change, make that clear. See PeRSEVERE principle **O5** for more about this: <https://persevereprinciples.org/principle-o5-continuing-data-collection/>.

 ***Suggested text***

*The following participation changes are possible, but only if the participant specifically says they have changed their mind about them.*

* + *Stopping data collection from routine healthcare appointments, where the appointments could be relevant to study outcomes;*
	+ *Withdrawing consent for monitor/auditor/inspector access to medical notes;*
	+ *Withdrawing consent for sharing of de-identified data for further research* ***[where relying on consent for this];***
	+ *Withdrawing consent for future uses of collected tissue samples, e.g. in a biobank;*
	+ ***[Add other aspects as required].***

*It is made clear to participants before they take part that these aspects of participation will continue until they say they want them to stop.* ***[If applicable]*** *Participants are reminded of these aspects continuing after they stop other aspects of participation via the end of participation communication* ***[refer to section below].***

*Research staff must make reasonable efforts to establish what participants want to do – i.e. which aspects of participation they want to stop and which they are willing to continue with – when they say they want to stop taking part. The levels of participation in* ***[section below]*** *can be used to help with this.*

*The details of individual cases must nonetheless be considered. In some cases, individual participants’ circumstances, or the circumstances of them changing their level of participation, mean that it is not justifiable to assume that their previously given consent remains in place. In case of doubt, contact the study coordinating centre to discuss.*

* + 1. **Levels of participation**

It can make things simpler for participants and research staff to organise the possible participation changes into levels. These options can be made clear in the protocol, and can be provided to participants around the time they are considering stopping or reducing their involvement, so that they know what their options are. Deviations from the levels may still be possible if participants want their participation to change in a different way – make this clear in the protocol if so. It is not recommended to present this information to participants before they start taking part, as this could give a confusing message about what taking part involves (although a similar idea is to make some aspects of the study optional).

An example of levelling options is given below. When generating a study-specific version of this, remember that it is intended as a way to make things easier - so it should not be an exhaustive list of possibilities, but a short, rational list of options.

The example below relies on the ‘presumed ongoing consent’ approach mentioned above. This means that some ‘passive’ aspects of participation continue until a participant specifically says they want them to stop (with some conditions). If this approach is not being used, the text will need to be amended accordingly.

One or more of the levels could refer to the idea of a ‘minimum dataset’, that would still inform the main study objectives (e.g. with a focus on the primary study outcome measure and other key outcome measures). In practice, this might include the participant reducing their completion of questionnaires to only the most important one(s), or allowing collection of primary outcome data from routine appointments while stopping all other data collection. This might not be possible in all studies, but should be considered where it could help participants reduce their involvement while still helping the study.

 ***Suggested text***

*Although many different participation changes are theoretically possible, we have organised participation into levels to make things simpler for everyone involved in the study (including participants). These levels can be used to guide conversations with participants who are considering stopping or reducing their involvement in the study.*

*When reporting participation changes to the study coordinating centre, the levels can be used to clearly communicate how each participant’s involvement has changed.*

*It can be possible for participation to change in ways that do not directly fit to one of the levels – contact the coordinating centre if this is the case.*

*Participation levels in this study are:*

|  |
| --- |
| 1. *Participating in all aspects of the study*
 |
| *(2) Stopped study intervention only, continuing all other aspects* |
| *(3) Stopped study intervention, most questionnaires and most study-specific clinic visits but willing to provide minimum dataset* ***[define or refer to where this is defined]*** |
| *(4a) Stopped study intervention and no longer completing study questionnaires; still attending study-specific clinic visits* | *(4b) Stopped study intervention and no longer attending study-specific clinic visits; still willing to complete questionnaires* |
| *(5) Stopped study intervention, questionnaires and study-specific clinic visits but willing to allow relevant data to be collected from routine healthcare visits and from routine healthcare data providers* |
| *(6) Stopped study intervention, questionnaires and study-specific clinic visits and not willing for relevant data to be collected from routine healthcare visits. Other passive aspects of participation continue* ***[refer to ‘presumed ongoing consent’ section if using this approach in the study]*** |
| *(7) All aspects of participation stop, including ‘passive’ aspects, but data already collected is retained.* |

