

Notes on using these slides

- We have made these slides available as a re-useable resource, allowing others to learn about PeRSEVERE and present PeRSEVERE content to others.
- Please feel free to re-use and amend the slides as needed for the situation. If possible, make clear which content is from PeRSEVERE and which is your own additions.
- In the Notes section, you will find explanatory text to go with each slide (unless it is self-explanatory).
- Please leave in the final acknowledgements slide.



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Part 1: introduction to PeRSEVERE



“Participation changes”

- Persevere is about participation stopping (wholly or partly) before originally due to stop
 - Explicit participant wish (‘withdrawal of consent’)
 - Loss of contact (‘loss to follow-up’)
 - Others recommending/deciding participation should stop (‘clinician withdrawal’)
- In/out of scope
 - Improving how participation changes prepared for and managed
 - Relevant in any research with some sort of active, ongoing participation
 - **Not** changes in capacity to consent
 - **Not** participants dying while study is ongoing
 - **Not** about reducing proportion of participants who decide to stop taking part
 - **Mostly not** about collection/storage of biological samples
 - **Mostly not** about consent as it applies to privacy, confidentiality, consent to use personal data

- The Persevere project is about managing ‘participation changes’ in clinical trials and other research. This includes most situations where participants stop or reduce (or increase) their level of involvement. The most common scenarios may be a) where a participant says they want to stop taking part, b) where a participant and researchers loss contact with each other, and c) others – particularly clinicians – recommend or decide that some aspects of participation should stop.
- “Withdrawal of consent” is a crucial idea in research ethics – that participants can withdraw their consent to participate at any time, without having to give a reason and without detriment. However, it is not the only possible source of participation changes.
- Is Persevere about improving ‘retention’ in studies, i.e. trying to get as many participants as possible to provide study outcome data? Yes, but not directly. If Persevere’s recommendations are followed closely, then there may be some improvements in retention compared with the status quo (though we need more evidence to demonstrate this). Some in the UKCRC Registered CTU Network have seen cases where a participant’s involvement in a study changes to a greater extent than would seem to be justified (by participants’ wishes or anything else). Persevere aims to address this point in particular. If participants’ involvement changes only as much as justified, in some cases this might mean study outcome data is collected where it could have been missed.
- Some specific areas are not (or mostly not) in scope of Persevere.
 - Changes in capacity to consent are addressed in some detail already by laws and guidance (in a UK setting, in any case). The Persevere steering group therefore agreed it would not be useful to include this within the Persevere scope.
 - Participants dying while a study is ongoing is out of scope, because mostly Persevere is about what happens after participation changes – and clearly in the case of participants’ death, there is limited scope for anything to happen from the participants’ point of view. Various rules and policies are clear that collected study data is retained in that scenario.
 - Issues of consent as they relate to human tissue samples, and privacy/confidentiality/personal data use are mostly out of scope. The Persevere steering group agreed that these were either too general and not specific to research, and/or there was already enough guidance around to support researchers with these topics.

What is the PeRSEVERE project?

- PeRSEVERE: PRincipleS for handling end-of-participation EVEnts in clinical trials Research
 - Devise principles to guide how trials should be designed and run given some participants will stop, reduce or change their participation before it was originally due to end
 - Explore how to implement the principles
- Not all *new* ideas; perhaps first attempt to produce **comprehensive** list



- The full title of the project is PRincipleS for handling end-of-participation EVEnts in clinical trials Research
- There were two aims: devise guiding principles, and explore how to put them into practice. Overall, it's about managing 'participation changes' (see later slide) in ways that do the best by study participants and studies.
- It is important to note that the ideas in PeRSEVERE are not all new, but they are probably the first attempt to bring all relevant ideas into one place

Shared desire for change within UK CTUs

- In 2019, >80% Registered Clinical Trials Units agreed there was a problem to solve
- Prior to 2019 workshop, attendees asked “what are the top three things that could be done better in handling withdrawal or loss to follow-up in ongoing trials?”

Suggestion	% responders (n=35) giving this answer
More clarity regarding what is being withdrawn from / different 'levels' of withdrawal possible	40
Improve site training / knowledge around handling withdrawals	34
Give participants more choice about follow-up method/timing and/or reduce burden of follow-up	26
Use clearer terminology / definitions	26
Make clearer protocol instructions / ensure clear procedures in place for handling withdrawal	23
Continue collecting data post-withdrawal where possible	20
Better data collection (trial forms etc)	20

- The project started because of a shared desire across the UKCRC Registered Clinical Trials Unit Network to improve how participation changes were planned for and handled. A large majority of trials units agreed with the suggestion that there was a problem to solve, and expressed an interest in helping solve it.
- The table on this slide shows some responses to a pre-workshop survey in 2019 about what could be done better – this should help illustrate what PerSEVERE is about.

Ethical reasoning behind PeRSEVERE

- Recognising participants' right to stop taking part in research at any time, without detriment and without having to explain their decision
- *And* recognising the role (duty of care) of those overseeing participants' care (and their participation in general) to recommend that aspects of participation should stop
- *And* that participants' rights & interests always come first versus those of science and society (where there is potential conflict)



- The Persevere principles are not just about improving study quality or study retention. They do not contradict existing ethical research principles, but rather build on them – in particular the Good Clinical Practice aims of promoting participants' interests and study integrity (i.e. the interests of future participants, who would be affected by the results of each study).
- This and the next few slides cover the ethical reasoning supporting the Persevere principles.
- Firstly, we recognise the well-established 'right to withdraw consent', as in GCP. Persevere does not change this.
- Secondly, as part of protecting individual participants, it is important that those with a duty of care have the ability to recommend that aspects of participation should stop where they might otherwise not be in the participant's best interests.
- Thirdly – again as per GCP – individuals' rights come first above those of science and society (where there is potential conflict).

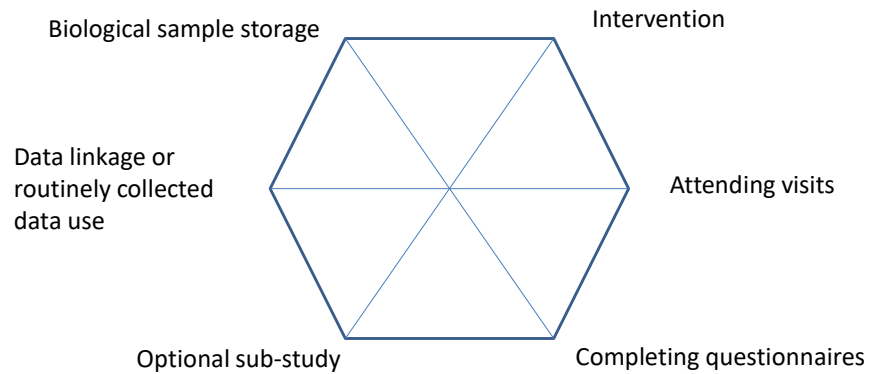
Ethical reasoning behind PeRSEVERE

- *However*, also recognising that participation changes can come in many forms



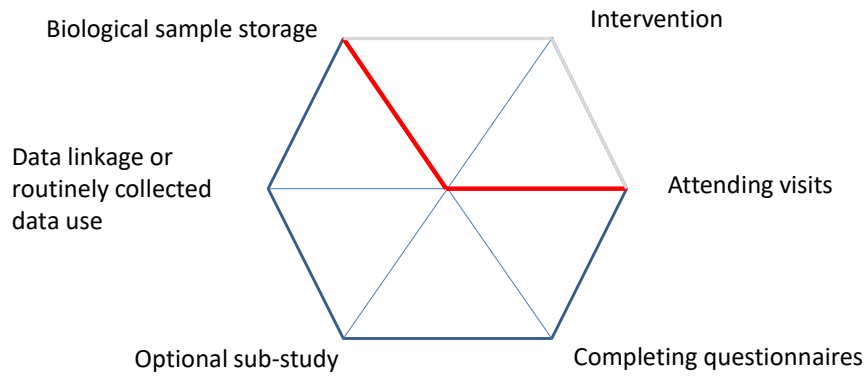
- But we also need to recognise that participation changes may come in many forms. The next few slides illustrate this.

