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Note that this document shows draft PeRSEVERE principles from early 2021. The final principles are available at persevereprinciples.org.

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

Principles and explanation (draft 0.2, January 2021)

PeRSEVERE collaborative group (see end of document for full contributor list)

Contents

Introduction

Background and aims

All guidelines, policies and laws about clinical trials and other research with human participants (from here on referred to as ‘studies’) are clear that, before taking part in research, individuals[1] must voluntarily give informed consent, and that they can withdraw that consent at any time after having given it, without providing a reason.[2] [3] [4] Study participants can therefore stop participating whenever they like.

Participation in a study may often be made up of different elements, for example undergoing the medical treatment that the study is evaluating, attending hospital visits for study-specific medical assessments, completing study-specific questionnaires, and so on. It is possible for some of these to stop while others continue (with some limitations – for example it would not be safe for a study participant to continue receiving study treatment while stopping medical assessments intended to monitor their safety).

We argue that the spirit of the right to withdraw consent suggests that individual study participants must stay in charge of their own destiny. It should therefore be they who decide which elements of study participation they are happy to continue and which they would like to stop, rather than being given an all-or-nothing choice. For example, if it is possible in a given study for participants to stop study-specific visits but continue providing relevant data from routine healthcare visits, participants should be given the choice to accept or refuse this arrangement, and they should be given adequate information to inform this choice. The only exception to this is where others need to take action to protect study participants, for example if those responsible for the participant’s clinical care feel it is in their best interests for them to stop receiving study treatment.

The third principle of the ICH Guideline for Good Clinical Practice[3] says: “The rights, safety, and well-being of the trial subjects [study participants] are the most important considerations and should prevail over interests of science and society.” This points to the potential for conflict between the needs of individual study participants wanting to stop participating, and the needs of the study and the robustness of its results (“science and society”), which will be negatively affected by participants stopping participation earlier than was planned in the study protocol.

Despite this, we argue there is at least theoretically a way to prepare and run studies so that participants’ rights are not compromised but *also* the negative impact on the study results is kept to a minimum (while not being completely eradicated).

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[1] Here, this means individuals with capacity to give informed consent – see ‘Scope and limitations’, below.

[2] Declaration of Helsinki: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

[3] ICH Guideline for Good Clinical Practice: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf

[4] 2001 EU Clinical Trials Directive: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

We must aim to achieve this for at least the following reasons: a) the results of clinical studies are used to inform and improve healthcare for the rest of society, so they must be as useful and reliable as possible, and b) when a study does not produce useful results (this means we don't learn anything *new* from the results, regardless of whether what we learn is 'positive' or 'negative'[5]), the study's participants have given their time and been exposed to any risks associated with study participation for no benefit to society.

The draft principles in this document have been developed through a project called PeRSEVERE (PRincipleS for handling end of participation EVEnts in clinical trials REsearch). They are intended to guide how study participants' right to withdraw their informed consent should be applied in practice so that we can achieve the following aims:

- **Do the best by individual study participants:** individual study participants should get the best possible information to inform their choices about ongoing study participation, and be as involved as possible in any decisions that are made about their participation. All decisions to change (or not change) the nature of their study participation must be informed and freely-made, in the same way as initial consent.
- **Do the best by the study:** the actual or perceived robustness of study results should not be impaired by individual study participants' decisions to stop participating unless it is completely unavoidable.
- **Do the best by research and society in general:** studies should be transparently reported so that it is clear what changes in participation occurred, and how these changes were handled in the study analyses.

Our draft principles have been developed through extensive discussion and debate within our collaborative group (see full list of contributors at the end of this document) which was formed through the UK CRC Registered Clinical Trials Unit Network and which includes patients, statisticians, methodologists, clinical trial managers, data managers, and specialists in quality assurance and research regulation. In developing our principles, we have been guided by the high-level principles of ethical research conduct (including good clinical practice), our knowledge and understanding of existing clinical research regulations and guidance, and our collective experience of designing, running, analysing, reporting on and participating in clinical trials and other research.

In general, we suggest it is best to be proactive in ensuring the above aims are achieved. This means designing studies and preparing to run them in the right way, rather than only reacting to problems as they occur. We have aimed to keep this in mind as we have developed the principles.

We acknowledge that some of our principles are already reasonably well-established in clinical research (at least in the UK). However, we consider it important to present them all

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[5] A trial could reliably show that a new treatment is *not* better than an existing treatment. This might be disappointing, but this would still be something new we had learned, and would be a useful result. The worst outcome from a trial is that the results are not reliable and so we have learned nothing new.

as a complete, coherent set. We are not aware of any previous attempts to comprehensively define, as we have done here, how the ethical right of study participants to withdraw their consent should be put into practice.

Other relevant background information guiding our principles has included:

- The SPIRIT statement[6], which says what should be included in clinical trial protocols.
- The CONSORT statement[7], which says how trials should be reported clearly and transparently.
- Current data protection laws in the European Union and UK (the EU General Data Protection Regulation[8] [GDPR] in the EU and the 2018 Data Protection Act[9] in the UK). These give special protection to data used in research, including to allow researchers to keep data after a study participant decides to stop participating in a study, as long as certain conditions are met. These laws also mean that potential study participants must be clearly informed, before they join a study, about how their data will be used in the study, including about any limitations on their usual data protection rights and about any possible international data transfers.
- Laws governing how to run studies involving medicines[10] mandate that all data collected in a study must be kept for a long time after the end of the study (in some cases, as long as 25 years). This includes data about study participants who stopped participating early. This is so that it is possible for the regulatory authorities to check the results of the study are accurate at any time during this period. This is particularly important when a study led to changes in the standard of care for a particular health condition.