*If a participant says they want to stop taking part but do not specify which aspects of participation they want to stop, sensitively try to establish what they want to do, using the levels above as a guide.*

*If there is no opportunity to discuss it further, the participant would move to* ***level 5*** *unless there is good reason to conclude that consent to passive aspects of participation has also been withdrawn (contact the study coordinating centre in case of doubt).*

*Participants are informed before they initially consent that some aspects of participation continue until they say they want them to stop.* ***[Add if applicable]*** *They are also reminded of continuing aspects of participation via the end of participation communication* ***[refer to section below].***

*If contact is lost with the participant during the study (see* ***[section on losing contact, below]****) then the participant moves to* ***level 5*** *unless there is good reason to conclude that consent to passive aspects of participation has also been withdrawn (contact the study coordinating centre in case of doubt).*

*Participants’ preferences for being contacted about the study should be considered independently of any participation changes. Therefore, the levels of participation given above are not linked to implications for changes in contact preferences. See* ***[section below]*** *on contact after participation changes.*

*Data already collected (including data generated but not yet on study forms) is retained and used in the study analysis. See* ***[section below]*** *for more on this.*

*See* ***[section below]*** *for**how to manage requests for data deletion.*

1. **Managing different participation change scenarios**

Participants’ level of involvement in a study can change in different circumstances – including where participants say they want to stop taking part, where members of the research team decide some aspects of participation need to stop, or where participants lose contact with the research team. Different situations need managing in different ways. The following sections give some guidance and example text for some common scenarios.

Checklists for managing some types of changes are available on the PeRSEVERE website: <https://persevereprinciples.org/checklists-for-managing-individual-participation-changes/>

As mentioned in the section above on types of participation change, often the extent and circumstances of a participation change need to be considered together. Ensure these sections are complementary but not unnecessarily overlapping. Add in cross references as required to make sure the instructions for research staff are clear. This might mean they consult this current section for the process to follow when a participant says they want to stop taking part, but it refers to the section above for specific actions to take when a participant stops taking intervention and stops attending study clinic visits (for example).

* 1. **Participant (or their representative) reporting that they want to stop, reduce or change their participation**

Make clear what research staff should do in response to being informed by a participant (or someone acting on the participant’s behalf, where applicable) that they want to change their level of involvement in the study.

If there is more than one way for participants to communicate their wishes about changing participation (e.g. communicating directly with research staff or filling in an online form) then details of each method should be provided.

Some of the suggestions in the example text below may pose some practical challenges, for example about making ‘reasonable efforts’ to find out how participants want their participation to change. If there is more detail to add to the protocol about this then that can be added, otherwise this sort of issue can be addressed through further training or guidance alongside the protocol.

 ***Suggested text***

*On notification by a participant that they want to stop taking part or change their level of involvement, research staff should make reasonable efforts to find out exactly how participants want their involvement to change, i.e. which aspects of the study they want to stop, and which they are willing to carry on. The levels of participation mentioned in* ***[section above]*** *can be used to make the participant’s options clear to them.*

***[Include the following if using such a method]*** *Participants should be asked if they would be willing to complete the* ***[participation change form]*** *to indicate how they would like their involvement to change. This is optional, and they can stop or change their participation without completing the form. Staff are nonetheless encouraged to explain the benefits of using the form, i.e. that it means the research team will have a clear view of the participant’s wishes. The participant may take the form away to complete in their own time, if they wish.*

***[Include the following if using such a method]*** *Participants are reminded that they may discuss their participation with* ***[someone independent of or separate from the usual study team]*** *if they would find that useful.* ***[Give details of who that independent/separate person or group is and how they can be reached.]***