Participation can stop *or change* (1)



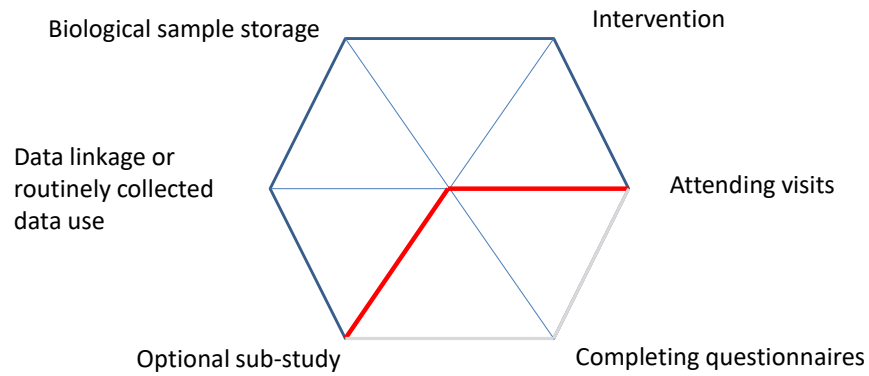
- The hexagon is just an example, illustrating a hypothetical study with 6 aspects of participation (we could imagine more).
- At the start of participation – assuming a participant agrees to all optional aspects of a study – all these aspects would be happening.

Participation can stop *or change* (2)



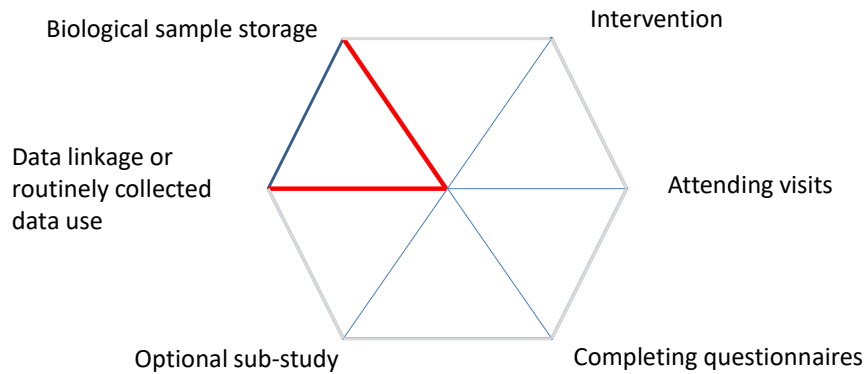
- A participant might stop receiving study intervention but carry on with everything else – in which case we could think of their participation being more like this (red line)

Participation can stop *or change* (3)



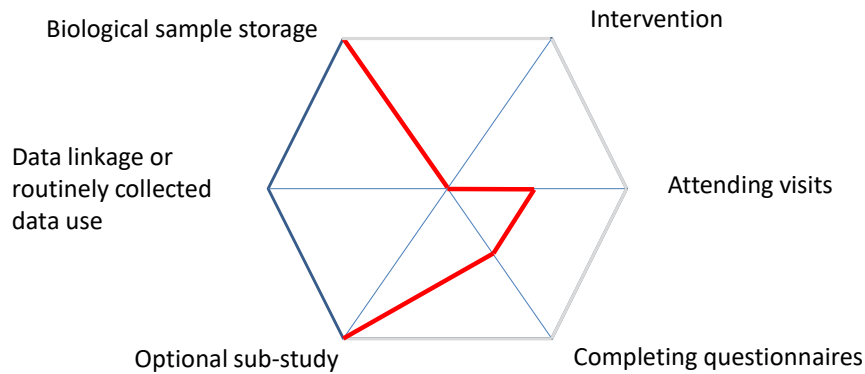
- They might just stop completing questionnaires, in which case their participation looks like this.

Participation can stop *or change* (4)



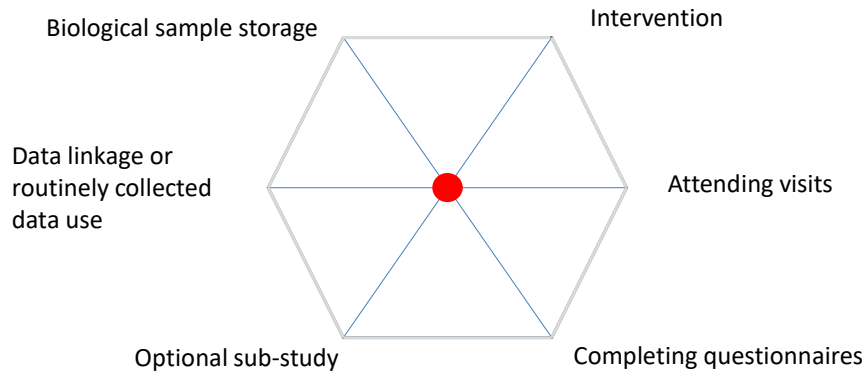
- They might stop all *active* aspects of participation – where they have to do something. Their participation might then look like this, with just the more ‘passive’ aspects happening.

Participation can stop *or change* (5)



- It might be possible for them to change their participation in more complex ways, for example like this – no more intervention, only attending some visits and completing some questionnaires. This would only be if they want to do this, if it's feasible for the research team to manage it and if it still helps the study meet its objectives.

Participation can stop *or change* (6)



- The participant might stop doing more or less everything, then their participation might look like this – though we know that data about them that has already been collected would usually be retained and used in the study analysis.

Ethical reasoning behind PeRSEVERE

- *And* remembering that it is also a fundamental part of 'good clinical practice' that the results of studies should be as reliable as we can make them – impact on future patients



- This is the other important aim of GCP. While we prioritise participants' interests, we also need to guard against any factors that could impact on study integrity/quality – as this affects patients in future.

Ethical reasoning behind PeRSEVERE

- Therefore *everyone's* decision-making regarding participation changes should be with the knowledge/understanding that if key planned study data is not collected, the study will be less reliable
- And therefore the extent and nature of participation changes should be in line with participants' wishes – no more, no less
 - Though with safeguarding by those responsible for care/treatment
 - And only within limits allowed by each study



- Where the first point here mentions 'everyone', this means *everyone* – research staff but also participants, if possible. It does not mean that this consideration overrides others, but that it should not be forgotten – it should be part of anyone's decision-making about changing participation.
- All of this means leads to the last point here – that the *extent and nature* of participation changes should be in line with participants' wishes. This goes further than most existing regulatory and ethical texts, which tend to focus on 'withdrawal' as a more binary idea – i.e. participants might be taking part or withdrawn (and nothing in between).
- The caveats on the last point are important – safeguarding from those with a duty of care, and participation changes may only be within limits allowed by each study in terms of feasibility and making sure the study's objectives are being met. It would not be ethical for a participant to continue participating in some way that does not actually help the study meet its objectives.

