



Note: this document contains materials that were part of the starting point for developing the PeRSEVERE principles. The final principles are available at perseverepinciples.org.

Principles for handling withdrawal and loss to follow-up in ongoing trials: Suggestions from the Clinical Trials Research Unit, University of Leeds

- Although trials should be designed to *prevent* withdrawal and loss to FU (in balance with its intended aims and generalisability), some level of dropout from intervention or follow-up schedule is inevitable. We should design trials to cope with this and minimise the harm to the trial's objectives, while still protecting the rights of trial participants.
- The principles below have been developed through discussion at the CTRU at University of Leeds based on our collective experiences.
- Notes on assumptions and scope:
 - The table below sets out proposed principles for handling patient-level withdrawal and loss to follow-up in ongoing trials. It does not cover site-level withdrawal in cluster-randomised trials, but some of the some considerations may apply.
 - These principles assume that we have a CTU that works with sites, and sites that recruit and follow up trial participants. Clearly this is not the only model for conducting trials, but hopefully many of the principles can extend to other settings.
 - Notes on terminology used here:
 - 'Withdrawal' indicates that a participant has expressed a wish to stop participating in some or all aspects of the trial.
 - 'Lost to follow-up' indicates the participants has not expressed any wishes about further participation, but their site can no longer make contact with them; once a certain amount of effort has been made to contact them, they may be considered 'lost to follow-up' and the CTU may not request more data for them (in accordance with the trial protocol).
 - 'Dropout' is used as a general term to cover both of the above.
 - This terminology is arguably flawed (see proposed principle about this), but is used here for ease because the terms are commonly used.
 - This list represents the ideal from a trials unit perspective; clearly patients may have a different view, and site staff have a difficult job to do in managing sometimes sensitive situations – so sometimes the ideal may not be possible. However, this exercise is about getting everyone at least on the same page with these ideals.

#	Proposed principle	Example of issues in current practice	Comments/Caveats
1. Designing trial processes			
1.1	Follow-up schedules should allow flexibility in mode and frequency of follow-up where appropriate.	Protocols may be inflexible; for a patient finding the visit schedule a burden, a site may only be able to offer stopping all visits rather than just reducing them.	We may or may not make this a formal part of the protocol/PIS – depending on risks of ‘encouraging’ people to reduce their follow-up.
1.2	We should design processes to be able to collect data from other (non-trial) sites if required.	Patient moves to have regular visits at non-trial site and we can collect no more data about them, although data exists.	e.g. GP surgeries, other hospitals. A possible mechanism could be to prepare a set way for trial sites to request updates from other centres; once returned, these could then be treated as source data and used to complete (e)CRFs. May be hard to do in practice, and patients may not view this favourably. If became widespread approach, would need to be formalised (e.g. with agreements with non-trial sites and formal resourcing arrangements.)
1.3	Trial protocols (or statistical analysis plans) should include trial-specific definitions of withdrawal, particularly in relation to how the trial outcome measures are defined, and how they will be handled in the analysis.	Specific example from cancer trial: patients starting new treatment might be considered ‘withdrawn’, but the treatment change may well be due to failure of the previous line of treatment (and therefore there has been a progression event).	N/a
1.4	Trial protocols should define how to handle cases where contact with participants is lost.	Sites do not have clear process to follow when they cannot contact a participant. Difficult for CTUs to request that sites take certain actions for these patients if they have not been pre-agreed in the approved protocol.	N/a

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1.5	We should aim to move towards use of electronic health record data where this would reduce the follow-up burden on patients and sites, or provide a reliable backup data collection mechanism.	N/a	Still many barriers to this being routine, and data quality (including timeliness of availability) uncertain; but seems likely to be long-term direction of travel.
1.6	We should incentivise sites to collect follow-up data in a similar way to the way recruitment is incentivised.	Sites aim to recruit many participants (as they are rewarded for this) but do not have enough resources to keep up with data collection demands; possibly less willing to keep collecting data for withdrawn patients as a result.	Finer detail of how this would work might be complex; and would put greater onus on Sponsors to justify data collection requirements, especially for amendments proposing increase in these.
2. Informing participants			
2.1	Trial participants should be adequately informed about implications of dropout on data collection; we should facilitate an 'informed withdrawal' wherever possible.	Participants are given some information at initial informed consent about what might happen if they stop taking part; this might not be clearly explained, and they might not remember it. They may not be reminded of the relevant points at the point when they express a wish to stop participating in all or part of the trial.	'Informed withdrawal' is a nice idea, i.e. giving information about withdrawal at the time of withdrawal - but likely not very practical in many cases. There may be a danger of patient or site staff perceptions of barriers to withdrawal if we ask people to read information before deciding what they want to do. We are therefore still very reliant on information given pre-trial.

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2.2	We should tell participants that they have the right to ask us to stop collecting data about them for the trial, but that we will not stop collecting data unless they clearly tell us not to.	In cases where patients stop trial visits but still attend hospital for some routine visits, we might still like to get occasional patient status updates (if the patient has not explicitly said we cannot do this). However, if it is not made clear in the patient information sheet, this may not be fair to the participants, and sites may not agree to send any further data.	This relates to the principle below about the default being to continue data collection if data exists and we have no information on patient wishes. Clearly this would need to be explained carefully and in a way that sounds fair, and we would need to be explicit about how patients can express their wishes on this matter.
2.3	We should tell participants that, if we lose contact with them, we will attempt to contact them or their GP.	When sites have lost contact with patients, we might like to ask them to contact GPs to find out what might have happened. Without having explained this clearly in the patient information, it may come as a surprise to the patient, or sites may refuse to help with this if they feel it is not fair or transparent.	This needs to be explained carefully in the context of the need to make the research (which many people have given time to) as good as it can be.
3. Training sites			
3.1	All involved in conducting trials should be aware of, and implement, the intention-to-treat principle.	Patients being allowed (or even encouraged) to stop taking part in a trial if they do not get allocated to the treatment arm they would like; At the point of a patient expressing desire to stop some participation in the trial, site staff not necessarily taking action most likely to ensure data collection can continue	Important to acknowledge that site staff do a difficult job, and that withdrawal cases can sometimes be very sensitive.