*Once it is established which aspects of participation will be stopping, refer to* ***[section above]*** *for the actions required in relation to each aspect.*

*While participants are not obliged to give a reason for their decision, research staff should ask if participants are willing to provide any information, if there is an opportunity to ask. This should be done sensitively and without putting any pressure on participants. Participants can be reminded about why it can be useful to the study to have this information, and the sort of information that is useful (e.g. whether their changing their participation level has anything to do with the intervention received, or with changes in their health).* ***[Mention if there might be specific reasons to ask about, for example to inform study analyses.]***

*In some cases, based on the circumstances of a participant changing their level of participation, it may be inappropriate to ask participants for further information. Research staff should use their professional judgement in this respect.*

*Research staff should make reasonable efforts to find out if participants want to receive any further communications about the study, for example the final results of the study.*

*If possible, confirm back to the participant exactly how their participation has changed, i.e. which aspects of participation have stopped and which continue.*

***[If applicable]*** *The participant should be sent or given a short communication as described in* ***[section below]*** *to confirm how their participation has changed****.***

*Details of any discussion with the participant about changing their level of involvement should be documented in their medical notes. This includes a clear record of participants’ stated wishes about how they want their involvement to change, and whether they would like further contact about the study. If the participant provided limited information about their wishes (e.g. they just said they wanted to ‘withdraw’, and there was no opportunity to ask for further clarification) then this should be clear in the notes.*

*Notify the study coordinating centre about the participation change, providing a clear record on the study forms. Discuss with the coordinating centre in case of any doubt about how to provide the requested details.*

***[Add details of any other specific actions to take around this time with reference to the section above about specific types of participation change (taking care to avoid unnecessary duplication). This might include specific safety assessments if the participant is stopping study intervention. It might include specific data collection requirements, for example to collect data to inform the primary outcome measure, or to ask participants if they might still be willing to do that later. Protocol instructions (or associated documents) should guide research staff with how to approach these sorts of requests sensitively.]***

* + 1. **Participants communicating their wishes via [e.g. online route]**

The PeRSEVERE guidance suggests that participants might be offered a route to stopping their participation without having to speak to anyone. There are risks to this approach, for example that participants might not always be making a fully informed decision if they have not had the opportunity to discuss their participation with someone. However, it might mean some participants communicate their wishes where otherwise they might not have (i.e. they might just have stopped contacting the study team), as there is evidence that participants can find conversations about ending their involvement difficult.

The communication route might be online, but could conceivably be done by post or automated phone line, or it could be built into an eConsent system. Participants would be notified of the route at the time of their initial consent to take part.

The section of the study protocol here would cover what to do if the study team receives a notification via this route. The method could involve asking some of the questions mentioned in the section above, for example giving optional spaces for the participant to say why they want to stop taking part, and what their preferences are for further contact. It could also have built-in the point about communicating how the participant’s involvement has changed. These aspects therefore do not need to be explicitly mentioned as instructions in this section of the protocol.

 ***Suggested text***

*On receipt of a notification via the* ***[e.g. online route]*** *that a participant wants to stop or reduce their level of participation, the* ***[recipient notifies the other members of the study team]. [Add details of other actions to take e.g. to ensure the participant’s wishes are carried out.]***

*Refer to* ***[section above]*** *for the actions required in relation to each aspect of the study that will be stopping.*

* 1. **Loss of contact**

Loss of contact between study staff and participants is not the same as an explicit statement from a participant that they want to stop or reduce participation. The protocol should provide a standardised ‘definition’ to help decide when contact has been lost, and a process to follow when this happens.

* + 1. **Defining loss of contact**

A suitable ‘definition’ for loss of contact will depend on the study, the participant population and the follow-up schedule, amongst other things. It might be that a participant has not responded to any contact for a certain amount of time, or has not responded to contact relating to a certain number of follow-up appointments in a row, or to contact attempts via certain contact routes. There may be a role for research staff judgement, too, alongside minimum expected attempts at contact.

