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

Part 4: patient information, participant communication and consent

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PeRSEVERE collaborative group*

From the PeRSEVERE project: PRincipleS for handling end of participation EVEnts in clinical trials REsearch

PeRSEVERE

*** For a full contributor list, see https://perseverepriciples.org/about-persevere/.**

This guidance document is part of the PeRSEVERE project (PRincipleS for handling end of participation EVEnts in clinical trials REsearch). The full set of guidance available is:

- 1: General considerations
- 2: Policies and processes
- 3. Trial funding, protocol development and statistical planning
- **4. Patient information, participant communication and consent**
- 5. Risk assessment and monitoring
- 6. Training and support
- 7. Data collection about participation changes
- 8. Analysis and reporting

The suggestions in these guidance documents are more detailed than the general recommendations in the PeRSEVERE Principles and Explanation guidance (https://perseverepriciples.org/the-persevere-principles/). We still expect individual trial teams to make their own judgements, based on their knowledge of their trial, their research area, and the patients they work with. We recognise there will sometimes be good reasons to deviate from our recommendations.

Although we encourage use of this guidance in other settings, it has been written primarily for Registered CTUs within the UKCRC Network. This is reflected in the terminology used (e.g. ‘CTUs’) and some assumptions about trial settings. We aim to accommodate different arrangements of CTUs, sponsors and participants. This includes trials where CTUs have no direct contact with participants (i.e. because participants are only in contact with ‘trial sites’), trials where CTUs have some participant contact, and trials where there are no trial sites (i.e. where the CTU works only directly with participants). We have aimed to accommodate all trial designs, not just randomised controlled trials.

We use ‘trial staff’ as a general term to mean all those working on behalf of a trial, in any capacity. We use more specific terms where needed (e.g. ‘CTU staff’, ‘trial site staff’, ‘clinical staff’ etc). We use ‘trial team’ to mean those responsible for designing and managing the trial.

Key to notes and symbols used

- Links to specific PeRSEVERE principles are denoted by the relevant reference code in square brackets, e.g. **[O5]** with a link to the relevant principle's 'title' in a footnote.
- Symbols used in these guidance documents:

Indicates an area where more research is needed

Indicates a link to a different PeRSEVERE implementation guidance document

Contents

1. Informing potential participants

NB For the purposes of keeping this guidance focussed on management of participation changes, we have not covered other, more general considerations when communicating with patients and research participants. We suggest following all current guidance and best practice for how to make information engaging, understandable and accessible, and regarding which types of information or communications need ethical approval before use in a clinical trial.

a. How can information about changing participation be communicated to potential trial participants clearly and comprehensively, without being overwhelming?

Potential research participants must be made aware of their right to withdraw their informed consent at any time after having given it.

Trial staff must also be transparent with potential participants about the trial's approaches to managing participation changes so that the individuals can take this information into account

when deciding whether to take part in a clinical trial. This information can also inform decisions about their ongoing involvement if they do take part.

If some details of the approaches are not included in the pre-study information, it can be inappropriate (or even unethical or coercive) to mention them only later when a participant wants to stop taking part. For this reason, some of the approaches we recommend (such as the 'presumed ongoing consent' approach[1]) can only be validly applied if they are mentioned up front.

Participants should not be surprised by any limitations on what they can stop or 'undo'. Any such limitations must be made clear to potential participants before they agree to take part. The practicalities around changing participation should also be clear – what participants can expect to happen if they stop or

[1] 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)

change their participation, and what might be expected of them at that time (if anything).

This collectively constitutes potentially quite a lot of information to convey to potential participants about participation changes. This has significant potential to be overwhelming or contribute to well acknowledged 'information overload' and over-long clinical trial information sheets.[2] Arguably, much of the detail about participation changing is not so relevant at the point when a patient is deciding to start participating and it might seem strange or unhelpful to give it too much emphasis then.

