Note that this document shows draft PeRSEVERE principles from early 2020. The final principles are available at perseverepriciples.org.

Introduction

The drafted principles begin on page 3. Read through the notes on the review process and specific questions first, if you need to.

Review process

- Please review the principles in Teams unless it's very difficult or impossible for you to do so. If that's the case, Word documents are available on request.
- Note that there are two documents – this one with just the principles in case that's simpler to review, and the other one with the explanatory notes to help with understanding decisions made, etc. You only need to comment on one of these.
- Note as well that in both documents 'group 7' principles are given first as they set the scene for the rest. We can re-order and re-number once we've refined, but existing numbers have been left in for now as that's what we've used so far.
- Please add comments rather than making changes, or else people reviewing after you won't see the principles as first proposed. It'll be really helpful to preface any comments with '**Major**' or '**Minor**':
    - Major changes would include suggestions to remove principles, add new principles, combine them or any other suggestions that affect several principles. These will be discussed to agree what changes to make.
    - Minor changes would include wording changes within single principles. These will be referred back to the groups that wrote the principles, for consideration.
- You don't need to review or comment on the explanations or notes (i.e. right-hand column of any tables) unless you want to. These won't be shared further in this form. These can in due course be tidied up and divided into: a) brief justification to help explain why each principle is needed, b) any caveats or exceptions, c) suggestions about how to implement each principle in practice and d) any other comments.
- Once we agree between us (which might follow another round of amendment and review), we will share with all the collaborators (n = ~90) for review.

Specific points for review/discussion

- General comments on wording, clarity, or anything else are welcome.
- Specific questions:
    - Can any principles be combined?
    - Should any be removed or amended due to being:
        - Superfluous / 'nice to have' rather than essential?
        - Not within scope? (The scope needs to be to do with handling end of participation when it happens, rather than reducing or preventing it - important though that is)
        - Too detailed? (Higher-level principles seem more likely to be widely agreeable - beyond our group - the more detail we get into, the more chance for disagreement about exactly how to achieve the high-level aims)
    - Issues around capacity to consent (or validity of consent, should any issues around that arise in a trial) seem an important consideration for our principles. Have we incorporated caveats in the right places?
    - Several groups suggested the need to monitor numbers and trends in early end of participation. Should we add a principle about this? If so, what should it say? (In other

words, should we suggest monitoring of trends in ongoing trials ought to happen, or is this something for individual trial teams to decide depending on risk?)

- There was a suggestion to add a principle saying that ending participation early does not affect a participant's right to find out the results of that trial (if they want to know). This could be a nice idea and link to an increasingly-discussed topic. What do others think?
- Might it be helpful to add a principle at the top of the list (or in some sort of preamble) along the lines of 'for the avoidance of doubt, trial participants have the right to stop any aspect of participation at any time…'? (Sort of like 'whereas' statements in legislation.)

7. Overarching principles

7.1

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

7.2

All those conducting or taking part in trials should, as far as possible, be made aware of the potentially negative impact of missing data on the reliability, interpretation and generalisability of trial results.

7.3

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

[Additional suggestions]

Trial publications should clearly state the number of participants who were included in the assessment of each outcome measure.

Trial participants should be offered the opportunity to receive the trial results when available, irrespective of their final participation status.

1. Trial and protocol design

1.1

Protocols should be designed and resourced to facilitate continued data collection and participant retention wherever possible, allowing for reduced participant commitment where appropriate/necessary.

1.2

Protocols should include trial-specific definitions where necessary, and clear instructions for how different situations should be handled.

1.3

Protocols and statistical analysis plans should include considerations for the impact of early end-of-participation on planned statistical analysis.

1.4

Protocols should include actions for monitoring the early end-of-participation and loss to follow up.

2. Participant information

2.1

Patients should be fully informed about study requirements and the importance of providing outcome data and completing the research in order to make an informed choice about initial and ongoing involvement.

2.2

Participants should be informed that they need to be willing to have any of the study treatments.

2.3

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 in order to discuss alternatives to withdrawal such as reduced data collection or routine data collection only.

3. Training

3.1

Everyone involved in conducting or overseeing trials should be trained and supported to manage retention issues in the interests of both the participants and the trial. This should include an understanding of the importance of further data collection (in particular primary outcome data), and appreciation that satisfying participants' wishes for reduced participation may not need to result in their participation stopping altogether.

4. Further data processing

4.1

Data collection and processing only stops if a trial participant explicitly requests for it to stop.

4.2

Demographic, outcome and process data collected in accordance with the approved protocol up to the point a study participant makes a request to stop providing data (either in part or full) should be used in the main trial analysis.

4.3

Demographic, outcome and process data collected in accordance with the protocol up to the point a study participant makes a request to stop providing data (either in part or full) may be shared for further or secondary research which is deemed ethical.

4.4

A procedure for continued collection of safety data when a participant decides to withdraw from a trial must be clarified in the protocol.

[Additional suggestions]

Minimise data collection

Include more clarification and explicit information in Patient Information Sheet (potentially some standard wording)

Training for Investigators, site staff and CTU staff re importance of data collection and follow-up (provide some generic slides)

5. Reporting to CTUs

5.1

Trial data collection about retention issues should include information, recorded in a standardised format, to usefully inform trial analysis; this should include, when available, meaningful data about why the participant has decided to reduce or stop their participation.

5.2

Trial data collection about retention issues should clearly communicate the participant's wishes, including which elements of trial participation they have asked to stop, which they have agreed to continue and which they have made no comment on; this information should be recorded in a standardised format to enable monitoring of trends.

6. Reporting from CTUs

6.1

Ensure consistency of reporting of trial participation status within and across all trials both during the trial and for end of trial reporting.

6.2

Stopping treatment should be handled separately.

6.3

Reporting during the trial should allow for the assessment of any trends in missing data and their reasons, to identify common issues so that timely and targeted action can be taken during the conduct of the trial to minimise further missing data (e.g. specific centres could be targeted; a protocol amendment may be required, operational issues can be identified). Interim reports of missing data should be interpreted with caution as data collection and cleaning is ongoing.

6.4

End of trial reporting 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.

6.5

A-priori defined analysis populations and analysis methods should be adequately described in the statistical analysis plan and end of trial reports to ensure transparency and to allow replication of results.