 ***Suggested text***

*If participants cannot be contacted or are not responding to attempts to reach them, research staff should make reasonable attempts to get back in touch. Staff should use their professional judgement and their knowledge of the participant and their circumstances when choosing how and when to try to contact the participant. A record of each attempt to re-contact the participant should be kept in the medical notes.*

*If a participant* ***[insert study-specific definition, e.g. does not attend three study visits in a row / does not respond to three separate attempts to contact them],*** *they are considered to have lost contact with the study.*

* + 1. **Process to follow when a participant is considered to have lost contact**

***Suggested text***

*If a participant is considered to have lost contact with the study (as defined above), the study coordinating centre should be notified within* ***[timescale].***

***[If applicable]*** *If the participant’s postal or email address are considered likely to be still correct, they should be sent a short written communication as described in* ***[section below]*** *to confirm that they will no longer be contacted about the study****.***

*The participant’s records should be updated to indicate that they should not be sent any further communication about the study until further notice.*

***[Any details of any other actions to take, e.g. data to be collected at the time a loss of contact is confirmed]***

* + 1. **Further data collection and attempts to contact the participant**

When participants lose contact with the study, they have not specifically said they want to stop taking part. They might want this, but they might not (they might have lost contact for other reasons). It can therefore be reasonable to collect further data about them, and attempt to contact them again later, as this does not go against the consent they previously gave. The protocol can explain the study’s approach to this.

 ***Suggested text***

*When participants have lost contact with the study, they move to* ***level 5*** *in the above level system* ***[reference section above]****. This means ‘active’ aspects of participation stop (including any requests for them to participate in these active aspects) but ‘passive’ aspects can continue unless there is doubt about validity of this ongoing consent – contact the study coordinating centre to discuss, if so.**Participants are informed of this approach before they agree to take part in the study.*

*If further data is recorded at the site that is relevant to the study (e.g. from routine appointments) then this can therefore be used for the study unless the participant has stated that they want no further data to be collected.*

***[Add details of further data collection that is expected to continue, e.g. data collection from other routine data sources such as NHS England in the UK]***

***[Add any specific plans to try to contact participants again later, for example near the time of the final study analysis. Give any relevant advice about how to do this sensitively, and whether any participants might be excluded from these further contact attempts, e.g. if site staff judge further contact to be inappropriate based on their knowledge of the participant’s circumstances.]***

***[If applicable]*** *Sites may be requested to contact participants’ GPs or other NHS sites for information to inform study outcomes.* ***[As applicable, mention that participants are aware or have given consent for such contact.]***

*If contact is regained and the participant subsequently has further involvement in the study, follow the instructions in* ***[section below on restarting].***

* 1. **Aspects of participation stopping following decisions by investigators or other research staff**

Investigators or other research staff can recommend that aspects of participation stop. This might be in the interests of participants’ health, where clinicians decide that receiving study intervention is no longer in participants’ best interests.

Research staff might occasionally conclude that a participant’s ongoing participation would no longer be helpful to the study. In this case, it is not a good use of that person’s time to continue taking part, and potentially unethical for them to be exposed to any ongoing risks associated with participation.

The PeRSEVERE principles make general recommendations about how to manage this sort of situation. The suggested text below can explain this approach in the study protocol.