A possible solution is to 'layer' the information. This can be done in two complementary ways. Firstly, layering of pre-trial information, with short-as-possible documents giving the key points that all potential participants need to know, and long-as-necessary detailed information available to those who want it (for example, online or on paper depending on patient preference). Secondly, assuming participants are given

[2] Symons & Davis (2022) Creating concise and readable patient information sheets for interventional studies in Australia: are we there yet? Trials. 23, 794. https://doi.org/10.1186/s13063-022-06712-z

information throughout their involvement in a trial (in line with the idea that consent should be ongoing), different sorts of information can be given different emphasis during the trial. For example, at the start of the trial the most important thing might be to confirm that the participant can change their mind about taking part whenever they want. At a later stage, should they be struggling to complete all trial activities, the information about participation changes becomes more relevant and can be highlighted. It may also be useful to consider what information the potential participant themselves is most interested to have.[3]

More research is needed to define the optimal split of information across these different layers in the context of information about participation changes.

It would be valuable to agree template wording for information sheets that could be acceptable for participants, ethics committees (who need to review and approve written trial information for potential participants) and suitable for trialists'

[3] Dranseika *et al.* (2017) Relevant Information and Informed Consent in Research: In Defense of the Subjective Standard of Disclosure. *Sci Eng Ethics.* 23(1):215-225. https://doi.org/10.1007/s11948-016-9755-4

needs. Use of graphics or visual aids could reduce the reliance on text.

It may also help avoid overwhelming participants to convey some points verbally as well as in writing (or potentially instead, though it may be important to always provide some of the points in writing). Trial staff training and experience and standardised processes can ensure the desired points are covered in discussions.

Trial staff should keep information balanced and calm, avoiding any risk of causing alarm. Others have suggested language emphasising ‘voluntariness’ and ‘encouragement’ over ‘requirement or expectation’ can reduce the risk of communications appearing coercive.[4]

[4] Lynch (2020) The right to withdraw from controlled human infection studies: Justifications and avoidance. *J Bioethics.* 34(8):833.838. https://doi.org/10.1111/bioe.12704

b. Considerations for information to convey (verbally and/or in writing) before participants agree to take part in a study potential participants[5]

Information for potential participants should be written with an understanding that **participation changes can take many forms,** rather than being a binary condition of participating/not, consenting/withdrawn **[O1[6]]**. Use language to convey this complexity. Suggestions for terminology to use are included in the PeRSEVERE Principles and Explanation document[7]. Consider 'participation changes' as a general term to cover all types of change.

Participants must be made aware that they have **the right to stop taking part in the study at any time**, without having to

[5] Some of the suggestions are derived from Kearney *et al.* (2018) Reducing attrition within clinical trials: The communication of retention and withdrawal within patient information leaflets. *PLoS ONE*. 13(10): e0204886. https://doi.org/10.1371/journal.pone.0204886

[6] O1 Participation can stop, reduce or change

[7] https://ukcrc-ctu.org.uk/wp-content/uploads/2022/04/PeRSEVERE-Principles-and-Explanation-January-2022.pdf

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 [O3[8]]**. They can also be told **why it can help the study when they give reasons for stopping, if they are happy to do so (or want to)**.

- When explaining about collecting as much as possible of the planned data, emphasise the main trial outcomes in particular. Make clear to potential participants what those are, how they are collected, when they are collected and how long they are collected for. The point should also be made positively. Explain how it is good for the study to collect more of the planned data or put this in the context of valuing participants' contributions, rather than referring to any potential negative impacts of missing data on trial results. Others have suggested it could be useful to take time to discuss any concerns the patient may have about the data collection process.[9]

[8] O3 The more data, the better

[9] Marie Curie Research: Missing data in palliative and end of life care trials.

- The point about providing a reason or motivation for changing participation can make clear what sort of information might be useful. This includes information to help trial statisticians assess whether the participation change has anything to do with the trial outcomes. Information on reasons for change can also inform the trial team about how they could improve the trial for participants. Participants can therefore also be reassured that they would not need to provide lots of additional, potentially sensitive detail about why their participation was changing. They should nonetheless be aware of the possibility that they may be asked if they would be happy to give a reason.
- All these points must be made sensitively, using wording approved by a research ethics committee (REC). Informing potential participants of these points gives them 'balanced' information **[D3[10]]** and allows them to make informed choices about stopping or changing their participation. It is unethical to put pressure on participants to continue participating in a study, or to provide a reason for stopping. However, it is also inappropriate to deny

https://www.mariecurie.org.uk/globalassets/media/documents/research/Missing-Guidance-Report-final-June-2022.pdf

[10] D3 Participant information about stopping participation

participants information about their choices, and information to guide those choices, if they may be keen to continue supporting the study as much as they can. Participants should be reassured that whatever they decide is acceptable, and there are no 'wrong' decisions.