The PeRSEVERE collaborator group is mostly based in the UK and we do not claim to be experts in laws and policies applying to research in other areas of the world. However, we have aimed for our principles to be general and enough to be able to apply, at least in theory, to other settings.

Scope and limitations

1. Types of research: the PeRSEVERE principles are intended to apply to all health research with human participants that involves some active, ongoing participation from those participants. This means the individual participants have given informed consent before taking part, and that taking part lasts for a period of time and involves receiving medical treatment, completing questionnaires, undergoing medical assessments or otherwise actively providing data for use in the research. The principles are particularly relevant to clinical trials research (including randomised controlled trials), but can also apply to

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[6] https://www.spirit-statement.org/

[7] http://www.consort-statement.org/

[8] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=EN

[9] http://www.legislation.gov.uk/ukpga/2018/12/pdfs/ukpga_20180012_en.pdf

[10] https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/

observational studies and other sorts of health research, if they include active, ongoing participation by individuals, as defined above.

The principles do not apply directly to research that involves only analysing biological samples that study participants have consented to be stored in a central location (for example a 'biobank') for research purposes, as this sort of research usually does not involve any active, ongoing participation from the individual participants.

Similarly, the principles do not apply to research only involving data obtained from healthcare databases held by the UK National Health Service or similar public organisations. This sort of research also does not usually involve any active, ongoing participation from its participants. It also often involves only anonymous data, and as the researchers cannot tell who the data they have is about, there is no way for them to contact or otherwise 'involve' the individual research participants.

2. Types of participation change: our principles mainly address study participation changes that could lead to expected data being unavailable or not measured for study analysis, for example participants no longer taking part in study follow-up arrangements (whatever those might be). When participants only stop study treatment or intervention, but carry on with study follow-up arrangements, this should not lead to missing outcome data and is therefore mostly out of our scope. Our principles also do not apply to cases where individuals' participation stops because the whole study is coming to a close earlier than planned.

3. Improving retention: we are aware of efforts to understand how studies can be run to *reduce* the proportion of study participants who decide to stop participating early[11,12] (often referred to as 'improving retention'). This might be by offering ethically acceptable incentives to study participants, making study participation less burdensome, or through other means. This work is important and complementary to our principles, but also out of our scope. Instead, we are looking to achieve the aims outlined above, no matter what individual study participants decide to do.

We suggest that researchers designing and running studies should continue to follow evidence-based best practice around improving study retention, as it continues to develop. We also suggest that it should be routine (if it is not already) for researchers to consider, in discussion with involved patients, how to minimise the amount time and effort taking part

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[11] Brueton, V. C., Tierney, J. F., Stenning, S., Meredith, S., Harding, S., Nazareth, I., & Rait, G. (2014). Strategies to improve retention in randomised trials: a Cochrane systematic review and meta analysis. BMJ Open, 4(2), e003821. https://doi.org/10.1136/bmjopen-2013-003821

[12] Brunsdon, D., Biesty, L., Brocklehurst, P., Brueton, V., Devane, D., Elliott, J., … Gillies, K. (2019). What are the most important unanswered research questions in trial retention? A James Lind Alliance Priority Setting Partnership: the PRioRiTy II (Prioritising Retention in Randomised Trials) study. Trials, 20(1), 593. https://doi.org/10.1186/s13063-019-3687-7

in the research will require of the participants. This includes limiting the amount of data collection to what is absolutely necessary.

4. Capacity to give informed consent: specific arrangements apply where potential study participants do not have the mental or legal capacity to give informed consent (for example due to being unconscious, having conditions such as dementia or being under the legal age of consent [16 for most situations in the UK]) or where study participants who gave valid informed consent later lose capacity to consent during the study. In the UK, the relevant laws include the Medicines for Human Use (Clinical Trials) Regulation[13] for most studies involving medicines, and for other studies the 2005 Mental Capacity Act[14] (applying in England and Wales) and the Adults with Incapacity (Scotland) Act 2000[15]. When dealing with these issues involving absence or loss of capacity to consent, researchers should follow the relevant laws. We have therefore decided that these issues are out of scope for this version of our principles, which therefore are focussed on study participants making decisions for themselves. However, where necessary we have noted where issues of capacity to consent may arise.

5. Biological samples: we considered issues to do with storage of study participants' biological samples to be largely out of our scope (this means what happens to stored biological samples if a participant decides to stop participating in a study). However, our principles do apply to data that has been generated from analysing study participants' biological samples.

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[13] http://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf
[14] http://www.legislation.gov.uk/ukpga/2005/9/pdfs/ukpga_20050009_en.pdf
[15] http://www.legislation.gov.uk/asp/2000/4/pdfs/asp_20000004_en.pdf

Terminology and language: describing end of participation

In our experience, there can be confusion and ambiguity around terms commonly used to describe stopping study participation, such as ‘withdrawn’, ‘lost to follow-up’, ‘drop-out’ or ‘off-trial’.

In general, we aim in this document to describe participation ending or changing as plainly as we can, using language with explicit meaning which, as a result, can mean the same thing to everyone. Some suggestions for clearer terminology are outlined below. We suggest these, or similarly clear terminology, could be used in many situations when designing, running, analysing and reporting studies, including in study protocols, study reports, and in communications between researchers and study participants.

This level of detail may not be necessary in all situations. For example, by the time of a study’s final analysis, it may be useful to simply summarise which participants we have study outcome data for and which we do not. However, use of the suggested terminology below does not prevent this sort of summarisation taking place when it is needed.

