Note that this document shows draft PeRSEVERE principles from mid-2020. The final principles are available at perseverepriniciples.org.

PeRSEVERE draft principles - notes for reviewers (<u>read this first</u>)

- This document contains the draft PeRSEVERE project principles as of the end of May 2020.
- Each principle has an accompanying explanation which aims to cover, in plain English wherever possible, why each principle is necessary. The explanatory text might be helpful to read if something in a principle doesn't immediately make sense to you.
- Before the principles is an introduction, which you do not need to review if you don't want to, though it might help explain some of the decisions that were made in developing the principles.
- Some principles (but not all) also have 'Other important considerations'. In previous drafts, these were called 'caveats', but the heading has changed to make it more broadly understandable.
- Some parts of the document have had less review than others, because they have been drafted nearer the time of this document being put together. These are clearly marked where relevant ('[*limited review so far*]').
- In addition – and *not* marked 'limited review' as it was impractical to do so – each of the principles has a few words in bold before it as a shorter way to reference each of them. These are new with this draft and have had limited input so far.
- The group involved in PeRSEVERE so far has also put together a substantial amount of very useful thought on *how* the principles included here might be implemented. This is not included in this document partly to keep it shorter, and also because that guidance would not form part of the planned consultation on the principles. (Reasoning: the more detailed information about how to implement the principles should ultimately be developed through further evidence generation and/or more formal consensus exercises. We may nonetheless share our suggestions for implementation alongside the finalised principles.)

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Introduction [*limited review so far*]

Background and aims

All guidelines, policies and laws about clinical trials are clear that, before taking part in research, individuals must voluntarily give informed consent, and that they can withdraw that consent at any time after having given it, without providing a reason.[1] [2] [3] Trial participants can therefore stop participating in a trial whenever they like. We argue that the spirit of this concept suggests that individual trial participants must stay in control of their own destiny, and also therefore do not *have to* stop participating when they don't want to. The only exception to this is where others feel they need to take action to protect trial participants, for example if those responsible for the participant's clinical care feel it is in their best interests to stop receiving trial treatment.

The third principle of the ICH Guideline for Good Clinical Practice[2] says: "The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society." This shows how there can be conflict between the needs of individual trial participants wanting to stop participating in a trial, and the needs of the trial and the robustness of its results ("science and society"), which will be negatively affected by participants stopping participation earlier than was planned in the trial protocol.

However, logically, it *must* be possible follow this principle in such a way that participants' rights are not compromised but *also* the negative impact on the trial's results is kept to a minimum. We must aim to do this because: a) the results of clinical trials 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 trial does not produce useful results (i.e. we don't learn anything *new* from the results[4]), the trial's participants have given their time and been put at risk for no benefit to society.

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

- **Do the best by individual trial participants:** individual trial participants should get the best possible information to inform their choices about ongoing trial

[1] Declaration of Helsinki: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
[2] 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
[3] 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
[4] 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.

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 trial participation must be informed and freely-made, in the same way as initial consent.

- **Do the best by the trial:** the robustness of trial results should not be impaired by individual trial participants' decisions to stop participating unless it is completely unavoidable.
- **Do the best by research and society in general:** trials should be transparently reported so that it is clear what changes in participation occurred, and how these changes were handled in the trial analyses.

Our principles have been developed through discussion and debate, using ethical, logical and practical reasoning. As the principles describe high-level aims, we suggest it is not really possible to base them on evidence. Instead, we have been guided by what we feel is the *right thing to do*.

Other relevant background information guiding our principles:

- The SPIRIT statement[5], which says what should be included in clinical trial protocols.
- The CONSORT statement[6], 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[7] [GDPR] in the EU and the 2018 Data Protection Act[8] in the UK). These give special protection to data used in research, including to allow researchers to keep data after a trial participant decides to stop participating in a trial, as long as certain conditions are met. These laws also mean that potential trial participants must be clearly informed, before they join a trial, about how their data will be used in the trial, including any limitations on their usual data protection rights.
- Laws governing how to run trials involving medicines[9] mandate that all data collected in a trial must be kept for a long time after the end of the trial (in some cases, as long as 25 years). This includes data about people who stopped participating early. This is so that it is possible for the regulatory authorities to check the results of the trial are accurate at any time during this period. This is particularly important when a trial led to changes in the standard of care for a particular health condition.

[5] https://www.spirit-statement.org/
[6] http://www.consort-statement.org/
[7] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=EN
[8] http://www.legislation.gov.uk/ukpga/2018/12/pdfs/ukpga_20180012_en.pdf
[9] https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/

Scope and limitations

Our principles mainly address trial participation changes that could lead to expected data being unavailable or not measured for trial analysis, e.g. participants no longer taking part in trial follow-up arrangements (whatever those might be). When participants only stop trial treatment or intervention, but carry on with trial follow-up arrangements, this should not lead to missing outcome data and is therefore mostly out of our scope.