It should be made clear that the **nature and extent of participation changes are primarily the participant's choice [O2[11]]**. This does not mean they would have limitless options to change, as they would still need to participate in ways that are safe for them and help the trial meet its objectives. Participants can be reassured that their choices would be made clear to them and that they would be offered help to understand their options and make the right choice for them.

Potential participants should get information about **generally what would happen if they decided to stop or reduce their participation later on.**

- This should include details of any particular action requested of participants, such as returning unused trial

[11] O2 Participants decide how their participation changes

medication, providing trial outcome data[12], or attending a final trial clinic visit for safety monitoring or other reasons. It should be clear that these requested actions are optional, or if they are more strongly encouraged, why that might be. Reasons for any requested actions should be made clear.[13]

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.**

- They can be advised to speak with their trial doctor or nurse **[D5[14]]** if they are finding participation difficult, in case something can be done to allow them to continue participating. It should be obvious to participants how to get in contact with the relevant person, and they might be provided with more than one way to do this. As above, it

[12] 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

[13] Gordon & Prohaska (2006) The Ethics of Withdrawal from Study Participation. *Account Res* 12(4):285-309. https://doi.org/10.1080/08989620600848645

[14] D5 Encouraging dialogue

should be clear to participants *why* they might be advised to do this.

- It may not be helpful to go into detail about the availability of reduced commitment options up front. Doing this might give a confusing message about what taking part in the study would involve or might encourage participants to opt immediately for the reduced option, therefore impairing the trial objectives.
- It could nonetheless be sensible to mention, if there is more than one trial site and site transfers are allowed in the trial, that the participant could decide to move to a different trial site (subject to that site's agreement). A link to further information (for example, online) about where the trial is running could be provided.
- It is still critical for trial teams to ensure that their 'standard' level of participation is as burden-free as possible for participants, and that they are only collecting data that is definitely necessary.

Depending on the nature of the trial and the treatments involved, 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.

- This may not be useful if it could cause participants unnecessary concern or worry, but may be important if a trial treatment is new and its safety is not well understood. Care must nonetheless be taken to express this in a balanced and sensitive way, to avoid unnecessary alarm or concern. Explain that the participant would be informed about any changes to their treatment and be able to ask questions.
- It should be clear that if trial intervention is stopped, if will be the participant's choice about whether aspects of participation will continue. It is possible to suggest that they will continue to be invited to further trial follow-up visits unless they object (in line with 'presumed ongoing consent' approaches).

Potential participants should get clear information about **what will happen if they lose contact with the trial staff during the trial [D4[15]]**.

[15] D4 Participant information about losing contact

- This includes any approaches trial staff might use to re-contact participants, or any plans for trial staff to contact other healthcare professionals (e.g. GPs, with participants' consent) to see if they have information on how participants are doing.
- It may be helpful to encourage participants to let trial staff know if they change their contact details during their time taking part in the trial **[D5[16]]**.

Mention any **limitations on participants' rights to stop or 'undo' aspects of participation**.

- This includes any limitations on participants' rights to have data about them deleted if it was collected before they decided to stop participating **[O6[17]]**. Participants could be reassured that the data about them will nonetheless be kept confidential. Collected data would also only be used in line with the consent that participants previously gave and with the information already given about how their personal data would be used (based on the 'transparency'

[16] D5 Encouraging dialogue
[17] O6 Retaining data

principle of data protection[18]). If steps will be taken to reduce the identifiability of retained data, these could also be communicated.

- It includes limitations on having any biological samples destroyed if they have already been used.
- It may not be possible to stop some sorts of data collection, such as collection of serious adverse event data in some clinical trials of medicinal products where this data collection is a statutory requirement.
- Content about limitations on rights could include the possibility of further contact with participants about the trial after they stop participation, regardless of their contact preferences. This might be necessary, for example, if there is any chance of the trial team deciding that it was in participants' best interests to share (via participants' clinical team) new safety information about the trial intervention.