Suggested terminology

- For aspects of study participation requiring ongoing commitment (for example receipt of intervention, attendance at clinic visits, completion of questionnaires):
    - When a participant decides to completely stop an aspect of participation before it was supposed to finish, we suggest using the phrase **"stopped … early".** For example "stopped study-specific visits early".
    - In some cases it might be useful to distinguish between participation changes following a participant’s decision and changes (particularly to medical treatment or procedures) guided by clinical decisions of a participant’s doctors. For example, if a participant’s doctor decided it was in their best interests to stop receiving a study treatment, they could be described as having “**stopped treatment early based on a clinical decision”.**
    - When a participant decides to *reduce* their level of commitment, without totally having stopped, we suggest using the term "**reduced…".** For example, "reduced frequency of study visits". This can also be used to describe changes in receipt of study treatment or intervention, but study protocols often make specific provisions around dose delays or modifications (if this is the case, the protocol’s terminology should be used).
    - When some alternative, specific arrangement has been made with a participant regarding their participation, we suggest this should be explicitly stated, for example “stopped study visits early; telephone follow-up only”. Alternatively, the general term **“changed…”** can be used, for example “follow-up changed from study visits to telephone follow-up only”.
    - When a participant has stopped an aspect of participation at the time that the study protocol specified it was supposed to stop, we suggest using "**completed…".** For example, "completed study visits".

  - In some studies, there may not be a set period of time when participants get treatment/intervention. For example, participants may continue receiving treatment until it does not seem to be working any more. In these cases, the idea of stopping treatment ‘early’ might not be quite right, but nor might it be right to say they have ‘completed’ treatment. In these cases, we suggest the phase “**(permanently) stopped treatment because [of]…”.** For example, “stopped treatment because it was no longer beneficial”, or “stopped treatment because of side effects”.

- For aspects of study participation that do not require ongoing, active commitment[16] (for example clinical trials units getting additional data for the study from routine healthcare data providers like NHS digital, or biological samples being stored for future research projects) we will say "**no longer agrees to…".** For example, "the participant no longer agrees to have their biological sample stored for future research”.

- Loss of contact:
  - We expect study protocols to specify how to manage loss of contact with participants (this means without them having expressed any explicit wish about stopping study participation). This should include a set process to follow, and criteria for judging when to stop trying to contact someone (or stop for the time being). At this point, we suggest describing the person as having **lost contact for now.** This implies that it should be possible to try again at a later date to contact them, for example prior to the final study analysis. The study protocol should specify when this later contact should be.
  - At the end of the study, there may be a group of participants who lost contact with the study without explicitly asking to stop participating and for whom no further data was ever obtained. We suggest these participants could be described as having **lost contact and never regained, with no further follow-up.**
  - If data about these participants is obtained through other sources (for example from routine healthcare data providers like NHS Digital, and always in line with participant consent), they might instead be categorised as having had **lost contact and never regained, but with some indirect follow-up.**

- **Change in participation status** or just **participation change**: general terms used to mean all instances where a participant makes a decision (or in some cases where a decision is made on their behalf) to end or reduce study participation.

The terms above are not mutually exclusive, as ending or changing participation can be complex and specific to an individual’s situation. The terms can be combined as appropriate with "but" or "and" in order to convey exactly what has stopped, reduced or still continues

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[16] Where a piece of research only involves this sort of activity, it may not be within the scope of the PeRSEVERE principles; see ‘Scope and limitations’, above. The point here refers to cases where research involves these activities as well as others involving more ongoing, active commitment.

in each case. For example, "the participant stopped intervention early and is on reduced study visits, but still agrees to their data being accessed through routine healthcare data sources".

Glossary: other terms

- We have used the word ‘**study**’ throughout this document as a generic word for all types of research that our principles apply to (see above).
- We have used the word '**participant**' throughout to mean people who take part in research, except where '**potential participant**' might be more appropriate (this means where we are referring to people who are only considering taking part in a study).
- We use '**researcher**' throughout the document as a general term to mean people who design, run, analyse or otherwise oversee research. We sometimes make an exception where we need to distinguish between those with organisational responsibility for running studies and those with clinical care responsibilities, for example clinical trials units and clinical trial 'sites'. In those cases, we have specified who we mean, for example 'those with responsibility for participants' care'.
- We have used the word ‘**data**’ to mean information that is used in study analysis or for running studies.
- We have used the word ‘**information**’ to mean details provided verbally or in writing to (potential) study participants to inform their initial and ongoing consent.

Summary of PeRSEVERE principles (key messages only)

Overarching principles

- 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.
- Everyone running or taking part in studies should be aware that the more of a study's planned data that is collected, the better.
- Losing contact with a participant should not be considered the same as a participant saying that they want to stop study participation.
- Data collection should continue until a study participant explicitly tells researchers that they want it to stop.
- Study data collected in accordance with the approved study protocol up to the point a study participant stops providing data should be used in the study analysis.

Study Development and Participant Information

- Studies should be designed and resourced to allow data collection to continue wherever possible, particularly for study outcome data.
- Study protocols should include clear instructions on how participation status changes should be managed.
- Study protocols and statistical analysis plans should include considerations for the impact of participation changes on planned statistical analysis.
- Before participants agree to take part they should receive clear and balanced information about what will happen if they want to stop participating.
- Participants should be informed before they consent to join a study what will happen if contact is lost during the study.
- Throughout the study, researchers should regularly check if participants are happy taking part and should be prepared to discuss changes to participation if required.
- Everyone involved in running studies should be trained and supported to manage participation changes for the good of both the participants and the study.

Data Management and Monitoring

- Data about study participation changes should be recorded in a standardised way and include enough detail to usefully inform study management, analysis and reporting.
- Researchers responsible for running and overseeing a study should, at appropriately regular intervals, review data about participation changes in the study.

End of Study Reporting and Results Dissemination

- End of study reporting of participation status should be consistent within a study, showing any changes in level of participation, preferably by randomised group.
- All study participants should be offered the opportunity to receive the study results when they are available and thanked for their contribution, regardless of any changes to their study participation.