Aiming to achieve balance

Researchers assuming that participant expressing *any* indication of doubt about participation means *all* aspects of participation must stop

Too cautious? Detrimental to studies *and* participants

Researchers reacting to participants' wishes by carrying out the minimum extent of participation change they can 'get away with'

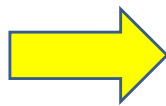
Researchers implementing onerous processes around participation changes (e.g. only allow stopping participation once individuals have read information sheet and confirmed in writing what they want to do)

Unethical; inadequate upholding of participants' rights; detrimental to studies in the long-run



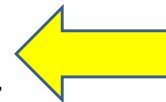
- The idea of 'balance' is important in the Persevere principles. But what are we are trying to 'balance' between?
- The following slides introduce this idea and explain the relevance of some of Persevere's 'overarching' principles.
- This slide explains the 'extremes'.
- On the one hand, we *could* assume that a participant expressing any doubt about their participation means all aspects of participation have to stop. This can be detrimental to studies for obvious reasons, as it means less outcome data might be collected. It can also be detrimental to participants as they might be interested (or it might be advantageous to them in some way) to continue participating but with reduced involvement, rather than stopping altogether.
- On the other hand, it is hypothetically possible for researchers to assume every expression of doubt from participants should be interpreted as 'minimally' as possible. This would be difficult to justify, ethically.
- If we accept the previous point that the extent of participation changes should be in line with participants' wishes, it seems important to have some process in place to establish what participants want to do. However, this can't get in the way of participants stopping without speaking to anyone or putting anything in writing.
- Both of these latter points pose are ethically difficult, and they are also likely to harm studies in the long-run as people may be less likely to take part under these conditions.

Aiming to achieve balance



Middle ground:

Extent and nature of participation changes to be informed, freely given decision by participant (as far as possible – Persevere principle O2)

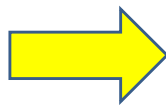


Avoiding the assumption that participants' wishes to stop or reduce their participation means all *involvement* needs to stop (principle O2 and O7)



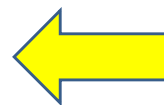
- So how could we achieve balance between these extremes? Some suggestions are given here.
- First, as we've already said, the extent and nature of participation changes should be an informed and freely-given decision by the participant. Persevere principle "O2" covers this.
- We should also not assume that an expression of doubt about participation means all involvement has to stop. This is covered by the same O2 principle, and also O7 – O7 says that stopping participation does not mean participants should not be able to get information they might want or need (such as information about the results of the study).

Aiming to achieve balance



Middle ground:

Accepting and being transparent about limitations on participation changes, including 'undoing' work already done (principle O6)

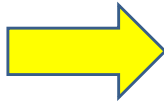


In some limited, conditional cases, allowing the assumption that previously given informed consent persists e.g. 'clinician withdrawal', loss of contact, continuing data collection (principles O2, O4 & O5)



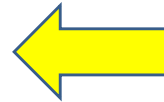
- We should recognise that not every imaginable participation change is possible (either from a practical point of view, or because of legal or ethical standards). Persevere principle O6, for example, confirms that data already collected until the point a participant says they want to stop data being collected, is retained and used in study analysis. We should be transparent with (potential) participants about these limitations.
- In some specific and limited cases, we can take previously given consent to stop be in place. There are several conditions to meet for this to be done fairly and transparently – and if there is doubt about whether it is fair then the approach should not be used. These conditions include being clear with potential participants before they take part in a study that their consent may be assumed to persist in some cases, and making reasonable efforts to find out what participants want to do when they say they want to stop taking part. More detail about the conditions is given in the Persevere guidance (see principle O5 on the website: persevereprinciples.org).
- The cases mentioned here where presumed ongoing consent could apply:
 - 'Clinician withdrawal' – where a doctor or other clinician recommends that some aspect of participation should stop, then that aspect stops but other aspects can carry on (under presumed ongoing consent) unless the participant says they want them to stop. Persevere principle O2 covers this.
 - 'Loss of contact' – Persevere principle O4 says that loss of contact between researchers and participants is not the same as participants saying they want to stop taking part. It is possible to assume that loss of contact means a participant wants to stop taking part, or that it means they do not – but either way, it is an assumption. In the case of loss of contact, it can be possible for some aspects of participation to continue (for example data collection from routine medical appointments) under presumed ongoing consent, assuming that the participant has not said they want those aspects to stop.
 - 'Continuing data collection' – Persevere principle O5 says that data collection - and sometimes other aspects of participation – should continue until participants say they want it to stop. As mentioned above, this is only fair if certain conditions apply.

Aiming to achieve balance



Middle ground:

Take a cautious approach - applying caveats, conditions and 'safety nets' throughout the approach so any assumptions affecting participants' rights **only** applied when they are reliable/justified, and only done in a transparent and fair way



- It is still important to be cautious and conservative, erring on the side of protecting participants' interests (as per GCP). As it says here, any assumptions affecting participants' rights (including anything to do with presumed ongoing consent) are only applied when they are reliable and well justified.

Developing the Persevere principles

- Collaboration based within UKCRC Registered CTU Network
- Discussion, debate, informal consensus
- Public consultation in 2021
- Final principles have input from over 300 people – various backgrounds and from outside UK



- The project started in 2019 when a query was sent around the UKCRC Registered CTU Network asking which clinical trials units had faced challenges managing 'withdrawal' in their studies. A large proportion of trials units responded to say they had experienced challenges and would be interested to contribute to a project addressing these challenges.
- A meeting was held in October 2019 to discuss the issues and start to focus on what 'should' happen with regard to participation changes, considering various areas such as participant information, site training and study reporting. Various different disciplines were represented at the meeting – including trial managers, data managers, statisticians, QA staff, trials unit leaders and others from over 30 trials units.
- Following the meeting, groups were set up to develop guiding principles in the same areas, plus a new group to consider 'overarching' principles. A patient and public involvement group was set up to contribute to development of the principles.
- After an iterative process of drafting and feedback, the draft principles were put made public in a consultation in 2021.
- The feedback from the consultation was that the principles were already clear and acceptable, but feedback was nonetheless used to refine the principles before finalisation.
- We collated all the more practical suggestions into 'implementation guidance', explaining how the Persevere principles can be put into practice. This included results of additional 'piloting' work within the Registered CTU Network to find out more about how trials units could respond to Persevere.

Part 2: the PeRSEVERE principles

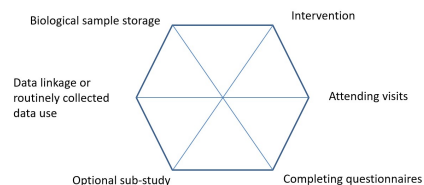


Overarching principles (O)

O1 Participation can stop, reduce or change: Everyone running or taking part in studies should be aware that participants may choose to **change, reduce or stop their participation** after they agree to join the study.