[18] https://ico.org.uk/for-organisations/guide-to-data-protection/guide-to-the-general-data-protection-regulation-gdpr/principles/lawfulness-fairness-and-transparency/

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 [O5[19]].**

- This means if a participant says they want to stop taking a trial treatment (for example) but does not say (even after having been asked) that they want to have the other participation aspects stop, then those activities can continue.
- If this approach is taken, it must be clear to participants how they can express a wish for data collection to stop, if that is what they want. Trial staff must also make reasonable efforts to find out the participant's wishes (usually through discussion with the participant at the time they are stopping or reducing their participation **[D5[20]]**).
- Regarding data collection, it should be clear that data **generated** prior to any participant decision about stopping data collection would still be collected for the trial **[O5]**

[19] O5 Continuing data collection

[20] D5 Encouraging dialogue

(unless the data collection itself has confidentiality considerations **[Part 2[21]]**).

- The approach could be linked to the 'participation tiering' idea **[Part 3[22]]**. For example, if a participant says they want to stop taking part but do not clarify further exactly how they want their participation to stop (even after having been asked), then a particular participation tier could apply (e.g. 'active' elements of participation stop but 'passive' ones continue). This must be made clear up front if this is the approach.

- Consider if it might be helpful to convey *why* this sort of 'presumed ongoing consent' position is taken, if it might otherwise sound unfair or unreasonable.

It should be clear that **stopping or changing participation will not mean that participants cannot receive the results of the trial** or other information **[O7[23]].** Participants could be asked for their preferences about receiving trial results when

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

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

[23] O7 Information after stopping participation

they agree to take part in the trial. They could be advised about how to update their preferences if they change their mind.

It should be clear what would happen to participants' involvement in the trial if they were to lose capacity to give consent. See further guidance on this topic elsewhere.[24]

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.

[24] https://www.capacityconsentresearch.com/

2. Consent

a. When to rely on consent

Consent needs to be sought for any aspects of managing participation changes that have implications for participants' confidentiality, or where planned trial processes might otherwise be considered by participants to be intrusive or burdensome (or not otherwise within participants 'reasonable expectations'[25]). An example mentioned elsewhere in this guidance is where trial staff might contact people other than the participant in the case that trial staff and participants have lost contact with each other **[O4[26]]**.

In some cases, it may be appropriate to seek others' consent. For example, if trial staff would like to collect details of a primary contact, then it would be fair to ask for that person's consent to involve them in the trial (although consent would not

[25] https://www.gov.uk/government/speeches/reasonable-expectations

[26] O4 Losing contact

have to be the lawful basis for processing their personal data under the UK General Data Protection Regulation[27]).

b. When it may be better not to rely on consent

Consenting to a 'presumed ongoing consent' approach: elsewhere in this guidance, the idea of a 'presumed ongoing consent' approach is suggested. This can justify continuation of data collection or other low-impact aspects of participation until participants explicitly say they want them to stop. Although this sort of approach needs explaining carefully to potential participants, and may not be considered acceptable by everyone, it is not advisable to rely on participant consent to apply it, i.e. to ask participants to *consent to the consent approach*. This would take a form like: "Do you consent to data collection continuing until you explicitly say you want it to stop?"

[27] https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-detailed-guidance/legal-basis-processing-data/

The ‘presumed ongoing consent’ approach aims to provide clarity where information is not available about participants’ wishes regarding specific aspects of trial participation. This is necessary partly because trial participation often comprises a range of activities, some of which involve more active involvement from the participant than others. The active aspects are more burdensome, tangible and obvious to participants, so it stands to reason that participants would be much more likely to say they want these to stop, and less likely to comment on the more passive aspects unless prompted to do so.

If we were to rely on participants’ consent to apply the presumed ongoing consent approach, the ongoing consent *to the approach* would likely be a ‘passive’ aspect of participation that participants might be less likely to spontaneously say they want to stop. This could therefore be another point about which participants’ wishes were not known when they stopped or reduced their participation.

In that case, trial staff could decide to assume that consent to the presumed ongoing consent approach had been withdrawn. This would negate any benefits of the approach because any

aspects of trial participation relying on the presumed ongoing consent would also then need to stop.

Alternatively, trial staff could decide to apply a presumed ongoing consent approach to the presumed ongoing consent i.e. assuming the *consent approach remained valid* until the participant explicitly said they no longer accepted it. This would call into question the value of asking for consent at all.