Overarching Principles

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 changes to participation should be clear about exactly what has changed, and what has not.

Explanation

In laws and other rules about research with human participants, 'withdrawal' of informed consent is described in all-or-nothing terms – participants have given consent to participate, or they have withdrawn their consent and are not taking part in any aspects of the study anymore.

In reality, things are often more complex than that. Study participants might choose to completely stop some aspects of study participation, for example taking study treatment, filling in study questionnaires, or attending study-specific hospital visits. Rather than stopping participation entirely, they might instead want to reduce participation, for example taking part less often. If possible within the study, participants might also change *how* they take part, for example they might take part in study activities at the same times, but in a different way (for example, via telephone calls with their research nurse instead of going into a clinic for a visit). Unless a participation change needs to happen in order to protect a study participation (usually in relation to whether or not they continue taking a study treatment), all changes in participation should be decided by the participants themselves.

It is important that everyone running and taking part in studies is aware of this complexity. We also need to use language that reflects this. Just describing study participants as 'withdrawn' or 'off-study' is unlikely to be useful in many cases, because we won't know exactly what participants' wishes are, or exactly what they want to stop.

See also:

- See the principles about study development D1 (protecting study integrity by design), D2 (protocol content) and D3 (statistical planning) for more on preparing for participation changes during the study design stage.
- The issue of clear language and communication mentioned above affects many aspects of how studies are designed, run and reported. As well as study protocols (see principle D2), this is important in communication between researchers and study participants (see principles D4, D5 and D6), training of researchers running studies (see principle D7), data collection (principle M1), monitoring study progress (principle M2) and study reporting (R1).

Glossary:

- **Study protocol:** this is the document (or set of documents) that describes why a study is needed, what it aims to achieve and how it should be run.

O2 The more data, the better: Everyone running or taking part in studies should be aware that the more of a study's planned data that is collected, the better.

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

Explanation

Clinical trials and other studies are designed to answer research questions by collecting certain data about a specific number of study participants. If the study analysis includes fewer participants' data than planned, this can make study results less reliable. For example, it might mean results are unclear about whether or not a new treatment is better, when in reality it is better. For this reason, it is important that as much of the relevant data as possible is included in the study analysis.

Everyone running and designing studies should be aware of this, so that they can take appropriate action to make sure the study collects enough data to answer the main research question wherever possible.

It is also important that study participants know how vital data collection is to the accuracy of study results. This information must not prevent study participants doing what is right for them – for example stopping study-specific hospital visits, or stopping data being collected entirely, if that is what they want to do. But they should be aware - before they join the study - of the effect of their data not being available for analysis, so that they can make an informed choice about any changes to their participation.

For example, it is sometimes possible for participants to stop study-specific visits but continue participating in the study in other ways that involve less commitment from them. Participants might like to do this, if they are given the choice. Studies should also be designed to allow this, where possible (see principle D1 on protecting study integrity by design).

See also:

- Participants should receive clear and balanced information, before they agree to take part in a study, about what will happen if they want to stop or change their participation later on. See principle D4 for more on this.
- There should be proactive discussions about participation between researchers and participants throughout the study. See principle D6 for more on this. These discussions will be more productive if participants are as informed as they can be about the implications of their decision.

O3 Losing contact: Losing contact with a participant should not be considered the same as a participant saying that they want to stop study participation.

Explanation

Sometimes researchers might find that a study participant is no longer contactable, during the time they're still expected to take part in study activities. A loss of contact should not be considered the same as a participant deciding they don't want to take part in the study anymore. Unless there is a specific reason to think it is not appropriate, reasonable attempts should be made to regain contact with the participant.

Study teams should make a plan, with patient input, when they are designing the study about what they will do in this situation. For example, they may wish to try to contact the participant directly or contact their GP to find out about their health and their whereabouts.

Study participants should be informed about what will happen in this situation, before they consent to take part in the study.

Other important considerations

In some cases, there may be evidence to suggest that the participant should not be contacted again directly (for example if it was known that their health was deteriorating quickly before they lost contact with the study). In these cases, it is still acceptable to find out what might have happened from, for example, the participant's GP, as long as it is in line with the consent participants gave before they joined the study.

See also:

- Study teams should make a plan when they are designing their study for how they will deal with loss of contact with participants. See principle D2 for more about this.
- See principle D5 about the need to inform participants, before they agree to take part in a study, of what would happen if contact is lost between them and the research team.

O4 Continuing data collection: 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 was made clear to participants before they joined the study, including how participants 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 study participant wants to stop, if they express the wish to stop or reduce their participation.

Explanation

If research participants want to stop their data being collected for the research, then it should stop. However, if they do not say they want it to stop, then it should not. This protects the quality of the research because the more of the relevant data about each participant is available for the study analysis, the better it is for the analysis.

When a participant says they want to stop taking part in a study, it could be because they do not want their data collected anymore, but it could be for other reasons. Stopping participation can mean a variety of things, and not all of these mean data collection needs to stop.

For example, a study might require a participant to attend extra hospital visits alongside some routine (non-study) visits that would happen anyway, even if they weren't in the study. After a while, a participant might find the study visits a burden and say that they no longer want to do them. They will continue to attend the routine visits as part of their usual care. Some data from the routine visits could be useful to the study.

If at all possible, the researchers should ask the participant if they are happy for their data from the routine visits to be used for the study. If the participant only says that they want to stop the study visits and doesn't say anything about not wanting their routine health data to be used for the study (even after having been asked their view on this), then the data should still be collected. They can still at any time say they don't want this to happen anymore.

This approach should be made clear to study participants before they agree to take part in a study. They should therefore be aware that until they say they want their data to stop being collected for the study, it will still be collected. However, it should also be clear that they can say they want data collection to stop at any time. Researchers must also make all reasonable efforts to find out what participants want when they say they want to stop taking part in a study, including to find out if participants are happy for their data to be collected from routine healthcare visits.