All **language and communication** about any participation changes should be clear about exactly what has changed, reduced or stopped, and what has not.

- Deals with binary misconception & resulting language



- The principles all have a short code for reference – reflecting the group they are in. O is for the ‘overarching’ group, D is for study development and participant information, M is for data management and monitoring, and R is for analysis and reporting.
- All the principles also have a short ‘title’ (the bit in bold here) aiming to communicate the principle’s purpose in a few words.
- The ‘overarching’ principles aim to set out an ethical approach to managing participation changes, aiming for the ‘balance’ mentioned earlier.
- The first principle, “O1” addresses the issue of participation changes incorrectly being considered a binary issue. It says that everyone – i.e. including study participants – should be aware that participation could change, reduce or stop. This includes, in some cases, *increases* in participation. Use of suitable languages around participation then follows.
- We can all have a role in implementing this principle by checking our own understanding and use of language, and encouraging others not to use language that suggests ‘withdrawal’ is a binary phenomenon.

Overarching principles (O)

O2 Participants decide how their participation changes: The nature and extent of participation changes should be the **participant's decision to make**, within the limits of what is possible for a given study. Their decision should be informed and freely-given.

The only exception to this is where aspects of participation need to **change or be stopped by someone else in order to protect a participant's safety or well-being**.

- New principle following consultation



- (Slide 1/3 on this principle, some aspects explained more on subsequent slides)
- Principle O2 confirms that the *nature and extent* of participation changes should be participants' choice. This is on the basis (as per O1) that participation can reduce or change as well as just stopping.
- This principle was added following the consultation. Although we had included similar ideas in our principles' introductory text, some consultation responses highlighted concerns that the Persevere principles meant a 'watering down' of participants' existing rights to withdraw their consent without having to give a reason and without detriment. By adding this principle, we wanted to emphasise that Persevere *builds on* existing ideas of Good Clinical Practice, rather than contradicting them.

Overarching principles (O)

O2 Participants decide how their participation changes

- Participation changes to have same qualities as informed consent
 - Informed
 - Freely-made (though guidance / advice likely helpful)
 - Avoid overloading with information or choices
 - Choices must not get in the way of stopping all aspects
 - Within limits of study (communicate to participant what limits are)



- Participants' decision should be informed and freely-given, in the same way as initial consent. This does raise some potential challenges.
- For example, how can we make sure that participants' decisions are well informed, including about the pros/cons of different levels of involvement in a study both for them as individuals and regarding the whole study?
- And how can we make sure the decision is freely-made despite that potentially conflicting information about pros and cons, and despite any study processes in place to inform them and establish what they want to do?
- One thing to avoid is information or choice overload. There might be many ways for participants to change their level of involvement, hypothetically, but it might be more manageable to present only a few choices – perhaps as 'levels' of involvement in a study.
- Giving participants choices cannot get in the way of stopping all aspects of participation, if that is what participants want to do.
- One final complexity is that there will usually be limits on what participation changes are possible – for example, it would not be possible to change in ways that are unsafe, unfeasible or do not meet the needs of the study. These limitations need to be made clear to participants, perhaps during discussions when they are considering stopping or reducing their participation.

Overarching principles (O)

O2 Participants decide how their participation changes

- 'Clinician withdrawal'

- Only relevant aspects should stop, unless participant wants them to
- Communicate decision to participant
 - (Ulrich CM, Knafl K, Foxwell AM, et al. Experiences of Patients After Withdrawal From Cancer Clinical Trials. JAMA Netw Open. 2021;4(8):e2120052. doi:10.1001/jamanetworkopen.2021.20052)



- The exception mentioned in this principle is important. There are some circumstances where others might decide that aspects of participation need to change. This might be a clinical decision, or in some rare cases decisions by sponsors that it is not suitable for participants to continue taking part. In these cases, only the relevant aspects of participation should stop, and all other aspects should stop or continue in line with participants' choice, as per this principle O2.
- The example given on this slide is sometimes termed 'clinician withdrawal', where a doctor or someone else with a duty of care recommends that study intervention should stop. As above, in this scenario only receipt of study intervention should be affected by this decision, and everything else is for the participant to decide.
- It is important that decisions made by others about participation changes should be clearly communicated to participants. They should also usually have the chance to ask questions about it and to understand why the change happened. Some evidence, such as in the link given here, suggests that this communication does not always happen.

Overarching principles (O)

O3 The more data, the better: Everyone running or taking part in studies should be aware that **collecting as much as possible of a study's planned data** can help a study reach a clear and reliable conclusion.

This should be made clear to potential study participants using ethically-approved wording **before** they agree to take part in the study.

- GCP: interests of individuals over those of science and society
 - Does not mean interests of study shouldn't figure in decision-making
 - Where action to protect study integrity *is not incompatible with participants' rights/wishes*, then take it
- Sensitivities around explaining this to patients/participants
 - Informing in the right way & at right time
- Consultation led to more emphasis on data *quality* as well



- Principle O3 says that everyone – including participants, as far as possible – should make decisions about participation changing with the knowledge that collecting as much as possible of the planned study data supports study quality.
- This principle has sometimes been misunderstood as advocating for collecting 'as much data as possible', but this is not the aim here. Doing that would be wasteful, potentially unethical and not in line with data protection principles. Instead it is about the planned data, i.e. data required to meet the study objectives and run the study.
- Good Clinical Practice says that the interests of individuals are more important than those of science and society. This is unchanged by Persevere. In this scenario, this means that an individual's choice to have no more data collected about them takes precedence, no matter how important the data is to the study ('science and society').
- However, it does not mean that the interests of the study should be ignored. If further data collection is not incompatible with participants' rights and wishes, then it is important that that data collection happens
- There are some risks around how to communicate the point to participants. It may be best to word it 'positively' (e.g. 'it helps to collect as much of the planned data as we can') rather than negatively (e.g. anything to do with how missing data makes study results less valid).
- It also has some potential to be coercive if communicated in the wrong way. For example, if it is only mentioned at the point a participant says they want to stop taking part, this would be problematic. Instead, it should be mentioned upfront before a participant agrees to take part in a study. See later principle about balance in participant information.
- In our consultation, some respondents pointed out that data quality was important as well as quantity. We gave this more emphasis in the final guidance accompanying the Persevere principles.

Overarching principles (O)

O4 Losing contact: Loss of contact between a participant and researchers should **not be considered the same as a participant saying that they want to stop** study participation.