Instead, we recommend being fully transparent about any presumed ongoing consent approaches and allowing participants to consent to trial participation – or not – on that basis.

Consenting to be asked for reasons behind participation changes: others have suggested that participants should be asked to give consent to be asked about why they want their participation to change.[28] We would not recommend this. It

[28] Marie Curie Research: Missing data in palliative and end of life care trials.

could increase the complexity of consent processes, and raises further complications at the time a participant wants to stop taking part in a trial.

For example, imagine if a participant were to say simply that they want to ‘withdraw from the trial’, having previously given trial consent that included specific consent to be asked for their reasons for wanting to stop. In this case, it could be difficult to ascertain whether that previous consent to be asked for a reason still applied, or whether it had been withdrawn along with other elements of their consent. Potentially a presumed ongoing consent approach could be applied, however we suggest it may be preferable to rely on the more general idea of *assent*, i.e. checking more informally whether the participant might provide a reason, but respecting their choice in any case.

https://www.mariecurie.org.uk/globalassets/media/documents/research/Missing-Guidance-Report-final-June-2022.pdf

3. Informing participants' decisions about changing their participation

Participants' decisions about changing participation need to be mainly informed by information given before they initially consented to take part. This is important so that they can take the conditions of early stopping into account when they make that initial decision.

While participants can decide to stop only based on the prior information, there may be ways to remind them of their choices, such as via discussions with trial staff about participation **[D5[29]].**

Informed consent is often described as being a process rather than an event.[30] Arguably, participation changes should be viewed in the same way, beginning with a participant's doubt

[29] D5 Encouraging dialogue

[30] O' Sullivan *et al.* (2021) An evaluation of the process of informed consent: views from research participants and staff. *Trials.* 22, 544. https://doi.org/10.1186/s13063-021-05493-1

about or difficulty with completing trial activities, and concluding with a participation change being carried out, along with any resulting, related actions.

Information could be important throughout this process. Alongside information being provided verbally to help the participant decide what to do, they could be reminded about the content in the original pre-trial information sheet, or given another copy if needed. If any sort of form is used to collect information on participants' wishes (see below) then this might also contain information to help guide choices, such as the implications, benefits and drawbacks of the different options. Clearly, any such wording would need ethical approval before use. It could likely only repeat points made in the pre-trial information, rather than making them for the first time when participants are considering stopping taking part.

4. Communication after stopping or reducing participation

Information provided *after* a participant stops or reduces their participation may serve a more supportive purpose. Participants who stop or reduce their participation before it was originally due to end may have specific 'information needs', particularly as stopping participation can be a difficult experience.[31,32,33] Participants may wonder what will happen next with their care or their involvement in the trial. They may not remember all the detail given before about the implications of stopping participation, so may appreciate a reminder.

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[31] Ulrich *et al.* (2021) Experiences of Patients After Withdrawal From Cancer Clinical Trials. *JAMA Netw Open.* 4(8):e2120052. https://doi.org/10.1001/jamanetworkopen.2021.20052

[32] Wilson *et al.* (2005) Enhancing cancer trial management: An intervention study of the impact of providing information, trial results and support to patients in phase I and II anti-cancer drug trials at trial conclusion. *Clinical Effectiveness in Nursing.* 9(3-4) 119-132. https://doi.org/10.1016/j.cein.2006.06.003

[33] Eborall HC *et al.* (2011) Accrual and drop out in a primary prevention randomised controlled trial: qualitative study. *Trials*. 11;12:7. https://doi.org/10.1186/1745-6215-12-7

Some of the relevant information may be conveyed routinely by clinical staff, for example about what will happen next regarding participants' care, or any specific arrangements for safely stopping trial intervention **[Part 3[34]]**.

Other points might not always be covered, for example confirming exactly how participation has changed and which aspects of participation may continue. When any aspects of participation stop because of decisions made by people other than the participant, the participant should have the decision and rationale explained to them and have the chance to ask questions of an appropriate person. CTUs may be able to provide training and tools to help ensure trial site staff convey all of these other points, verbally or in writing **[Part 6[35]]**.

It may be useful to provide participants with a written communication at the time they stop or significantly reduce their

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

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

participation (i.e. an ‘end of participation information sheet’ or similar).