Other important considerations

Different considerations will apply in situations where individuals have lost capacity to give informed consent: applicable laws and guidance should be followed in these cases.

There may also be cases where some data collection needs to continue even after a participant has said they would like study data collection to stop. For example, data about the safety of treatments needs to be collected by law in some drug studies (also known as clinical trials of 'investigational medicinal products', or 'CTIMPs') and this needs to continue even after a participant says they do not want their data to be collected for the study anymore. In studies where this sort of rule applies, it should be made clear to participants before they join the study and it should also be described in the study protocol.

See also:

- When a participant wants to stop or reduce their participation, this does not automatically mean they must stop all aspects of participation. In fact, participation can stop, reduce or change. See principle O1 for more on this.
- Participants' decisions about whether or not data collection continues should be informed by their knowledge of the consequences of their decision. See principle O2 for more about this.
- Participants should receive clear and balanced information, before they agree to take part in a study, about what will happen if they decide to stop or reduce their participation later on. This should make clear that data collection will continue until they ask for it to stop. See principle D4 for more on this.
- The discussions about the participant's wishes should form part of the ongoing discussions about their participation. See principle D6 for more on this.

Glossary:

- **Capacity** or **capacity to consent** means a person's ability to make decisions for themselves. In the context of research, it means a person's ability to give informed consent to take part in a study. Some people have a reduced ability to make decisions for themselves, for example people with dementia. By law, children also do not have capacity to consent, so their parents or guardian need to consent (or not) on their behalf.
- **Study protocol:** this is the document (or set of documents) that describes why a study is needed, what it aims to achieve and how it should be run.

O5 Retaining data: Study data collected in accordance with the approved study protocol up to the point a study participant stops providing data should be used in the study analysis.

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

Explanation

Laws about how data can be used in the UK and the EU recognise the need to protect research, particularly when it is being done in the public interest. Laws in other areas of the world may vary and should be followed appropriately. While in most situations outside of research, individuals can get organisations who hold data about them to delete that data, this right is limited when it comes to data that is being used for research. This only applies to legitimate research with the appropriate ethical approvals (where required). It also only applies when this limitation on participants' rights has been clearly explained to them before they joined the study.

If study participants could get the study data already collected about them deleted, or not used in the study analysis, this could seriously harm the study and its results. For example, it might mean the study no longer has enough data to be able to reliably answer the research question. This might mean that the study results are unclear about whether or not a new treatment is better, when in reality it is better. If lots of data was lost in this way from one of the treatment groups it might mean the study had biased, misleading results.

Data collected for research studies is routinely made available to other researchers at the end of the study for additional research. This is only done for valid research with appropriate approvals (where required), and usually done in such a way that individual study participants cannot be identified by anyone outside the original study team. Collecting data for research studies takes a lot of time and effort, and this data sharing is one way to make the most of the effort involved. The data that is made available in this way should include data collected up to the point that an individual says they want to stop participating in a study, as long as this is in line with what they have consented to.

Other important considerations

In some specific and rare situations data already collected may need to be deleted for legal or other reasons. Wherever possible, the potential for this sort of situation should be considered in advance (particularly in relation to the specific group of people who might take part in the study) and prepared for when the study is being designed.

In some research, data can be fully anonymised, so that it is no longer possible for anyone to say who the data is about. In these cases, it is no longer possible to delete individual participants' data, because it isn't possible to say which data is about them.

See also:

- This limitation on participants' rights to have data about them deleted may be easier for them to accept if they are aware that collecting less data than planned can have an impact on the quality of study results. See principle O2 for more on this.
- Participants must be informed of this limitation on their rights before they agree to take part in the study. Under UK and EU data protection law, it is also a legal requirement that they are informed of this. See principle D4 for more details.

Glossary:

- **Study protocol:** this is the document (or set of documents) that describes why a study is needed, what it aims to achieve and how it should be run.
- **Treatment groups:** many types of research study involve comparing groups of participants taking different treatments, to see which treatment which might be better.

Study Development and Participant Information

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 and does not negatively affect the scientific integrity of the study.

Explanation

We know that in almost all studies, some participants will want to stop planned study activity before it was supposed to stop, so researchers designing studies should prepare for this.

We should make sure there are adequate resources to complete all follow-up activity. This includes making sure research sites have enough funding to collect all the data required for a study. It is also important, and in line with guidance and laws on both clinical research and data protection, that researchers designing studies should not ask for more data than is really needed.

If participants are finding the commitment of study visits too much, it might be possible for them to reduce their active commitment but still provide data for the study. For example, a participant who has stopped study treatment but agreed to keep attending some study-specific hospital visits might be finding those visits difficult to keep attending, alongside the other commitments in their life. It might be possible for them to have occasional phone calls with their research nurse instead of going in for all the clinic visits. This could suit participants, because they can reduce their level of commitment but still contribute to the research. It can also suit the needs of the research, because data can still be collected.

It might not be appropriate or feasible in all cases to make adjustments like these. There are also a different set of considerations if study participants lose capacity to make decisions for themselves during their time on a study (see the Introduction to these principles for more on this). Where it is feasible and appropriate to make adjustments, researchers designing studies should plan for it in advance.

See also:

- The study protocol should be written with the knowledge that participation can stop, reduce or change, so participants’ wishes to reduce their participation might not need to result in them stopping all aspects of participation. See principle O1 for more on this.

- The available options for participants who want to stop or reduce their participation should be communicated to participants before and during the study when necessary. See principles D4 and D6 about this topic.
- Training and support for researchers should ensure they are aware of the options for participants who want to stop or reduce their participation. See principle D7 for more on this.