- Consultation: amended explanation/justification following objections
 - Some feel loss of contact should be interpreted as statement of withdrawal – we disagree but have clarified
 - Not unreasonable to try to regain contact / establish wishes
 - Researchers (with involved patients) should plan in advance
 - Sensitivity and a cautious/conservative approach – avoiding pressure
 - Possible provision of simple ‘no questions asked’ opt-out from all active involvement
 - Not ‘blank cheque’



- Principle O4 simply says that loss of contact between participants and researchers is not the same as a participant saying they want to stop or reduce their involvement. In the loss of contact scenario (sometimes called ‘loss to follow-up’) it is possible to assume that a participant does want to stop taking part. Equally it is hypothetically possible to assume that they want to continue and have lost contact accidentally. The point is that either of these is an assumption that may be hard to verify and may be incorrect. We should therefore proceed with caution rather than making either assumption.
- Some consultation respondents objected to this principle; we kept it in because a large majority of respondents supported it, but we amended the explanation and justification in response.
- The implications include that it is not unreasonable for researchers to try to regain contact and establish what participants want to do, when contact has been lost. However, the researchers should be cautious about this. If there are reasons to suspect that the participant would not expect the contact or that it would be unethical to contact them for some specific reason (e.g. if researchers know that a participant’s health was deteriorating quickly when they lost contact) then they should not attempt contact.
- Researchers, with public contributors, should make a plan before the study starts for what they will do if participants lose contact with research staff.
- There may be mechanisms we could implement to allow participants to communicate their wishes without having to engage directly with research staff. This might mean research staff have more information about what participants want to do, without having to make assumptions. The approach has pros and cons, though. See the Persevere website for more on this (“Persevere in practice”)
- It is possible for data collection from routine data, or other ‘passive’ aspects of participation, to continue in this situation of lost contact, in line with Persevere principle O5 (see next slide). This approach has conditions though, and is not a ‘blank cheque’ for researchers to do anything they want in the absence of information about participants’ wishes.

Overarching principles (O)

O5 Continuing data collection: Study data collection should continue **until a study participant explicitly tells researchers that they want it to stop.**

This approach is valid and fair only if it is **made clear to participants before they join** the study, including how they can express a wish for stopping data collection, if that is what they want.

Researchers should also **make all reasonable efforts to find out** exactly which aspects of study participation a participant wants to stop, if they express the wish to stop or reduce their participation. Any further data collection **must still be done in line with the informed consent that participants previously gave.**

This approach can also be applied to other aspects of participation, as long as those aspects are necessary and have a relatively low impact on participants, and as long as any further activity is done according to the conditions mentioned in this principle.

- Principle O5 is long – although it is important and valid, there are various caveats and conditions that we felt needed to be mentioned directly in the principle text, given the potential ethical sensitivity.
- The main message is in the first paragraph: study data collection should continue until a participant says they want it to stop.
- The last paragraph is also important. It says that this approach (elsewhere in Persevere guidance referred to as ‘presumed ongoing consent’) can apply to other aspects of participation, in some cases.
- The following slides explore the principle in some more detail.

Overarching principles (O)

O5 Continuing data collection:

- Long principle because potentially controversial
- Argues for a 'presumed ongoing consent' approach to (passive) data collection, with conditions:
 - Make the approach clear upfront
 - Make it easy/obvious how to opt out
 - Reasonable efforts to prompt participants to find out what they want to do
 - Honour the original consent (not 'blank cheque')
- Consider reminding participant of any ongoing contribution to the study at the time participation reduces/stops



- The main conditions to mention around this approach are covered here.
- Firstly, the approach needs to be clear to *potential* participants, before they agree to take part.
- It should be easy and obvious to participants how they can say they want data collection to stop, if that is what they want
- Research staff should make reasonable effects to find out what participants want to do, when they say they want to stop or reduce their participation. 'Reasonable' here is deliberately subjective, as it will depend on the situation. The Persevere guidance goes into some more detail about what this can mean. It means – as with other parts of Persevere – finding a balance between attempting to find out to what extent participants want their involvement in a study to change, but not burdening participants with information or choices, or pressuring them in any way.
- Any continued activity has to be in line with the original consent that participants gave.
- It can support the approach to remind participants of any ongoing contributions. If they do not want data collection (or any other aspects) to continue, then this gives them another opportunity to say that at that stage.

Overarching principles (O)

O5 Continuing data collection:

- Consultation: approach can be applied to other necessary, low impact aspects of participation under same conditions
 - E.g. retaining biological samples, accessing medical notes for monitoring purposes
- Consultation also clarified about data *generated* before participant says they want data collection to stop can still be *collected*
- Apply cautious/conservative approach
 - If hard to show that participant would *reasonably expect* activity to continue – and no information on participant's wishes – err on side of stopping
 - Situation-specific sensitivity – e.g. diminishing capacity to consent, worsening mental health
 - Specific rules to follow regarding *loss* of capacity to consent
- Situations where data collection must continue, e.g. safety information in CTIMPs

- The consultation responses suggested this principle could be applied to other aspects of participation. We agreed with this and added content to the final principles and guidance. Other, suitably 'passive' aspects of participation where the approach could be applied include retention of biological samples, and accessing medical notes for monitoring purposes. In real terms, this means these activities that are done based on participants' consent would continue until/unless participants say they want them to stop.
- Another change made following the consultation was to clarify that data *generated* before a participant says they want data collection to stop can still be collected. For example, if data exists in medical notes from a visit prior to data collection stopping but has not been added to study forms/databases yet, it is OK for it to be added (because in theory it already should have been). This does not apply in the same way if data collection has confidentiality considerations, e.g. if it requires research staff to have direct access to medical notes.
- In general, we encourage a cautious application of this principle O5. There may be reasons why it would not be fair to apply it in specific cases, such as diminishing or lost capacity to consent.
- Researchers should also be aware of any cases where data collection must continue (e.g. by law), such as some safety information in clinical trials of investigational medicinal products. Limitations on participants' rights like this should be communicated to potential participants before they agree to take part in a study.

Overarching principles (O)

O6 Retaining data: Data collected for a study up to the point a study participant stops providing data **should be used in the study analysis**, and **kept with the other study data until the study is over**.

The data should also be **made available for legitimate additional research** in line with participant consent and appropriate approvals.

- Standard approach, supported by GDPR & other rules/policies etc
- Consultation: clarified that it includes archiving period
- Consultation: some not happy with approaches to data sharing
 - Not amended principle – does allow for study-specific approach in relation to consent
 - “What does ‘legitimate’ research mean?”
- Limitation on data protection rights needs to be explained upfront
- Still need route for data deletion in some situations (or some study types)

- This principle O6 is fairly well established already – that data collected until a participant says they want data collection to stop is retained and used in analysis. We also emphasise the role of data archiving (‘kept with the other study data until the study is over’) and that the data should be used for secondary research, as long as this is in line with participants’ consent and any required approvals.
- Different researchers may take a different approach to consent for secondary research. It is not a regulatory requirement (in the UK, in any case) to ask participants for their consent to share data in ways that would not release identifiable information. However, some consider it fair and ethical to ask for consent. The wording in the principle allows for either approach.
- It is true that we do not define ‘legitimate research’ and some in the consultation objected to this. We considered this out of the scope of our project to define. Instead, the principle here means ‘legitimate research’ as the reader would consider it. More work would be needed to agree exactly what that means.
- It is important that the limitation on data protection rights is explained to potential participants before they agree to take part in a study, so that they can take this into account when they are deciding.
- There may still need to be a route for data deletion in some situations or some study types (e.g. in some qualitative research it is considered ethical to have a period during which interview participants can request for their data to be deleted).

Overarching principles (O)

O7 Information after stopping participation: Stopping participation early **does not affect participants' right to receive study-related information later on**, if they want to receive it or if it could be important for them to have.