We are aware of efforts to understand how trials can be run to *reduce* the proportion of trial participants who decide to stop participating early[10,11] (often referred to as 'improving trial retention'). This might be by offering ethically acceptable incentives to trial participants, making trial 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 trial participants decide to do. We suggest that people designing and running trials should follow evidence-based best practice around improving trial retention, as it continues to develop.

Specific arrangements apply where potential trial participants do not have the mental capacity to give informed consent (e.g. due to being unconscious, or having conditions such as dementia) or where trial participants who gave valid informed consent later lose capacity to consent during the trial. In the UK, the relevant laws include the Medicines for Human Use (Clinical Trials) Regulation[12] for most trials involving medicines, and for other trials the 2005 Mental Capacity Act[13] (applying in England and Wales) and the Adults with Incapacity (Scotland) Act 2000[14]. When dealing with these issues involving absence or loss of capacity to consent, people should follow the relevant laws. We have therefore decided that these issues are out of scope for our principles. However, where necessary we have noted where issues of capacity to consent may arise.

Terminology and language

In our experience, there can be confusion and ambiguity around terms commonly used to describe stopping trial participation, such as 'withdrawn' or 'lost to follow-up'. In general, we aim in this document to describe participation ending or changing as plainly we can, using language with explicit meaning which, as a result, can mean the same thing to everyone. The final section of this document goes into more detail about the terms used and the reasons for using them.

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[10] 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

[11] 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

[12] http://www.legislation.gov.uk/uksi/2004/1031/pdfs/uksi_20041031_en.pdf

[13] http://www.legislation.gov.uk/ukpga/2005/9/pdfs/ukpga_20050009_en.pdf

[14] http://www.legislation.gov.uk/asp/2000/4/pdfs/asp_20000004_en.pdf

Overarching Principles

O1 Many ways to stop participation: All those conducting or taking part in trials should be aware that, once enrolled, participants may reduce the level of their commitment to the trial or stop participation entirely. Language and standardised nomenclature should make clear exactly which aspects of participation have and have not stopped and give clarity about further use of data and data collection requirements.

Explanation

In laws and other rules about clinical trials, 'withdrawal' is described as an all-or-nothing concept. In fact, it is usually more complex. People participating in trials can choose to stop or reduce different aspects of trial participation, for example taking trial treatment, filling in trial questionnaires, or attending trial-specific hospital visits. They can also stop or reduce some aspects while not stopping others.

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

O2 The more data, the better: All those conducting or taking part in trials should, as far as possible, be made aware of the potential impact of missing data on the reliability, interpretation and generalisability of trial results.

Explanation

Clinical trials are designed to collect information about a certain number of trial participants. If the trial analysis includes fewer participants' information than planned, this can make trial results less reliable. For example, it might mean results suggest a new treatment does not work, when in fact it does work. For this reason, it's important that as much information as possible is included in the trial analysis.

It's important that everyone running and designing trials knows this, so that they can take appropriate action to protect the trial results where possible.

It is also important that people taking part in trials know this. This information must not stop trial participants doing what is right for them – for example, stopping trial-specific hospital visits, if that is what they want to do. But they should be aware - before they join the trial - of the effects of data not being available for analysis so that they can make an informed choice about what happens to their information. For example, it is sometimes possible for people to stop trial-specific visits but continue participating in the trial in other ways that involve less commitment from them. People might like to do this, if they are given the choice.

O3 Losing contact: Losing contact with a participant should not be considered equivalent to an explicit decision to stop trial participation.

Explanation

Sometimes a trial participant's clinical team might find that a trial participant is no longer contactable, during the time when they're still expected come in for trial-specific clinic visits. A lack of contact should not be considered the same as a participant telling their clinical team they don't want to take part in the trial anymore. Unless there is a specific reason to think it isn't appropriate, the clinical team should be able to make reasonable attempts to get in contact with the participant, and contact their GP to find out about their health and their whereabouts.

Other important considerations

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

O4 Data collection as default: Data collection and processing only stops if a trial participant explicitly tells the trial team they want it to stop.

Explanation [*limited review so far*]

It is right and fair that trial participants should be able to stop any more data about them being collected for use in a trial, if that is what they want. However, it should not be assumed that they want this, if they do not say it.

