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An online resource to guide trialists, research staff and patient contributors in how best to prepare for and manage clinical trial participation changes

Abstract

It is routine for a proportion of research participants in a given study to stop or reduce their participation before the end. Regulatory and ethical guidance does not adequately address real-world complexities around this, or guide all those involved in research about how best to uphold participant interests and study integrity. Without agreed standards to follow, there can be negative impacts in both of these important areas.

The PeRSEVERE project (PRincipleS for handling end-of-participation EVEnts in clinical trials REsearch) was initiated through the UKCRC Registered Clinical Trials Unit to address this issue. Through a wide-reaching, inclusive process, the project's main output was a set of guiding principles that elaborate on well-established ideas of Good Clinical Practice.

The scope of the PeRSEVERE principles is broad, impacting on all areas of research conduct and all stakeholders in research - including researcher professionals, study participants and public contributors. In this NIHR efficient / innovative delivery project, we developed a new online resource to help communicate the ideas within PeRSEVERE and provide resources to help anyone involved in research put them into practice.

The new website includes a short animation to help give people a brief introduction to PeRSEVERE. It also contains detailed 'implementation guidance', suggesting how the PeRSEVERE principles might be put into practice in different areas of research conduct. The additional resources include template patient information sheet wording (developed with input from over 20 patients) and role-specific guidance to help people with a particular involvement in research understand what the PeRSEVERE project might mean for them.

The resources are now available at https://perseverepriciples.org. We will share this link widely and continue to add or link to new resources to the site when they arise. We would welcome further suggestions or feedback, which can be submitted via the website itself.

Introduction

In almost all clinical trials, a proportion of the participants will stop or reduce their participation before it was originally due to end. Ethical and regulatory rules governing clinical trial conduct address the possibility of participation changing by the well-established 'right to withdraw informed consent'. This typically states that participants may change their mind about participating in research at any time during the research, without detriment and without having to give a reason for their decision.[1]

A fundamental problem with the existing 'right to withdraw' is that it is presented in binary terms, i.e. participants are participating or they have withdrawn. In practice, there are often various ways that a participant's level of involvement in a research study can change, reduce, stop or even increase.

There are also important distinctions to make between situations where participants actively state a wish to change or reduce their participation, situations where contact is lost between researchers and participants and situations where clinicians or others decide that aspects of participation should stop (particularly with regard to receipt of trial intervention).

While these nuances and distinctions are sometimes understood and put into practice by those running or overseeing research, it is not done consistently, and not reinforced by agreed, foundational standards. This variation in practice can and does have untoward impacts on participants and research studies, shown through empirical evidence and/or anecdotal observations. For example:

- Participants are not given good enough information about participation stopping;[2,3]
- Outcome data may be avoidably lost because participants are not informed of their choices to continue participating with reduced commitment where these choices exist;
- Data quality and clarity of trial reporting about participation changes are impaired;
- Participants may feel unsupported when stopping their participation early; [4,5]
- Participants are not offered information they want to have after they stop participating early (such as the results of a trial they took part in).

There is an argument that some of these consequences contradict the widely accepted condition of the right to withdraw consent that it must be without 'reprisal' or 'detriment'.

The PeRSEVERE project (PRincipleS for handling end-of-participation EVEnts in clinical trials REsearch) is a collaborative initiative, set up through the UK CRC Registered CTU Network. Its aim has been to develop high-level principles to guide how clinical trials and other research projects are set up and run, given that some participants will stop or reduce their participation before it was originally due to end. The project was started because of widespread impression across Network CTUs that there were not adequate, agreed standards in this area, and that practice was variable as a result.

Through discussion and debate within our collaborative group (over 80 collaborators, including individuals from over 40 registered CTUs within the UK) and an international consultation exercise in 2021, we established a consensus around our final set of principles, which were made public in 2022.

Release of our principles represented a significant milestone for PeRSEVERE. However, our wider aim has always been to impact on research culture and practice, ensuring that participation changes are managed in ways that do the best by participants and by the studies they participate in.

It is likely that implementing our principles is, in some ways, more challenging than implementing a simpler, binary approach to 'withdrawal', especially for aspects where what is currently done does not align well with our guidance. This was highlighted by the responses to our public consultation. Although respondents gave strong support overall to our suggested principles, a significant proportion of comments expressed uncertainty about how they might be put into practice.

The purpose of this NIHR efficient / innovative delivery project was to produce an online resource aimed at all those who design, run or oversee clinical trials and other applicable research (including methodologists, statisticians, operational research staff, recruiters, patient contributors and oversight committee members).

We aimed for the resource to provide guidance and training materials to help these target audiences discover and understand the PeRSEVERE principles and their implications. It would also provide guidance to show how the PeRSEVERE principles can be put into practice, signposting relevant tools and templates.

The aim of providing these would be to improve confidence and capability amongst all stakeholders in preparing for and managing participation changes in ways that maximally protect participants' rights and clinical trial quality (including to avoid the potential untoward impacts mentioned above).