Glossary:

- **Outcome data:** all research studies involve measuring something in order to reach conclusions. The thing being measured is the ‘outcome’, and data about it is the outcome data. For example, a healthcare study might give two groups of people different treatments, then measure how their health changes over time to see which treatment is better. The data about how the participants’ health changes over time is the outcome data. Outcome data is particularly important, because without it, studies cannot reach clear conclusions.

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

This should include, where necessary, study-specific definitions for different types of participation change expected over the time the study will take place. Protocols should also include a pre-defined plan, developed with patient input, for appropriate actions to take if study researchers lose contact with study participants.

Explanation

Study protocols should give clear instructions for the researchers running the study about what to do in different situations. The instructions should be designed with input from patient and public contributors.

Instructions should include what to do when participants stop their study treatment and what information to give to a participant if they say they want to stop their study visits. They should also include what to do if the research team loses contact with a study participant, which is different to participants saying they want to stop taking part.

Instructions for researchers should also say that when a participant says they want to stop taking part, the researchers should find out exactly which parts of the study they want to stop and which they are happy to continue.

Researchers should also be instructed to keep a written record (for example, in the participants' medical notes) of what the participant has said.

In each study, the reasons why study participants might stop participating will vary, and could be important to the study's research question. For example, if someone needs to stop receiving study treatment, this might be because the treatment has not worked. This would be important to know if we are looking at how well the treatment works. Researchers designing studies should think about this before they start the study, and think about whether they need to prepare for any particular situations.

See also:

- The instructions about what to do in the case of lost contact should be written in the knowledge that researchers losing contact with participants is not the same as participants expressing a wish to stop taking part. See principle O3 for more on this.
- In line with principle O4 (data collection as default), data collection should only stop if participants want it to stop.
- As per principle D6, participants should be encouraged to keep in contact with the researchers about how they are getting on with their participation in the study.
- The instructions in the study protocol should be reinforced through relevant training and support. See principle D7 for more on this.

- Good record keeping about participation changes means researchers can collect clear and complete data about the participation changes, and keep an eye on any general problems with participation in the trial. See principles M1 and M2 for more on this.

Glossary:

- **Study protocol:** this is the document (or set of documents) that describes why a study is needed, what it aims to achieve and how it should be run.

D3 Statistical planning: Study protocols and statistical analysis plans should include considerations for the impact of participation changes on planned statistical analysis.

This should include details, agreed before the study starts, of which groups of participants to include in each analysis and exactly how each analysis will be carried out.

Explanation

We know that in almost all studies, some participants will want to stop planned study activity before it was supposed to stop. Study participation can change, stop or reduce in various ways.

In some cases, for example if a participant wants to stop any further data being collected about them for a study, participation changes will lead to data being missing from study analyses. This means that the things the study is looking to measure in order to find out how successful a new treatment is (for example, participants' health status or quality of life) will not be available or not known.

Researchers designing studies need to think, before the study starts, about how they will analyse the study data. When they do this, they should think about how they will deal with the fact that some participants will have stopped their participation earlier than expected, as well as how the analysis might be affected if any study participants die while taking part in the study. Researchers should also consider any possible implications for the number of participants the study will need to have in order to produce reliable results.

See also:

- The statistical planning should be done in the knowledge that study participation may stop, reduce or change. See principle O1 for more on this.
- The study analysis needs good quality data about participation changes. See principle M1 for more about this.
- The statistical planning and details of exactly what was done to analyse participation changes in a study should be reported clearly at the end of the study. See principle R1 for more on this.

Glossary:

- **Study protocol:** this is the document (or set of documents) that describes why a study is needed, what it aims to achieve and how it should be run.
- **Statistical analysis plan:** this explains exactly how the study data will be analysed. It is important that this is written before the statisticians have seen any study data.
- **Missing data:** data that was planned to be collected might not be included in a study analysis because researchers do not have access to it, or because it does not exist.

All the planned data that is not included in study analysis is collectively called missing data.

D4 Participant information about stopping participation: Before participants agree to take part 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.

Explanation

Before potential participants consent to a study they should be informed about their right to stop participating and what this practically involves. Information given at the start of the study should make it clear that any data collected before someone stops some or all study activities will be kept and used as allowed by data protection laws (such as the UK and EU General Data Protection Regulations).

At consent, potential participants should also be aware that their data is important and is needed to help decide whether a treatment works or not, even if they have to stop taking the treatment for any reason.

Other important considerations

Under data protection laws, anyone using data about individuals needs a good reason to use the data. This reason is known as the ‘lawful basis’. In the UK, data in research studies is often used on the lawful basis that the research is being done in the public interest. In other countries, data is sometimes used on the basis of individuals’ consent. This means the data is only used when participants have agreed to their data being used, and if the participants change their mind then the data cannot be used anymore. In studies where data is used on the basis of consent, the information participants need to get before the start of a study will need to reflect this.

See also:

- Participants should be informed, before agreeing to take part in a study, about the importance of collecting as much of the planned study data as possible. See principle O2 for more on this.
- Participants should be informed about what would happen to data collection and to data already collected, if they decided to stop taking part in the study early. See principles O4 and O5 about this topic.
- Participants should be informed about what would happen if contact between them and the researchers is lost. See principle D5 for more on this.

- Participants should be encouraged to talk to researchers as they progress through study about how they are getting on, and to highlight any challenges early. See principle D6 for more on this.
- Participants should be encouraged to tell researchers exactly what their wishes are if they later decide to stop or reduce their participation. They should also be informed about why it is helpful for them to explain their decision to change their participation, if they are happy to. These will help ensure there is good data about how and why their participation changed. See principle M1 for more on this.
- Participants should be told, before they agreed to take part in a study, how they can find out about the study results when they are ready. They should be told that stopping participation early will not affect their right to find out the study results. See principle R2 for more on this.