For example, a trial might require a participant to attend extra hospital visits alongside some routine (non-trial) visits that would happen anyway, even if they weren't in the trial. After a while, a participant might find the trial 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 NHS care. Some data from the routine visits could be useful to the trial. If the participant only said that they wanted to stop the trial visits and didn't say anything about not wanting their routine NHS visit data to be used for the trial, then the data should still be used. They can still at any time say they don't want this to happen.

This approach is of course only fair if was made very clear to participants before they joined the trial. It must also be easy for participants to express a wish for no more data to be used, and obvious *how* they can express that wish, if that is what they want.

Other important considerations [*limited review so far*]

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

There may be cases where some data collection needs to continue even after a participant has said they would like trial data collection to stop. For example, in some trials involving medications, some data about the safety of those medications must continue to be collected indefinitely.

O5 Retaining data: Demographic, outcome and process data collected in accordance with the approved protocol up to the point a study participant decides to stop providing data (either in part or full) should be used in the main trial analysis and may be shared for further or secondary research which is deemed ethical.

Explanation [*limited review so far*]

If trial participants could ask for data already collected for the trial to be deleted, or not used in the trial analysis, this could seriously harm the trial and its results. For example, it might mean the trial no longer has enough data to be able to reliably answer the research question. This might mean that the trial results show that there is no difference between the treatments being given to the different groups of participants in the trial, when in reality there is a difference. If lots of data was lost in this way from one of the treatment groups in particular, it might mean the trial had biased, misleading results.

Laws about how data can be used in the UK and the EU[15] recognise this need to protect research, particularly when it is being done in the public interest. While in most situations, 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. It also only applies when this limitation on people's rights has been clearly explained to them before they joined the trial.

Data collected for clinical trials is routinely made available to other researchers at the end of the trial for additional research. This is only done for valid research with appropriate approvals, and only in such a way that individual trial participants cannot be identified. Collecting data for clinical trials 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 trial, as long as this is in line with what they have consented to.

Other important considerations [*limited review so far*]

There may be extenuating circumstances meaning data is *not* retained, such as in emergency/ trauma settings where retrospective consent is sought and declined.

[15] Advice on legislations in other regions would be useful here.

Trial development and patient information[16]

D1 Protocol flexibility: Protocols should be designed and resourced to facilitate continued data collection and participant retention wherever possible, particularly for study-specific important outcomes, allowing for reduced participant commitment where this is feasible and does not affect the scientific integrity of the trial.

Explanation

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

We should make sure there is adequate resource to complete all follow-up activity. This includes making sure research sites have enough funding to collect all the data required for a trial. It is also important that people designing trials should not ask for more data than is really needed.

If participants are finding the commitment of trial visits too much, it might be possible for them to reduce their active commitment but still provide data for the trial. For example, they could have occasional phone calls with their research nurse instead of going in for all the clinic visits. This could suit the 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. Where it is feasible and appropriate, people designing trials should plan for it in advance.

Other important considerations [*limited review so far*]

Continued trial activity (i.e. data collection) and participant retention may not be possible if participant loses capacity to consent.

[16] It had been suggested that this was just called 'Trial development', but nearly half the principles in this group are about patient information, so perhaps it is worth emphasising this in the title.

D2 Protocol content: Protocols should include clear instructions on how different participation change situations should be handled and, where necessary, trial-specific definitions for different types of participation change expected over the trial period.

Explanation

In each trial, the reasons why trial participants might stop participating will vary, and could be important to the trial's research question. For example, if someone needs to stop receiving trial 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. People designing trials should think about this before they start the trial, and think about whether they need to prepare for any particular situations.

Trial protocols should give clear instructions for the doctors and nurses running the trial about what to do in different situations. This might include what to do when participants stop their trial treatment, what to do if the research team lose contact with a trial participant, and what to say to a participant if they say they want to stop their trial visits.

D3 Statistical planning: Protocols and statistical analysis plans should include considerations for the impact of participation changes on planned statistical analysis, including prospectively defined analysis populations and analysis methods.

Explanation

We know that in almost all trials, some participants will want to stop planned trial activity before it was supposed to stop. This will sometimes lead to information being missing from trial analyses. For example, a trial might involve giving two groups of people different treatments, then seeing how well each group has done after a year. If some people stop their participation early, their health at that point in time might not be known. People designing trials need to think about how they will analyse the trial data, before the trial starts. When they do this, they should think about how they will deal with the fact that some people have stopped their participation earlier than expected.

D4 Information about stopping participation: Participants should be fully informed at consent and throughout the trial about study requirements. This includes the importance of providing outcome data and completing the research, and information relating to what will happen to their data if they stop participating in order to make an informed choice about initial and ongoing involvement.