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3.2	We should expect sites to help us trace lost-to-FU participants in line with the protocol.	Without clear instructions, site handling of loss to follow-up may be variable, meaning potentially obtainable data is lost from the trial.	'Trace' just means trying to reach the individual, or possibly their GP.
3.3	We should expect sites to clearly record participant wishes if they withdraw, including about further data collection.	Site just records limited detail using ambiguous terminology, such as 'off-trial', or just 'wishes to withdraw'.	Source data should accurately record patient wishes regarding further trial treatment, further visits, further data collection (including patient reported outcomes) and any other salient points – including where no preference expressed on any of these.
4. Implications of withdrawal and loss to FU on further data collection and use			
4.1	It should be impossible to delete data already collected.	Hopefully no longer any issues in current practice (i.e. understood that research data cannot be deleted).	General comment on this section: there may be some exceptions relating to loss of capacity to consent in some trials (non-CTIMPs). Data protection law now makes clear that research data can and should be kept beyond the point of any withdrawal.
4.2	In the case of dropout from trial visits, continued data collection should be the default when data are available and there is no information on patient wishes.	A patient says they would like to stop trial visits but makes no comment (or are not asked) about whether they are happy for data about them to be collected from routine hospital visits. They continue to visit their site from time to time, but the site decides on their behalf that they will send no more data for use in the trial. CTU asks if further data can be used, and the site will also not ask the patient their wishes on this, using 'they are off trial' as justification.	To be clear, patients retain the right to ask for data collection to stop; this is about further collection being the default when the patient has not said anything about stopping it. This approach needs to be made very clear at initial consent, and sites should understand it too. We should make it very clear how patients can tell us/their sites what they want to do.

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4.3	In the case of dropout from trial visits, any planned data linkage to electronic health record data should continue when there is no information on patient wishes.	Data linkage stops for all patients listed as 'withdrawn', even though they may not have expressed any wishes regarding this aspect.	As above, where there is no information on patient wishes regarding this work, it should continue. This should be made very clear in patient information sheets. It is, however, arguably more risky than the point above as it involves data being sent elsewhere.
4.4	We should be able to attempt to re-contact lost to FU participants before the end of the trial.	Patients are considered to be lost to follow-up after a period of being uncontactable, but then do eventually return to their site for routine visits. Without clear processes in the protocol around this, the CTU never finds out about this and the trial loses some data.	'Before the end of the trial' might be in the period running up to analysis- to check if there are in fact any updates on any of the lost to follow-up patients. This is easier to do (and would be easier to get sites' assistance) if it is written into the protocol.
4.5	Availability of anonymous data at the end of the trial for secondary research should be unaffected by participant withdrawal or loss to FU.	Patients deciding to stop trial visits is interpreted as meaning data cannot be shared (anonymously) for secondary research; secondary research is harmed by some trial data not being available.	<p>This is separate to cases where a specific consent item asked people to opt into or out of data sharing.</p> <p>This approach is justified because sharing is anonymous, and because data is shared only for bona fide research in the public interest. It is nonetheless fair to be open about this approach at the time of informed consent.</p> <p>Data sharing is sometimes linked to biological sample sharing; different consent issues apply to that.</p> <p>This point suggests that people cannot opt out of data sharing for further research; in practice, if someone explicitly asked for their data not to be shared, we might agree rather than argue the case.</p>

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5. Reporting at the point of withdrawal or loss to FU			
5.1	We should aim to collect reasons for dropout wherever possible.	Limited data to explain why patients stopped taking part; handling missing data in the analysis becomes more difficult.	Provision of a reason cannot be any sort of barrier to participation stopping. Might it be feasible to standardise a list of reasons? Or decide on a trial-by-trial basis depending on what suits analysis plan?
5.2	Withdrawal and loss to FU should be managed through CTU-site discussion and case review rather than simple reporting from site.	Reporting of withdrawal/loss to FU cases comes only via a form, with some detail/nuance lost; higher chance of misreporting (e.g. site misreporting patient wishes due to limitations of terminology used) and more difficult for CTU to suggest best action (i.e. action that might allow continued data collection).	Instead of just collecting a CRF, CTU could say that first step when patient wants to withdraw (or might be lost to FU) is to have a discussion with the CTU to establish exactly what has happened. Relying on the form means CTU has no input into what action is taken, and may lead to misreporting from site. This may be 'good practice' rather than a principle. In some cases, the time taken to do this might outweigh the benefit to the trial.
6. Reporting at the end of the trial			
6.1	Common definitions and terminology should be used to aid consistent reporting.	Terminology commonly used is ambiguous and can easily lead to misinterpretation ('off-trial', 'withdrawn', 'loss to follow-up').	This applies equally during a trial as much as for post-trial reporting. It may be useful to base categories on exactly what the participant has said they would like to stop – while recognising that these are not necessarily mutually exclusive.
6.2	Trials should accurately report their dropout numbers to inform future trials.	Reporting may be inadequate; new trials in a given population with a given intervention have limited information on which to base their withdrawal/loss to FU predictions (and therefore these are inaccurate).	Hopefully CONSORT has somewhat dealt with this; though terminology needs clarifying (as above). It could be useful to record dropout over time (or changes over time if not constant).