***Suggested text***

*Sometimes it can be justifiable for aspects of participation to stop because of decisions by investigators or other research staff, rather than by participants. Whenever these decisions are reached, they must only apply to relevant aspects of participation.*

*For example, if a clinician decides that it will be best for a participant to stop study intervention, only that aspect of the study (receiving study intervention) should stop as a result of the clinician’s decision. Other aspects stop only if the participant wants them to stop.*

*Any such decisions made on behalf of a participant must be clearly communicated to the participant. The participant should have the chance to ask questions of an appropriate person so that they can understand the decision and what their choices are.*

*A clear record should also be kept in the participants’ notes about the decision and its justification.*

* + 1. **Clinicians recommending that study intervention should stop**

***Suggested text***

*Treating clinicians remain free to recommend that it is no longer in participants’ best interests to continue receiving study intervention. See* ***[section elsewhere – not in scope of this guidance]*** *for specific rules around when intervention should stop.*

*As above, clinical decisions that intervention should stop only affect intervention receipt, and do not mean other aspects of participation should stop. It is therefore expected that all other study follow-up continues unless the participant says they want those to stop, as per* ***[section on participants saying they want to stop taking part].***

***[Mention if specific information needs to be recorded about the reason for stopping intervention in these circumstances, e.g. to inform study analyses – or refer to the section above]***

* + 1. **Investigators or other research staff deciding that other aspects of participation will stop**

***Suggested text***

*Investigators or other research staff may decide that other aspects of participation should stop, for example if further participation is causing participants distress of any kind, or continued participation is no longer feasible or no longer helps meet the study objectives, or there is doubt about participants’ ability to carry out required study procedures.*

***[Add study-specific content about specific scenarios where participation would need to stop. Mention any study-specific instructions about recruiting ‘replacement’ participants, or refer to them if they are elsewhere in the protocol.]***

*In any such cases, the general instructions above apply about such decisions only affecting relevant aspects of participation, and clearly communicating such decisions to participants.*

*Contact the study coordinating centre if there are particularly complicated cases to discuss.*

* 1. **Loss of capacity**

Ensure there is adequate planning in place a) to cater for recruitment of people without capacity to consent, if that is possible in the study, and b) to manage loss of capacity during study participation, in line with local laws. These issues are not within scope of the PeRSEVERE project, but resources relevant to the UK setting are available at <https://www.capacityconsentresearch.com/>.

* 1. **Participants moving to a different study site**

Make clear if participants can move between study sites, and the procedure for doing this.

 ***Suggested text***

*If participants relocate during the follow-up period, it is possible for them to be transferred to a different study site if this would be more convenient, or if otherwise they might have to stop taking part.*

*If a participant mentions that they are planning to move home, remind them that they might be able to continue taking part in the study elsewhere, and provide them with information about where else the study is being run (contact the study coordinating centre for an up-to-date list). Ask them to consider if they are willing to continue taking part in the study at a different site, and which site would be best, if so.*

*Once the participant has chosen which site they would like to transfer to, notify the study coordinating centre. The study coordinating centre will contact the other site to find out if they could take on the additional participant.*

*If the transfer is agreed by all parties:*

* + *The originating site provides all outstanding data and responds to all outstanding queries by the time of the transfer, if possible. If not possible, these actions remain the responsibility of the originating site.*
	+ *The data collected until the point of the transfer is retained at the originating site* ***[provide further relevant details about how this is done].***
	+ *A copy of the same data is securely provided to the new site, along with the participant’s consent forms and any other relevant information* ***[provide further details about how this is done].***
	+ *All required referral processes must be completed in a timely manner to allow the participant to stay on the planned follow-up schedule.*

*Participants are not required to complete an updated consent form to confirm they agree to the transfer. Consent to continue participating is implied by attendance at the new site.*

* 1. **Increasing or re-starting participation**

As it is primarily participants’ choice how their level of involvement in a study changes, it is possible that they may increase their participation. The protocol should cover this topic, even if it is expected to be rare.