This can explain to participants what will happen next, confirm exactly how their participation has changed, remind them of the implications of changing their participation, and remind them what choices remain for them about their participation. It can also include a reminder of any aspects of participation that are continuing, either because participants’ rights to stop or undo them are limited, or because a ‘presumed ongoing consent’ approach applies. Where such an approach applies, participants can be reminded how to say they want those aspects to stop, if that is what they want.

The information sheet could also confirm to participants what further contact they should expect about the trial (if any), based on their previously given contact preferences. Detailed guidance is available for trial teams who would like to implement this sort of written communication, or otherwise to consider how to communicate these points to participants.[36]

[36] https://ctru.leeds.ac.uk/information-to-support-participants-who-stop-taking-part/

It is conceivable to send a similar communication when trial staff have lost contact with participants (based on the protocol's definitions and guidance about this **[Part 3[37]]**) as long as the participant's main contact details are thought to still be correct. This could include similar information to the communication mentioned above, with confirmation of the participant's change in participation status, and any information about what further attempts at regaining contact (if any) the participant might expect.

As well as asking participants if they would be willing to provide information on their reasons for changing their participation, it may be useful to ask if they have any feedback on their experience in the trial. This could be useful to help improve the trial processes (with potential knock-on benefits for recruitment or retention) and improve participants' experiences participating in trials more generally. It is even not out of the question that this feedback process could lead to further discussion about difficulties the participant experienced in the trial, and ways they could, in fact, continue to contribute. This should not be ruled out, as long as the decision is informed and freely given

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

[O2[38]], though it would be understandable if trial staff only felt comfortable to discuss this if the participant instigated that conversation.

[38] O2 Participants decide how their participation changes

5. Other ways to support freely-given participant decisions

According to the PeRSEVERE principles, the nature and extent of participation changes should primarily be driven by informed, freely-given decisions by participants **[O2]**.

We acknowledge that achieving this may be a challenge. For example, it could be challenging to ensure participants make a truly 'informed' decision while not making this information step any sort of barrier to stopping participation. Given participation in trials can be multi-faceted **[O1[39]],** there is a risk of participants being overwhelmed by choices (though the use of 'tiers' of participation could help with this **[Part 3[40]]**). It may benefit the 'informedness' of decisions for participants to discuss what they want to do with someone **[D5[41]]**, but their main trial contacts may have a real or perceived conflict of

[39] O1 Participation can stop, reduce or change

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

[41] D5 Encouraging dialogue

interest (in that they work on the trial) which could affect how ‘freely-given’ the participant’s decision can be.

Below, we propose some mechanisms that may support participants to make informed and freely-given decisions about how they want their trial participation to change. Some of these may already be done to some extent. We acknowledge challenges or risks inherent in some of these proposals, so they should be adopted only if the likely benefits outweigh those risks.

Further work to assess the feasibility of these proposals and exactly how to put them into practice would be welcome. 

a. **Participants could be offered an optional form to confirm how they would like their participation to change.**

This would always need to be optional, and it would need to be clear for participants that they could stop their participation without completing the form.

The benefits of completing the form could be conveyed on the form, i.e. it helps make clear to the trial staff exactly what the participant wants to do.

The form could reduce the complexity of choices by offering the participant 'tiers' of participation **[Part 3]**. Information on the form would explain what each 'tier' involves and whether there is further flexibility (i.e. other options not mentioned in the tiering).

The form could give participants an opportunity to explain the motivation(s) or other factors influencing their participation change, if they are happy to do so. They could be reminded of why this can be useful to those running the trial. Specific questions or standardised lists of possible reasons (rather than open questions) could help reassure participants that only a certain amount of detail is needed **[Part 7[42]]**.

The form could include questions about participants' preferences for further contact about the trial, for example to

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

find out if they would still like to receive trial updates and the overall results of the trial when they are ready.

The form could be in a standalone paper or electronic format or could be part of an eConsent system. (Other examples of participants managing their ongoing consent more closely via 'dynamic consent' systems have been reported in the scientific literature previously.[43,44])

b. Participants could be given the chance to discuss their participation with someone independent of the usual trial staff.

This could help remove the impression of conflict of interest when the participant discusses their participation with trial staff.