- New principle following the consultation, based on previous one just about sharing study results
- Information participants *want or need*
 - Also information specific to early-stoppers
- Evidence that early-stoppers are sometimes excluded
- Might withholding information conflict with need for withdrawal 'without negative consequence'?
- Checking preferences for further contact
- Practical challenges in implementing
- Complexities around loss of capacity and death



- The final principle in the 'overarching' group says that stopping participation does not affect participants' right to receive information they might want or need. This could include things like results of the study, general updates, or updated information about the safety of study interventions.
- Participants who stop early might have some specific information needs too, for example about what happens next for them after they stop. There is Persevere guidance about how to communicate this to them.
- There is some evidence that participants who stop taking part are sometimes excluded from receiving information without a clear justification. Anecdotally, research staff often express uncertainty about whether it is acceptable to share information with participants who stopped taking part.
- The well-established 'right to withdraw consent' usually says that participants can stop taking part without any detriment or being denied things they would otherwise get. There is an argument that denying participants who stop things like the results of the study, even when they might like to receive those, is in conflict with the right to withdraw in this respect.
- Practically, it may be useful to check preferences for further contact at the point participants stop taking part.
- We accept there are practical challenges sometimes in staying in contact with participants who stop, and complexities around loss of capacity, death, and worsening health.

Study development principles (D)

D1 Protecting study integrity by design: Studies should be designed and resourced to **allow data collection to continue wherever possible**, particularly for study outcome data.

Participants should be allowed to **continue participating while making less commitment** to the study, where this is feasible, safe and does not negatively affect the scientific integrity of the study.



- The next group of principles covers study development – or in other words, things to consider before a study starts.
- Principle D1 says that researchers should plan to allow data collection to continue wherever possible, particularly for study outcome data.
- In practice, this means considering ways that participants could continue to be involved in a reduced capacity, rather than stopping altogether. This could be through offering alternative methods or schedules for study follow-up.
- There are some limitations to what might be possible, particularly that reduced participation must be feasible for research staff to support, must be safe for participants and must not impair the scientific integrity of the study.

Study development principles (D)

D2 Protocol content: Study protocols should include **clear instructions** on how participation changes should be practically managed.

This should include, where necessary, study-specific definitions for **different types of participation change expected** over the time the study will take place. Researchers should decide **how these participation changes affect the specific research** question they want to answer.

Protocols should also include a pre-defined plan, developed with patient involvement, for appropriate **actions to take if study researchers lose contact** with study participants.



- Principle D2 covers what should be in study protocols (or otherwise planned and documented as part of study setup)
- Protocols should be clear for all research staff who will use them about what is expected from a practical point of view – for example when a participant says they want to stop taking part, or they lose contact with research staff
- Research teams should consider what sorts of participation change might be likely in their study. They should think about how these affect their specific research question (technical term: 'estimand')
- Research teams should make a plan for what should happen if researchers lost contact with participants. This could include things like how many attempts researchers should make to contact participants, and via what methods.

Study development principles (D)

D3 Participant information about stopping participation: Before participants agree to take part in a study, they should receive **clear and balanced information** about what will happen if they want to stop participating.

This should include information about how it is **good for the study if participants can provide outcome data until the study ends**.

This way, participants can make an informed choice about initial and ongoing involvement.



- Principles D3 and D4 are both about information for potential participants. The Resources section of the Persevere website includes template wording (developed with public contributors) to implement Persevere's recommendations.
- D3 covers what potential participants should be told about ending their participation. They should get information that gives them clear expectations for what would happen if they later decide they want to stop or reduce their involvement.
- The information they get should be balanced, meaning it should mention participants' right to stop taking part at any time, but also the value of each individual's contribution and the usefulness of collecting as much of the planned data as possible (as per Persevere principle O3).
- Providing balanced information supports free and informed decision-making for participants, as per Persevere principle O2.

Study development principles (D)

D4 Participant information about losing contact: Participants should be informed, before they consent to join a study, about **what will happen if contact is lost** during the study.

If any participants might feel that the ways that researchers may try to get back in touch are intrusive, participants should have the chance to provide **freely-given, informed consent to allow these contact methods** to go ahead.

Researchers may not carry out these attempts at further contact if participants have not given consent.



- Principle D4 says it should be clear for participants what will happen (generally) if they lose contact with the researchers. This includes things like whether data collection would continue, or what sort of further contact participants might expect.
- Sometimes researchers might plan to contact someone else in this situation (e.g. a participant's GP). This sort of thing could be considered intrusive by participants, so should only happen with participants' prior consent.

Study development principles (D)

D5 Encouraging dialogue: Throughout each study, researchers should make **reasonable efforts to check that participants are still willing and able** to take part.

Researchers should be **prepared to discuss possible changes** to participation, where these might allow participants who are still willing to make a contribution to the study to do so.

Participants should be **encouraged to contact the researchers** at the earliest opportunity if they are experiencing difficulties with any part of the study or if their circumstances may be changing in ways that will make taking part more difficult.



- Principle D5 is called 'encouraging dialogue'. Its underlying idea is that it will be better for participants and studies if participants feel able to talk about changing their participation, and research staff feel comfortable to raise it too.
- The first point here is about research staff checking in with participants at suitably regular intervals, to check they are still happy to take part. A balance needs to be struck with this. They should check often enough to pick up any issues, but not so regular that it is burdensome or off-putting for participants. Research staff should be encouraged to use their professional skill in this area.

Study development principles (D)

D6 Training and support: Everyone involved in running studies should be **trained and supported to manage participation changes** for the good of both the participants and the study.

This should be done in line with applicable regulations and include an understanding of the **importance of continuing study data collection** wherever possible.

Training should acknowledge that satisfying participants' wishes for less involvement in a study may not need to result in their participation stopping altogether.



- Managing participation changes can be difficult, perhaps particularly for research staff who are in direct contact with participants and therefore might have to help establish what participants want to do. The Persevere principles encourage 'balanced' approaches in various ways, but this can be challenging and research staff might worry about getting it wrong.
- Principle D6, therefore, covers training and support for all those involved in running studies.
- Training should cover the balance to be struck and the need to manage participation changes for the good of participants and studies.
- The importance of continuing data collection should be covered (as per Persevere principle O3), as well as the implications of different sorts of participation change for data collection and retention (as per principles O5 and O6).

Data management/monitoring (M)

M1 Informative data collection about participation changes: Data about study participation changes should be recorded in a standardised way and include **enough detail to usefully inform study management, analysis and reporting**.

Data should include, when available, meaningful information about **when and why the participant has reduced or stopped** their participation.

Collected data should also clearly **communicate the participant's wishes**, including which elements of study participation they want to stop, and which they have agreed to continue.



- The next two principles are about data collection and monitoring.
- Principle M1 covers data collection. Good quality data is critical to managing participation changes. Without it, research staff cannot have a clear picture of what participation changes are happening and why. Good quality data supports study management, analysis (including handling missing data) and study reporting.
- It can be useful to know when participation has changed, and also why.
- The question of 'why' can be difficult because the 'right to withdraw' says that participants have a right to stop taking part without giving a reason. But this just means they do not have to give a reason, not that they cannot be asked for a reason. It is important to be sensitive in asking this sort of question (or sometimes not asking, if it is inappropriate), but where there are opportunities to find out why participants' involvement is ending or reducing, we should take them.
- Participants should not be surprised about being asked why they want to stop. The information they get before they agree to take part should leave open the possibility that they might be asked for a reason why they want to stop. If the information only says that they do not have to give a reason, so that they have the expectation that they won't be asked, then it may not be appropriate to ask them.
- See more detailed recommendations about data collection on the Persevere website (persevereprinciples.org – 'Persevere in practice')

Data management/monitoring (M)

M2 Monitoring: All those responsible for running and overseeing a study should, at appropriately regular intervals, **review summarised data about participation changes** in the study.