* + 1. **Spontaneous increases in participation**

***Suggested text***

*It is possible for participants to re-start study activities that they have previously stopped. Study staff must not put pressure on participants to do this, but if participants freely express a wish to make a contribution to the study again, it is acceptable to discuss this with them. This could happen if participants stay in touch with the study staff after having stopped taking part, or if participants regain contact after having lost touch previously.*

*In cases of potential increases in participation, study staff should contact the study coordinating centre to agree whether there are grounds to ask the participant to formally update their consent on a consent form, or whether their consent could be implied (e.g. by restarting completion of questionnaires).*

*In all cases, study staff must be satisfied that participants understand what they are agreeing to, and are doing so freely. Staff should make participants’ options clear to them (using the levels of participation mentioned in* ***[section above]*** *as a guide) and help participants decide exactly what they want to do.*

*A clear record must be kept in the medical notes of any discussions between study staff and participants about restarting participation.*

* + 1. **Planned increases in participation**

***Suggested text***

*An increase may be planned, for example, if it has been agreed that a participant would take a break from some aspects of participation. In this case, there is no need for the participant to complete another consent form. However, the same points apply as above regarding study staff being satisfied that the participant is giving an informed and freely-given decision, and keeping a record in the medical notes of any associated discussions.*

1. **Communication with participants after a participation change**

Stopping or reducing participation does not mean participants cannot have information they might want or need. Participants’ communication preferences should be considered independently of the level of their participation. Some participants who stay involved in all aspects of the study might not be interested to receive information about it. Some who stop taking part might remain interested to receive study updates.

Suggested text, below, covers two areas: information to provide to participants at the time they reduce or stop their participation, and further communication beyond that point. Further guidance on informing participants when they stop taking part is available via the PeRSEVERE website: <https://persevereprinciples.org/information-to-support-participants-who-stop-taking-part/>.

If a study has specific processes or mechanisms in place to help participants keep their contact details updated, for example an online system or specific instructions for research sites, this could be mentioned in this section.

* 1. **Informing participants following substantial participation changes**

***Suggested text***

***[If applicable]*** *After substantial reductions in their level of participation, participants should be sent a short, written communication to confirm how their participation has changed and what further level of involvement in the study they should expect, if any. A template is available for participant-led participation changes and loss of contact. The communication should not be sent if there are strong reasons to suggest the participant would not want to receive it. For any queries relating to this process, contact the study coordinating centre.*

* 1. **Other contact**

***Suggested text***

*It is acceptable to keep participants updated about the study after they stop taking part, if they want this. This includes informing them of the study results (see* ***[section below]****).*

*In general, participants’ contact preferences should be considered independently to changes in their level of participation. Some participants who continue taking part might not be interested in further information about the study, and some who stop taking part might want to continue receiving updates.*

*Sites should maintain up-to-date information about participants’ contact preferences, particularly where participants say they want to receive no further information. Where participants’ wishes are unclear, relevant information is provided unless there is good reason to consider it inappropriate or otherwise likely that the participant does not want to receive the information.*

1. **Implications of stopping data collection on data retention and further processing**

It is important to consider the exact implications of participants stopping further data collection. The example text below covers implications for retention of data already collected, inclusion of the data in planned analysis, potential use in secondary research and what to do about data that has been *generated* but not yet added to study forms or systems. While some aspects of this section are expected to be standard, the exact approach to take will vary depending on the study and its data collection and consent arrangements. Different options for standard text are given to cover the most common scenarios.

 ***Suggested text***

*If a participant says they want no further data collection, data already collected on study forms/systems by that time is retained, used in study analysis and kept until the end of the study archiving period. Participants are informed of this limitation on their data protection rights before they agree to take part in the study.*

***[If no confidentiality considerations with putting generated data onto study forms]*** *Data not yet on study forms/systems but* generated *by the time a participant say they want no further data collection, i.e. recorded in source notes and relating to events that occurred already, can also be entered onto study forms/systems.*

***[If adding generated data onto study forms has confidentiality considerations, e.g. if it involves people outside participants’ usual care team accessing medical notes or other confidential information]*** *Data collection involves access to confidential medical information by individuals outside participants’ usual care team. Data that exists in source notes but has not yet been added to study forms/systems by the time a participant say they want no further data collection should not therefore be entered onto study forms/systems.*