Glossary:

- **Outcome data:** all research studies involve measuring something in order to reach conclusions. The thing being measured is the ‘outcome’, and data about it is the outcome data. For example, a healthcare study might give two groups of people different treatments, then measure how their health changes over time to see which treatment is better. The data about how the participants’ health changes over time is the outcome data. Outcome data is particularly important, because without it, studies cannot reach clear conclusions.

D5 Participant information about losing contact: Participants should be informed before they consent to join a study what will happen if contact is lost during the study.

Where necessary, participants should give consent to the efforts the researchers may make to get back in touch, for example if it would involve contacting their GP.

Explanation

While some participants actively say they no longer want to participate, others more passively lose contact with the study team by missing visits, not returning questionnaires or not answering calls, letters or emails. This can be due to changes in a range of personal circumstances, for example moving home or developing new physical or mental health problems. Before potential participants agree to join a study it is important they know what activities will continue unless they ask for them to stop, for example data being taken straight from medical records.

Participants should also be told how the study team might try to regain contact for example using a different contact method (telephone, mail and so on), contacting their GP, or using any family and friends contact numbers given by the participant at the start of the study. Some methods of trying to regain contact may require participants to give consent first. Ethics committees can advise on which ways of making contact might require participants' consent.

Study teams should decide what they will do in this situation when they are designing the study.

See also:

- Loss of contact between participants and researchers is not the same as participants saying they want to stop participating. See principle O3 for more about this.
- Participants should be made aware, before they agree to take part, that data collection will continue until they say they want it to stop. See principles O4 and D4 for more about this.
- Study protocols should include a plan for what action to take if researchers and participants lose contact. See principle D2 for more on this.
- Participants should be encouraged to discuss with the researchers if they are having problems taking part in the study, or if they know about something that might prevent them taking part until the end of the study. See principle D6 for more about this.
- Researchers should be adequately trained and supported to deal with situations where contact is lost. See principle D7 for more about this.
- Researchers with responsibility for overseeing the progress of a study should keep an eye on the number of cases of lost contact, to see if any changes might be needed to the way the study is run. See principle M2 for more on this.

Glossary:

- **Study protocol:** this is the document (or set of documents) that describes why a study is needed, what it aims to achieve and how it should be run.

D6 Proactive discussions about participation: Throughout the study, researchers should regularly check if participants are happy taking part and should be prepared to discuss changes to participation if required.

Participants should be encouraged to contact clinical or research staff at the earliest opportunity if they are experiencing difficulties with any part of the study or will be moving house.

Explanation

Consent is an ongoing process and study participants can stop their involvement at any time. Where possible, it is helpful to discuss any burden, side effects or challenges completing study activities, as they emerge. This allows for an open discussion of the problems and the potentially acceptable solutions that may avoid participants stopping all study involvement. For example, there may be alternative methods of data collection that might be less intrusive and more acceptable for the participant, such as reduced study visits or only using data collected from routine healthcare activities.

See also:

- When they discuss, both participants and researchers should be as well informed as possible about participants' rights, but also about why it is important for studies to collect as much of the planned data as possible. See principle O2 for more on this.
- If a participant is thinking about stopping or reducing their participation, they should be reminded that data collection will continue until they want it to stop, and encouraged to express their wishes about whether data collection can continue or not. See principle O4 for more about this.
- Any potential alternative methods of collecting data that would allow the participant to stay in the study should be specified in advance in the study protocol. See principle D1 for more on this.
- Researchers who are in direct contact with participants should be appropriately trained and supported to have these discussions. See principle D7 for more on this.

Glossary:

- **Study protocol:** this is the document (or set of documents) that describes why a study is needed, what it aims to achieve and how it should be run.

D7 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 should 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.

Explanation

Every member of staff involved in research studies (be that nurses at research sites or individuals responsible for the study [Sponsor]) should have clear training about managing participation changes. We should recognise that helping participants do what is best for them, while also trying to do the best for the study, is a challenging task. The nurses, doctors and other staff who run studies should be given help and support in order to do this.

Training should focus on the importance of continuing study data collection (especially the data needed to answer the research questions of the study). Training should also focus on understanding that if a participant wants to reduce their participation (for example only attend for routine clinic visits) this does not mean that they need to stop taking part in the study completely.

See also:

- Researchers should be aware, through their training, that researchers and participants losing contact with one another is not the same as participants saying they want to stop taking part in a study. See principles O3 and D5 for more on this.
- Researchers should be aware that study data collection should continue until a participant says they want it to stop. When a participant says they want to stop or reduce their participation in a study, the researchers should be trained and supported to make all reasonable efforts to find out whether or not the participant wants data collection to continue. See principle O4 for more on this.
- Training should make researchers aware of any ways for participants to continue contributing but with less commitment, so that they can discuss this with participants who are thinking about stopping participation. See principle D1 for more on this.
- Researchers should be trained and supported to have proactive discussions with participants about their participation. See principle D6 for more on this.
- Researchers should be trained and supported to collect complete and accurate data about how and why participation has changed. See principle M1 for more about this.

Data Management and Monitoring

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 data about when and why the participant has reduced or stopped their participation. Data collection should also clearly communicate the participant's wishes, including which elements of study participation they have asked to stop, which they have agreed to continue.

Explanation

There are several reasons why researchers running a study should collect good quality data about the number and nature of participation changes occurring while the study is ongoing.

Good quality data is essential for study analyses. It is also important for clear reporting of studies and so that researchers running and overseeing studies can keep an eye on any trends in participation changes. Collecting data in a standardised way where possible is important – so that data from different places (within a study or even between studies) can be more easily used, combined and compared.