This allows them to identify common issues or developing trends in study participation, and reasons for these trends, so that timely and targeted action can be taken.

Those running and overseeing studies should also consider **reviewing information about the participation changes of individual study participants**, if this might be important for their study.



- Principle M2 covers monitoring, meaning the activity research teams carry out to check how a study is being run, while it is being run.
- Firstly, it encourages study teams to regularly review summary data about participation changes – this likely happens already in many studies.
- The principle then also encourages teams to consider reviewing information about individual participation changes, if it could be important. This might mean reviewing medical notes (with participants' consent) to check that participation changes have been reported correctly.

Study analysis and reporting (R)

R1 Analysing studies with participation changes: When participation changes mean that not all the study data has been collected as planned, researchers should analyse the study in ways that give the **best chance that the study will still have reliable results**.

The analysis should be done using methods that are **planned in as much detail as possible** before the study starts, and that **follow current best practice** for the specific research questions in the study.

- i.e. handling missing data / intercurrent events
- New principle following consultation, based on previous one about statistical planning
- Linked to estimands
- Emphasis on trained and experienced statisticians
- Prior planning still emphasised



- The final two principles are about analysis and reporting. There has already been quite a bit of work in this area (separately to Persevere) but they were important aspects to include in our principles.
- The idea of analysing clinical trials and other studies that have ‘missing data’ is well established. This principle R1 expresses the basic aim in simple terms – i.e. when not all the planned data is available due to participation changes, researchers (statisticians or other qualified analysts, in this case) should analyse in ways that give the best chance of reliable results. This usually involves making some assumptions, and having a good knowledge of best practice in doing this sort of analysis.
- The principle emphasises prior planning, in line with well-established practice that most or all aspects of statistical planning should be agreed in advance of studies starting.
- The part about ‘specific research questions’ again is referring to ‘estimands’ – research questions that take account of participation changes.

Study analysis and reporting (R)

R2 Consistent and complete reporting: End of study **reporting of participation changes should be done consistently** within a study, showing any changes in level of participation, preferably split by treatment group.

This helps with the assessment of the quality of the study and of the reliability of the results. It can also inform the size, design and conduct of future studies.

Methods used to handle missing data should also be described, to allow interpretation and replication of results.



- Principle R2 covers study reporting and emphasises consistency within and between studies. It also mentions the importance of reporting methods and assumptions used when handling missing data in studies.
- The general principle is already well-established, partly through the CONSORT statement. However, in our Persevere implementation guidance, we propose some additional points that could improve reporting of participation changes further.

Part 3: how to use the Persevere principles



General uses

- “Toolkit”
- Use in planning new studies – to prepare for participation changes
 - Deciding approach to managing different sorts of participation changes
 - Making sure study processes are as good as possible
 - Improving specific processes or documents – e.g. can data collection form be improved?
- Use in deciding what to do in ongoing studies
 - How should a participant’s level of involvement change?
 - Is it fair to continue data collection / use of samples / etc?
 - Reassurance about approaches
- Training staff, setting standards & expectations, “getting on the same page”



- We don’t expect people to read the Persevere guidance front to back. Instead, people can perhaps consider it like a ‘toolkit’, choosing the appropriate bits of the guidance they need for the issue they’re dealing with.
- The Persevere principles can guide development of new studies, along the lines of the examples given here.
- They can also provide guidance to ethical approaches in ongoing studies, e.g. if something unexpected has happened.
- For research organisations, the Persevere principles and related guidance can be used to train staff, set standards and expectations and make sure everyone is ‘on the same page’.

Role-specific guidance (see [‘PeRSEVERE and you’](#))

- Currently introductory pages for:
 - Data Managers
 - Public contributors
 - Quality Assurance staff
 - Recruiters to research
 - Statisticians
 - Trial Managers
 - Monitors
- Intro to PeRSEVERE project
- What is your role in helping manage participation changes?
- Which principles might be most relevant to you?
- Which resources might be most useful?



- In the ‘Persevere and you’ part of the website (<https://persevereprinciples.org/persevere-and-you/>) there are a few introductory pages for different stakeholder groups, as mentioned here. These were developed with representatives of those groups.

Example scenarios (see [Resources](#) page)

- Currently 5 scenarios
- For each: what should be done, and how can PeRSEVERE principles help prepare?

Scenario #1

You are preparing to share a summary of the study results with the study's participants. Some of the participants are recorded as having 'withdrawn consent', with differing implications for their ongoing participation – some withdrew from further clinical data collection, some withdrew from completion of further posted questionnaires, and some withdrew from all further researcher contact (and some a combination of these).

- **Who can the researchers contact?**
- **How can the Persevere principles help prepare for this?**

Read More



- The 'Resources' section of the website includes a set of example scenarios – see screenshot here. These can show how the Persevere principles can be used in practice.

PeRSEVERE implementation guidance

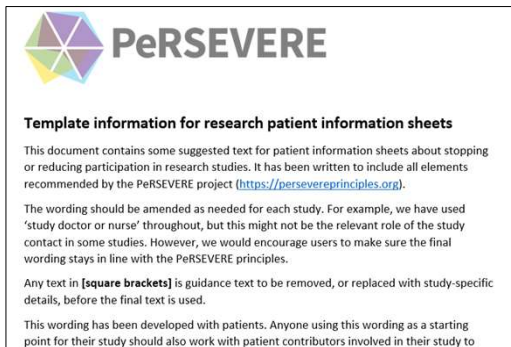
- Developed from several sources
- Available via perseverepinciples.org (see [PeRSEVERE in practice](#))
- Includes guidance on:
 - Protocol development
 - Patient information, participant communications, consent
 - Risk assessment and monitoring
 - Training and support
 - Data collection about participation changes
 - Study reporting



- The implementation guidance goes into more detail than the Persevere principles about how the principles could be put into practice. This might make the principles a bit more 'concrete'.

Template patient information wording (see Resources page)

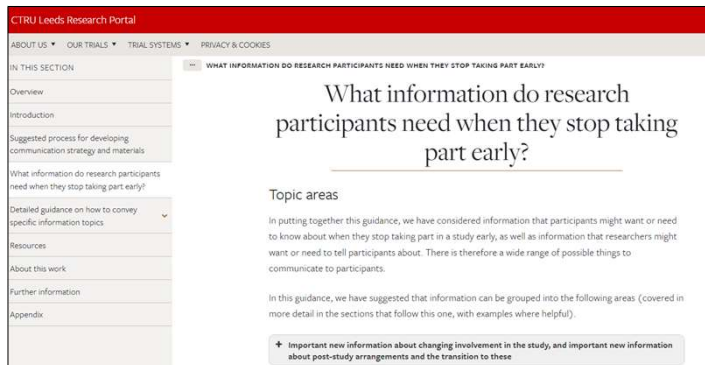
- Patient and public involvement exercise, 2023
- Layered information, aligning with PeRSEVERE principles & other guidance



- Template wording for participant/patient information was developed in collaboration with a public contributor group. It aligns with all of Persevere's recommendations around participant information.
- The information is 'layered', meaning it contains a shorter summary of key points that all potential study participants would be expected to read before giving consent, and more detail for those who want it.