***[If relying on consent for sharing de-identified data for secondary research]*** *Data already collected is made available for secondary purposes at the end of the study unless participants have actively withdrawn their consent for this. Otherwise, consent is presumed to be ongoing, as mentioned in* ***[section above]. [Refer to data sharing section for more information.]***

***[If not relying on consent for sharing de-identified data for secondary research]*** *Data already collected is made available for secondary purposes at the end of the study.* ***[Refer to data sharing section for more information.]***

*To comply with UK clinical trials regulations, any Serious Adverse Reactions or Suspected, Unexpected Serious Adverse Reactions must continue to be reported to the study coordinating centre until the end of the study. Participants are notified of this limitation on their data protection rights before they agree to take part.*

The protocol could give a general instruction to follow in case of any requests (e.g. from participants) for study data to be deleted. This may involve contacting the study coordinating centre as soon as possible to review and discuss details of the case.

***Suggested text***

*If a participant expresses a wish for the data about them collected in the study to be deleted, contact the study coordinating centre so that this can be considered as a request for erasure of personal data under the UK General Data Protection Regulation. The participant can be referred to the participant information sheet, which contains information about their rights and who to contact in case of queries.*

**Suggested content to be added to other protocol sections**

1. **For the section on Informed consent**

Protocols will typically mention that participants must give informed consent before taking part in a study, and that participants have the right to withdraw that consent at any time.

All wording should reflect PeRSEVERE principle **O1** about how participation could stop, reduce or change, and should reflect other PeRSEVERE principles about informing participants and encouraging communication during the study.

 ***Suggested text***

*Potential participants must be informed of their right to withdraw their consent at any time, without having to give a reason and without their usual care being negatively impacted. In practice, this means participants can stop, reduce or change their level of involvement in the study* ***[refer to protocol section that goes into more detail about what participation changes are possible or expected]****.*

*Potential participants should be encouraged to raise any issues with their participation with the research staff to establish how they want their level of involvement to change. It should be made clear that it is primarily up to participants how their level of involvement changes. It should be made clear how participants can find out what their choices are about changing their participation.*

*Potential participants should be informed of the potential benefits of collecting as much of the planned study data as possible. This means as long as they remain involved in the study in some way, even if it is a reduced level of involvement, they are still helping. Potential participants should also be informed about why their feedback can be useful for the study, including feedback about why they want to stop taking part.*

*Information given to participants verbally and in writing should present a balanced view of changing their level of participation, making clear the advantages and disadvantages of different choices for the participant and for the study. This allows participants to make an informed choice about taking part and about changing their participation.*

1. **For the section on intervention delivery**

Protocols will often contain specific rules about when intervention should stop, for example due to adverse events. Guidance on writing this sort of content is available in several of the existing sources in the **References**, below, and is therefore not duplicated here.

The section on ‘stopping rules’ should reiterate the point that stopping study intervention does not mean that other aspects of participation have to stop. It could refer readers to the relevant sections in the ‘Participation changes’ section, namely about what actions to take in case of study intervention stopping (for any reason), and the process to follow when someone other than the participant decides that any aspects of participation should stop.

1. **For the section on study follow-up**

Ensure the follow-up schedule has been designed to be as easy or burden-free as possible for participants.

Make the schedule as flexible as possible without jeopardising study objectives or becoming unfeasible to manage. Flexibility could be in the frequency, timing or mode of follow-up assessments.

Consider giving options for continued participation with reduced time commitment, such as reducing frequency of follow-up, or explicitly allowing planned follow-up assessments to be skipped (if this could avoid participants stopping follow-up altogether).

Sometimes it might be preferable to leave the details of possible flexibilities out of the protocol, for example because there might be a few potential options. In this case, research staff could be instructed to contact the study coordinating centre to discuss potential options.

In the section on follow-up or the section on managing participation changes (see above), give instructions about how and when alternative follow-up options should be raised with participants.