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[43] Kaye *et al.* (2015) Dynamic consent: a patient interface for twenty-first century research networks. *Eur J Hum Genet.* 23, 141–146. https://doi.org/10.1038/ejhg.2014.71

[44] Williams *et al.* (2015) Dynamic consent: a possible solution to improve patient confidence and trust in how electronic patient records are used in medical research. *JMIR Med Inform.* 13;3(1):e3. https://doi.org/10.2196/medinform.3525

(Trial staff have themselves reported difficulties managing their 'dual roles' in giving clinical care and running the trial.[45])

The expectation would be that the 'independent' person would be able to give balanced advice, understanding the pros and cons of different options from the point of view of the participant and the trial.

The independent person may need specific training to fulfil this role. It could be someone with clinical expertise or not. It could be someone affiliated with the trial (e.g. the 'concierge' role used in some pharmaceutical-sponsored trials[46]) or affiliated with a trial site, or a representative of a relevant charity or support organisation.

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

[46] https://www.ppd.com/blog/value-patient-concierge-services-clinical-trials/

c. Participants could be offered a route to stopping their participation without having to speak to anyone.

This might primarily need to be online, but it could conceivably be done by post or automated phone line. It could alternatively be a built-in part of an eConsent system.

Some evidence suggests that some participants feel awkward about saying they want to stop taking part, or feel they might be letting the trial staff down.[47] This may be the reason for some cases where contact is lost between trial staff and participants, i.e. the participant wants to stop taking part but does not want to talk to anyone about it.

A 'risk' with this approach is that participants may not be making an informed decision (as PeRSEVERE principle **O2**[48] says they should), i.e. they may not have understood the implications of their decision for them or the trial. If may be

[47] Eborall *et al.* (2011) Accrual and drop out in a primary prevention randomised controlled trial: qualitative study. *Trials*. 11;12:7. https://doi.org/10.1186/1745-6215-12-7

[48] O2 Participants decide how their participation changes

possible to implement the approach in ways that do help inform the participant about the main implications.

It would not be ideal if participants mistakenly thought this was the main way to communicate that they wanted to stop participating (as opposed to choosing this route only because they did not want to talk to the trial staff about their participation).

It is therefore important to consider whether the benefits outweigh these risks, and to implement this approach with care. Emphasis should still be placed on having a conversation with the trial staff as the preferred option where that was acceptable to the participant **[D5[49]]**. The benefits of the discussion to the participant could be made clear, particularly the possibility to keep contributing in some different way.

The option to stop or reduce participation without speaking to anyone should be considered alongside the participation

[49] D5 Encouraging dialogue

‘tiering’ **[Part 3[50]]**, i.e. regarding which participation tier the participant moves to following a notification via this route.

A potential benefit of the approach might be to reduce the number of participants recorded as having lost contact with the trial, by giving participants a way to confirm their wishes without having to speak to someone, at least providing some clarity for the trial team in the process.

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

6. Other participant communications

There may be other occasions where it would be useful or necessary to convey information to participants about participation changes. All communications should be written with an understanding that participation changes can take many forms **[O1[51]]**.

Sometimes trial participants are given contact cards (or other trial-related information in a similar format, e.g. diary cards for recording when they take their trial intervention). These could include the message to contact trial staff if they are having any trouble completing any trial activities, or a general message about what to do if they might like to reduce or change their level of participation in the trial. If any of the additional mechanisms mentioned in section **5,** above, have been implemented, then these could be mentioned as well.

Newsletters or other communications provided to participants during their time on trial could remind participants of some of

[51] O1 Participation can stop, reduce or change

the points covered in the pre-consent information, including about rights to stop taking part, reminders about 'passive' aspects of participation such as data collection from routine sources, or the importance of retention and collecting as much of the planned data as possible. As mentioned above, most content about participation changes needs to be provided up front so that participants can take it into account when deciding whether to take part. However, it can help reduce the potential for information overload to give different information different emphasis at different times, depending on how relevant it is to participants' current stage in the trial.

Processes to ensure trial results and other important trial-related information are easy to find on the internet can help address PeRSEVERE principle **O7**[52]. This sort of general communication means many participants can more easily find this information regardless of how their participation changed during the trial.

[52] O7 Information after stopping participation