End of participation information (see Resources page)

- What information might participants need or want around the time they stop taking part?
 - “What does stopping my involvement early mean for me?”
 - “Have I still made a useful contribution to the study?”
 - “What happens next, and what are my choices?”



- This Persevere-linked resource guides researchers on what information participants might need or want at the time they stop taking part in a study, and how it can be sensitively communicated to them.
- It includes example wording to use in participant-facing communications and ethically approved example documents.

Other live & planned resources

- Checklists for managing individual participation changes
- Suggested terminology

- Protocol wording/sections [planned]
- Flow diagrams to establish how participation should change [planned]
- Further training slides for different groups [planned]



- The checklists can be used by anyone involved in managing individual participation changes to check that all relevant actions have been completed.
- The suggested terminology was included in our initial Persevere guidance. It was then included in our public consultation, where nearly 75% of respondents agreed they were an improvement on language and terminology that tends to be used at present.
- Other resources, including those mentioned here, will continue to be added when they are ready for release.

Part 4: applying the PeRSEVERE principles to studies you work on



Applying PeRSEVERE principles to specific studies

- Consider trials you work on/with or have done:
 - Are there any specific risks or considerations around participation changes in these trials that might be useful to think through in advance?
 - Consider how well the design and conduct of each trial (or in your experience in general) is already in line with the PeRSEVERE principles, or where there are opportunities for closer alignment
 - What is already done well?
 - What might be done better?
 - Are there aspects that are out of your control?



- This activity could be carried out within a clinical trials unit or other research organisation to help understand the Persevere principles and how they affect existing practice.

Part 5: could the Persevere principles improve study retention?



- The following slides include some considerations for how the Persevere principles interact with work around improving 'retention' in studies – i.e. increasing the proportion of participants who provide outcome data.
- The hypotheses set out are just that – hypotheses. Further research on any of these questions would be worthwhile.

Could following PeRSEVERE improve study retention?

- Behaviour changes: can we make people less likely to decide to stop participating (whatever the burden of participation)?
- Study burden: can we design study so they're 'easy' to complete (regardless of whether we change people's behaviour or not)?
- **Study resilience: can we design and run studies in a way that reduces the impact of participants' decisions (whatever those decisions are)?**
- Better quality data about participation changes to support retention research



- We might arguably consider the 'retention' question to be several related questions.
- Firstly, are questions about (ethically) influencing participants' behaviour so that they are less likely to decide to stop taking part (regardless of the study). Persevere does not really address this.
- Secondly, we could look at how to reduce the burden of study participation, so that it is easier for participants to continue taking part. Persevere addresses this somewhat, for example in the principle D1 about building in options for participants.
- Persevere is most relevant in the context of the third point on this slide – the idea of resilience. The Persevere principles advocate for designing studies so that participants wanting to reduce their level of involvement does not have to mean the study integrity is impacted (or not impacted more than necessary).
- The final point is also important. Persevere principle M1 endorses good quality data about participation changes. This data is also critical to support further research into retention questions.

Planning to allow reduced participation, not just stopping

- PeRSEVERE principle D1:
 - “Studies should be designed and resourced to allow data collection to continue wherever possible, particularly for study outcome data.
 - Participants should be allowed to continue participating while making less commitment to the study, where this is feasible, safe and does not negatively affect the scientific integrity of the study.”
- E.g. choice of data collection options
- Possible effects on study retention?
 - Some participants accepting reduced or changed participation who would otherwise stop altogether



- Persevere principle D1 could support study retention as set out here.

Better training

- PeRSEVERE principle D6: “Everyone involved in running studies should be trained and supported to manage participation changes for the good of both the participants and the study.”
- Confidence in approaches
- Skills to manage difficult conversations
- Recognition that this is challenging

- Possible effects on study retention?
 - More chance that recruiters communicate ‘value of retention’ to potential participants?
 - More chance that participants are aware of / reminded of their choices?
 - More chance of good decisions being made at trials units/equivalent?



- Better training for everyone involved in running studies – as per Persevere principle D6 – could help improve retention in a few ways, as set out here.
- All of these points might mean it’s more likely for participants to reduce their level of involvement, rather than stopping altogether.

Other ways to support participants' decisions

- Informing participants' decisions about changing participation
- Using optional form to record participants' wishes
- Opportunity for participants to discuss participation with someone independent of usual research staff
- Route to stop participation without having to speak to anyone
- eConsent / dynamic consent?
- Possible effects on study retention? Or on the number of 'lost contact'?
 - More awareness of choices & pros/cons of each
 - Better data about what participants want to do – less reliance on assumptions
 - More information about participants' wishes where otherwise there might be none
 - Reduced risk of pressure in the decision or its communication



- Persevere principle O2 says that participants should be the ones to decide on the extent and nature of their participation change (with some exceptions) and that their decisions should be freely-given and informed. This is potentially challenging to achieve, but there are some possible ways to help achieve it.
- We might inform participants' decisions (before or while they are making them) about changing participation. It might be challenging to 'intervene' at this point, but the Persevere website contains some suggestions in this area.
- We might use an optional form to record participants' wishes. This would make it clear what participants' choices were, and provide researchers with a clear record of what participants want to do.
- We might give participants an opportunity to discuss their participation with someone outside the usual care team, in case they feel uncomfortable raising it with the usual team, for whatever reason.
- We might offer a route to stop participation without having to speak or engage directly with anyone – for example via a website. There would be pros and cons to this approach. See the Persevere website for more guidance on this.
- It might be that eConsent, in combination with a 'dynamic consent' approach where individuals can update their own consent easily during a study, might provide opportunities to facilitate participants' decision-making.
- All of these may affect retention in a few ways.
- They might improve participants' awareness of the pros and cons of the different options regarding their participation.
- Researchers might get better data about what participants want to do, meaning there would be less reliance on assumptions.
- Researchers might sometimes get information about participants wishes where there would otherwise be no information (i.e. in cases where participants and researchers otherwise lose contact with each other, as per Persevere principle O4).
- These approaches might reduce the risk of participants feeling pressured during the process of stopping or reducing their involvement, which would be a good thing for them.

Data collection

- PeRSEVERE says (principle **M1**):
 - Collect data about participation changes to usefully inform study management, analysis and reporting
 - Where available, collect data about when and why participation reduced or stopped
 - Collect data about participant's wishes
- Might standardisation make it easier for research staff to ask & participants to say?
- Possible effects on analysis and reporting?
- Benefits to retention research
- Feedback for ongoing studies



- More standardised data collection about participation changes might make it easier for research staff to ask participants about their motivations for stopping, and might make it easier for participants to give some information. For example, it might make it more obvious that researchers are only interested in some information and don't need lots of personal details about participants' lives.
- Better quality data could benefit analysis and reporting of studies and retention research. It could also benefit ongoing studies by providing useful feedback.

PeRSEVERE website & contact

<https://persevereprinciples.org>

persevere@leeds.ac.uk



- Feel free to get in touch if you have suggestions for amendments to these slides, or other suggestions for Persevere resources.

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