Be clear about any limits on flexibility, i.e. where adjustments to frequency, timing and mode of follow-up are not possible (so the participant would have to stop follow-up; see section above on research staff deciding that participation will stop).

As required by the SPIRIT statement (see **References**), describe any other strategies in place to promote retention and complete follow-up.

1. **For the section on data sharing**

The data sharing section of the protocol should be clear about how participation changes affect availability of participants’ data for data sharing. Not all studies may rely on participants’ consent to share de-identified data.

Where studies are relying on consent, this could be a suitable situation to apply a ‘presumed ongoing consent’ approach, as mentioned elsewhere in this document. Where studies are relying on consent but not using a presumed ongoing consent approach, study teams will need to decide exactly how different participation changes will affect availability of data for data sharing.

 ***Suggested text***

***[Where not relying on consent]*** *All retained study data will be made available for secondary research, including for participants who stopped taking part in some or part of the study.*

***[Where relying on consent with a ‘presumed ongoing consent’ approach]*** *All study data will be made available for secondary research for participants who gave consent to this and did not explicitly withdraw that consent.*

1. **For the section on sharing study results with participants**

Information about how study 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.

 ***Suggested text***

*Participants who stop taking part in some or all of the study can still receive study results, if they want them. Research sites should keep a record of participants’ wishes about receiving study results.*

1. **For the section on statistical considerations**

The protocol, along with related documents (particularly the statistical analysis plan), should contain adequate information about how participation changes will be planned for and handled in study analysis. The rest of the protocol should also have input from statisticians to ensure the way the study is designed and run will support high quality analyses.

There is already considerable guidance available about what statistical content about participation changes should be included in protocols and statistical analysis plans. We are therefore not duplicating that guidance here, and instead refer to guidance given in the **References** section below, particularly guidance from the UK Health Research Authority and ICH, and in the publications with lead authors Gamble, Chan, Homer and Lynggaard.

# **References**

We have consulted the following sources in developing this resource:

* Chan A, Tetzlaff J M, Gøtzsche P C, Altman D G, Mann H, Berlin J A et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials BMJ 2013; 346 :e7586 <https://doi.org/10.1136/bmj.e7586>.
* Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337–2343. <https://doi.org/10.1001/jama.2017.18556>.
* Homer V, Yap C, Bond S, Holmes J, Stocken D, Walker K et al. Early phase clinical trials extension to guidelines for the content of statistical analysis plans BMJ 2022; 376 :e068177 <https://doi.org/10.1136/bmj-2021-068177>.
* ICH guideline M11: <https://www.ich.org/page/multidisciplinary-guidelines>.
* Kahan *et al.* The estimands framework: a primer on the ICH E9(R1) addendum BMJ 2024; 384 :e076316 <https://doi.org/10.1136/bmj-2023-076316>.
* Lynggaard, H., Bell, J., Lösch, C. et al. Principles and recommendations for incorporating estimands into clinical study protocol templates. Trials 23, 685 (2022). <https://doi.org/10.1186/s13063-022-06515-2>.
* SPIRIT statement: <https://spirit-statement.org/spirit-statement/>
* TransCelerate Biopharma Inc Common Protocol Template: <https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions/>
* UK Health Research Authority protocol templates: <https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/>.
* US National Institutes of Health protocol templates: <https://grants.nih.gov/policy-and-compliance/policy-topics/clinical-trials/protocol-template>

1. Kahan *et al.* The estimands framework: a primer on the ICH E9(R1) addendum BMJ 2024; 384 :e076316 doi:10.1136/bmj-2023-076316. [↑](#footnote-ref-1)
2. The concept of ‘intercurrent events’ is relevant to the estimands framework. They are defined in Kahan *et al.* as post-baseline events (or post-randomisation events in randomised trials) that affect either the interpretation or existence of outcome data. [↑](#footnote-ref-2)