It can be particularly important for study analyses to know *why* participation changes have occurred. This is so that researchers analysing the data can understand how the participation changes might have affected the study results. We know that study participants don't always give a reason for stopping participation, but when a reason is available, it should be reported to inform study analyses, possibly based on some sort of standardised list.

Whenever the participation change is the participant’s choice, a clear record of participants' wishes allows clarity for researchers about what further study activity will take place for a participant, if any. Researchers running studies have a duty to find out exactly what a participant wants when they say they want to stop or reduce their participation. If, despite these efforts, the participant has not given detailed information about their wishes, the data recorded for study purposes should make this clear. This can be important when thinking about, for example, whether any data from routine healthcare visits could be collected for use in the study.

Researchers should also check and make a note of whether or not the participant wants to find out the results of the study when they are available, regardless of whether the participant completed all parts of the study or not.

See also:

- Data collection should be planned with the knowledge that participation can stop, reduce or change, and the data collected should reflect this complexity. See principle O1 for more about this.
- Data collection about participation changes should make a difference between participants saying they want to stop taking part, and researchers losing contact with participants. See principle O3 for more on this.
- Clear data about participants' wishes is important so that researchers know if participants are happy for data collection to continue or not. See principle O4 for more on this.
- Data collection should be informed by the study protocol and the statistical planning. See principles D2 and D3 about this.
- Collection of good quality data about participation changes relies on researchers being trained and supported to collect it. See principle D7 for more on this.
- Good quality data about participation changes is essential for oversight of studies while they are ongoing, and for clear reporting of studies when they are finished. See principles M2 and R1 about this.

M2 Monitoring: Researchers responsible for running and overseeing a study should, at appropriately regular intervals, review 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.

Explanation

Those responsible for running and overseeing how a study is run routinely look at all aspects of how well the study is progressing. The frequency of these reviews depends on the nature and risks of each study.

These regular reviews should include useful, consistently-collected data about study participants stopping or reducing their participation and why this is happening. This data might show that some action is needed, for example if lots of study participants are stopping study participation early.

Decisions about what action to take should be made by those responsible for running the study, with the help of any patient and public involvement contributors. Proactive changes could benefit participants by, for example, making the study less burdensome to take part in. It could also benefit the research by helping to ensure as much relevant and accurate data as possible is available for the study analyses, making the study results as reliable as possible.

Other important considerations

Data collected and reviewed while the study is still ongoing should be interpreted with caution as it may not yet represent a full picture of participation changes in the study.

See also:

- The monitoring activity and actions taken in response to any findings should be guided by statistical considerations in the study. See principle D3 for more on this.
- The actions taken in response to review of the data might include new or different training for study researchers. See principle D7 for more on this.
- This ongoing review of studies is dependent on having good quality data about participation changes. See principle M1 for more on this.

End of Study Reporting and Results Dissemination

R1 Consistent and complete reporting: End of study reporting of participation status should be consistent within a study, showing any changes in level of participation, preferably by randomised 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.

Explanation

When reporting a study's results, it is essential that the level of and reasons for missing data due to changes in participation are presented. This helps the reader to assess the quality of the study and reliability of the results. It should be clear what happened to all study participants, including whether they completed all aspects of the study or had to stop any of them early, including reasons why they stopped, where reasons are available. Adoption of this principle, in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidance, will ensure consistency across studies.

If any participants stopped taking part in some or all aspects of the study before the end, this may have to be taken into account when analysing the study data. The analysis methods used should be reported, so that anyone reading the study results knows what has been done and why.

Complete reporting allows researchers planning future studies to learn how often and why participation changes during studies. This means they can make evidence-based adjustments to sample size calculations and adjust their study design to improve participation. Consistent and complete reporting allows other researchers to use the results for further research, for example in a 'meta-analysis', where results from several studies are combined to get an overall result.

See also:

- Reporting of data on participation changes should be done in the knowledge that participation can stop, change or reduce. See principle O1 for more on this.
- There should be separate data reported about participants who said they wanted to stop and those who lost contact with the research team. See principle O3 for more on this.
- Study researchers should plan in advance for how they will analyse the study data, including how they will account for any participation changes. See principle D3 for more on this.

- Clear reporting is reliant on good quality data collected during the study about participation changes. See principle M1 for more about this.

Glossary:

- **Missing data:** data that was planned to be collected might not be included in a study analysis because researchers do not have access to it, or because it does not exist. All the planned data that is not included in study analysis is collectively called missing data.
- **Sample size:** before a study starts, researchers need to work out the minimum number of participants they will need in order for the study to reach a clear conclusion. This number is called the sample size. The number should not be much more than this minimum number, because once there is a clear conclusion, people outside the study (that is, patients receiving routine healthcare) should benefit from the study results.

R2 Study results for all: All study participants should be offered the opportunity to receive the study results when they are available and thanked for their contribution, regardless of any changes to their study participation.

Explanation

Everyone who takes part in a research study should be given the results of that study, if they want to have them. This applies to participants who stop their participation early just as much as participants who finish all aspects of study participation. When participants stop taking part early, they should be asked about their preferences for receiving study results, and this should be recorded as part of the data that is collected about the participation change.

Participating in research involves time and effort, and can involve some personal risk or inconvenience. All study participants should therefore be thanked for the contribution they have made to improving healthcare for patients like them in future. This also applies to participants who stop study participation early.

See also:

- Participants should be informed, before they agree to take part in a study, about how they can get results of the study when they are ready. They should also be informed that stopping participation early does not affect their right to found out the study results. See principle D4 for more on this.
- Participants' preferences for getting study results can be checked by researchers during ongoing discussions about participation. See principle D6 for more on this.
- Data about participants' preferences for getting study results should be recorded along with other data about participation changes. See principle M1 for more about this.

List of contributors