Explanation

When people are thinking about taking part in a clinical trial it is important that they are aware of what will be expected from them. This includes the number of appointments they need to attend, frequency and type of questionnaires/ treatment/ data collection activities (including follow-up). Participants should be aware that their data is needed to help decide whether a treatment works or not, even if they have to stop taking their treatment for any reason. Information given to people at the start of the trial should also make it clear that any data collected before someone stops some or all trial activities will be kept and used as per the General Data Protection Regulation.

Other important considerations

Where a trial is working with other countries where 'consent' is used as a lawful basis for data processing this will need to be revised.[17]

[17] This may need to be expanded on for future drafts.

D5 Information about losing contact: Participants should be informed during consent what will happen if they lose contact with the trial without telling the trial team that they wish to stop some or all trial activities.

Explanation

Whilst some participants actively say they no longer want to participate, others simply lose contact with the trial team by missing visits, not returning questionnaires or not answering calls, letters or emails, this can be due to, for example, moving home. Before people join a trial it is important they know what activities will continue unless they directly ask for them to stop e.g. data being taken straight from medical records. Participants should also be told how the trial team might try to regain contact e.g. using a different contact method (Phone, Mail etc), contacting their GP, using any family and friends contact numbers given by the participant at the start of the trial.

D6 Discussion when stopping: 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 relocating) in order to discuss alternatives to stopping all trial activities, such as reduced trial visits or using routine data collection only.

Explanation

Where possible, it is helpful to discuss any trial burden, side effects or negative aspects of a research study before a participant tells the trial team they want to stop some or all trial activities. This allows for an open discussion and the opportunity to suggest alternative methods of data collection or study involvement that might be less intrusive and more acceptable for the participant.

D7 Training and support: Everyone involved in conducting or overseeing trials should be trained and supported to manage participation changes[18] in the interests of both the participants and the trial. This should be done in line with applicable regulations and should include an understanding of the importance of adhering to trial visit schedules (in particular visits where research questions are answered), and appreciation that satisfying participants' intention for reduced participation may not need to result in their participation stopping altogether.

Explanation

Every member of staff involved in clinical trials (be that nurses at site or individuals responsible for the trial (Sponsor)) should have clear training on retention issues. We should recognise that helping patients do what is best for them, while also trying to do the best for the trial, is a challenging task. The nurses, doctors and other staff who run trials should be given help and support in order to do this.

Training should focus on the importance of patients attending hospitals for trial visits (especially those which are needed to answer the research questions of the trial). Training should also focus on understanding that if a patient wants to reduce participation (for example only attend for routine clinic visits) this does not mean that they need to stop taking part in the study completely.

[18] In this draft, changed from 'retention issues' to 'participation changes' for consistency with other principles.

Trial and Data Management and Monitoring[19]

M1 Adequate data collection: Data about trial participation changes[20] should be recorded in a standardised format and include information to usefully inform trial analysis including, when available, meaningful data about why the participant has decided to reduce or stop their participation. Data collection should also clearly communicate the participant's wishes, including which elements of trial participation they have asked to stop, which they have agreed to continue.

Explanation

We know that participants don't always give a reason for stopping participation, but when a reason is available, it should be reported to inform trial analyses, possibly based on some sort of standardised list. To put it another way, this is to provide meaningful information for trial analysis (i.e. end of trial)

A clear record of participants' wishes (including clarity about elements of trial participation they have not commented on) allows clarity for sites and clinical trials units about what further trial activity will take place for a participant, if any. If participants ask to stop trial visits but have not commented on further data collection, data collection from any routine visits will continue as long as required for the trial (this is mentioned in another principle, and we'd expect this to be made clear to participants from the outset). To put it another way, this is to provide meaningful information for trial management (i.e. period between date of issue and end of trial).

[19] Suggestions for improving this title are particularly welcome.

[20] In this draft, changed from 'retention issues' to 'participation changes' for consistency with other principles.

M2 Monitoring [*limited review so far*]: Those responsible for trial oversight should regularly review information on participation changes, for the assessment of any emerging trends in missing data and their reasons, and to identify common issues so that timely and targeted action can be taken to minimise further missing data.

Explanation [*limited review so far*]

People who manage and oversee the running of trials will routinely look at certain aspects of how well the trial is progressing. These regular reviews should include useful, consistently-collected data about trial participants stopping or reducing their participation. This will allow them to see if there are a lot of people struggling to complete all the trial activities, and take some timely action in response. Their action could benefit patients by making the trial less burdensome to take part in. It could also benefit the research by helping ensure as much relevant data as possible is available for the trial analyses, making the trial results as reliable as possible.

Other important considerations [*limited review so far*]

Data collected and reviewed while the trial is still going on should be interpreted with caution as they may not yet represent a clear picture of participation changes in the trial.

End of trial reporting and results dissemination

R1 Adequate trial reporting: End of trial reporting should be consistent within and across trials, and should be adequate to allow accounting for all trial participants, assessment of external validity and attrition bias, and informing future trials' power calculations, design and conduct. Methods used to handle missing data should also be adequately and transparently described to allow interpretation and replication of results.

Explanation [*limited review so far*]

When a trial's results are made public, it is very important that all aspects of the results and how the trial was run are clear. This way, if a trial's results might have an impact on patients' healthcare, we can make sure that the results are definitely reliable. Clear reporting is also important for anyone using the trial's results for further research, for example in a 'meta-analysis', where results from several trials are combined to get an even more reliable result. Clear reporting is also important for people designing future trials in the same area, and for people doing research about how to encourage more people to keep participating in trials.

Clear reporting means that it must be possible for people reading the trial results to see what happened to each trial participant, including whether they completed all aspects of the trial or had to stop any of them early. When people stop taking part in some aspects of a trial early, the statisticians analysing the trial data need to adjust the analyses to ensure the results of the trial are still reliable. Clear reporting also therefore means that it is clear what adjustments were made, and what assumptions that the statisticians made in deciding how to adjust the analyses.

R2 Trial results for all: [*limited review so far*] All trial participants should be thanked for their participation and offered the opportunity to receive the primary trial results when they are available, regardless of any changes that have occurred to the individuals' trial participation.

Explanation [*limited review so far*]

Everyone who takes part in a clinical trial should be given the results of that trial, if they want to have them. This applies to people who stop trials early just as much as people who finish all aspects of trial participation.

Participating in research involves time and effort, and often some personal risk. All trial participations should also therefore be thanked for the contribution they have made to improving healthcare for people like them in future. This also applies to people who stop trial participation early, particularly if those people might feel bad about having stopped.

Terminology: describing end of participation

In general, we aim to describe participation ending or changing as plainly as possible, using language with explicit meaning which, as a result, can mean the same thing to everyone.

- For aspects of trial participation requiring ongoing commitment (e.g. 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 (or in some situations, they stop based on a clinical decision), we will use the formula **"stopped … early".** For example "stopped trial-specific visits early".
    - When a participant decides to *reduce* their level of commitment, without totally having stopped, we will use the term "**reduced…".** For example, "reduced frequency of trial visits". This can be used to describe changes in receipt of trial treatment or intervention, but trial 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, this will be explicitly stated, for example "stopped trial visits early; telephone follow-up only".
    - When a participant has stopped an aspect of participation at the time that the protocol specified it was supposed to stop, we will say "**completed…".** For example, "completed trial visits".
    - In some trials, participants may not get treatment/intervention for a set period of time. 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 formula "**stopped treatment because [of]…".** For example, "stopped treatment because it was no longer beneficial", or "stopped treatment because of side effects".

- For aspects of trial participation that do not require ongoing, active commitment (e.g. trials units getting additional data for the trial 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".

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

- Loss of contact:
    - We expect protocols to specify how to manage loss of contact with participants (i.e. without them having expressed any explicit wish about stopping trial 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 trial analysis. The protocol should specify when this later contact should be.
    - At the end of the trial, there may be a group of participants who lost contact with the trial without explicitly asking to stop participating and for whom no further information was ever obtained. We suggest these people could be described as having **lost contact, never regained.**
    - If data about these participants is obtained through other sources (e.g. from routine healthcare data providers like NHS Digital, and always in line with participant consent), they might instead be categorised as having had **no further direct follow-up.**

- **Change in participation status**: a general term 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 trial participation.

Relationship to existing, commonly-used terminology

Existing terminology can often be vague or ambiguous. The following is a list of some of these and how they relate to the explanations given above:

- **"Withdrawn":** is sometimes used to describe any of the situations given above, but usually indicates that the participant has made a statement of their intent to stop participating.

- **"Lost to follow-up":** is sometimes used in a general sense in final trial reports to describe all participants who have not provided outcome data for the trial. Otherwise, it is used to describe participants who have no further involvement in a trial after a certain point, often with the implication that they have lost contact with the trial rather than having explicitly stated their decision to stop participating.

- **"Discontinued":** may most often be applied to stopping trial treatment/intervention.

- **"Non-compliant":** indicates that participants are not taking trial treatment/intervention as instructed, but the term is not totally clear about whether

they are taking no treatment at all, or less treatment, or taking it in a different way (e.g. right dose but wrong times).

- **“Dropout”, “Off-trial”:** these are used to describe different situations and are generally not clear terms.