Methods

Compiling the PeRSEVERE implementation guidance

The PeRSEVERE principles and explanatory guidance are deliberately 'high-level', focussing on what should be done more than how it should be done. However, PeRSEVERE generated many suggestions for good practice, and the project steering group agreed these should be collated into 'implementation guidance' to accompany the principles. These suggestions arose from several sources, including published literature, comments added to the public consultation in 2021, and contributions to a piloting exercise conducted across 8 UK clinical trials units in 2022. Prior to finalisation, the draft implementation guidance was shared for review with the PeRSEVERE steering group, and those involved in the pilot and in previous PeRSEVERE project work.

Website, social media and visual identity

With the help of an in-house web designer at the Leeds Clinical Trials Research Unit, and using University of Leeds web templates, we created a website for PeRSEVERE (its previous web presence was on the UK Clinical Research Collaboration website). This would be the primary home for the PeRSEVERE principles and accompanying explanatory guidance, the implementation guidance and associated resources. We also set up a profile on Twitter (now X) as another route for sharing our recommendations (handle: @trialspersevere).

An in-house graphic designer developed a new project logo to give the project's outputs a visual identity (as a means to improve the visibility and impact of the project). This built on the way that the key idea in PeRSEVERE – that participation changes in trials should not be thought of as binary in nature – has been visually communicated in past presentations.

Animation

We developed a short animation as a more engaging way to introduce people to the PeRSEVERE project and communicate its main ideas. This followed a standard process, working with the chosen service provider to agree the voiceover script, the visuals, and the choice of voiceover artist and music. We produced seven additional versions with translated captions as a way to potentially increase the reach of the project. A small group of patients and research professionals from the PeRSEVERE collaboration were involved in reviewing the voiceover text, suggestions for on-screen visuals and drafts of the animation.

Patient information sheet wording

Several of the PeRSEVERE principles have implications for the information given to potential research participants, and prior evidence has highlighted the inadequacies with existing information sheets (see references given above). Development of template wording for research patient information sheets was therefore an important resource to add to our website.

We identified a group of patient contributors to help with this workstream. The invitation to contribute was sent via various different routes, as the project was not specifically relevant to one patient population. Patients already involved in PeRSEVERE helped choose the final group of patients to join the focus group. A group of researchers from the wider PeRSEVERE collaboration were also involved in an advisory capacity.

Template wording was developed across three group meetings, beginning with an open exploration of the topic (i.e. about what information to give to potential research participants about stopping their participation), reviewing examples of existing wording, prioritising topics for inclusion and exploring good and bad ways to communicate the information.

The PeRSEVERE project lead drafted template wording based on the discussions, and all focus group members (and the advisory researchers) were asked to review. A second draft was created based on their feedback, and this was then shared with a larger group of patients who had not been chosen for the focus group but who had expressed an interest in taking part in the review.

The final wording was translated into five other languages commonly spoken in the UK, to encourage inclusive practice in UK-based research.

Role-specific guidance

Appreciating that the PeRSEVERE guidance is extensive and has a broad scope, we aimed to create short guidance notes for different stakeholder groups, to help them navigate the available guidance and understand which sections may be more relevant to them. The groups we planned to involve were trial managers, statisticians, data managers, monitors, recruiters and patient contributors.

Individuals representing the clinical trials unit roles were recruited through the Registered Clinical Trials Unit Network mailing lists, which include a representative for each stakeholder group within each trials unit. Recruiters were identified via Trials Methodology Research Partnership groups. Patient and public contributors who have contributed to the PeRSEVERE project or related work were invited to help create the guidance for patient contributors.

The guidance notes were created through holding a structured discussion with the representatives from each stakeholder group, to explore the challenges they find when managing participation changes in research, and which aspects of PeRSEVERE might therefore be most relevant to them. The contributors were given a chance to review the draft guidance before it was made public.

Other resources

Template wording for protocols was generated as part of ongoing work in the Leeds Clinical Trials Research Unit to update the local protocol template. The final output took into account the SPIRIT guidelines[6] and the content of the Health Research Authority protocol template[7].

Training materials were created from training materials used previously to convey the main messages in the PeRSEVERE project. The materials explicitly allow and encourage re-use and onward sharing. We planned to produce short **audio guides** as an additional way to engage with the PeRSEVERE guidance.

We planned to **signpost existing, relevant resources** so that the PeRSEVERE website would be a single place for all guidance on the topic of managing participation changes in research. We gathered existing resources through scoping literature reviews conducted through the PeRSEVERE project and related work. We also asked members of the PeRSEVERE project steering group if they had additional suggestions for links to add.

Results and conclusion

The new online resource is available at [perseverepriciples.org](). This includes the PeRSEVERE principles, in more easily navigable form than in their previous document format, and all of the comprehensive implementation guidance. The animation is shown on the website's homepage as an immediate way to understand what the project is about.

Several resources are available with the first release of the website, including the template wording for patient information sheets that was developed as part of this NIHR funding. The final wording is not a radical departure from the sorts of wording used in current studies, but does address all of the PeRSEVERE recommendations about patient information. It presents wording in a 'layered' fashion, helping to avoid information overload for patients. It takes into account the new standards for patient information that the Health Research Authority released 2023[8].

The remaining resources will be added to the website in due course, following finalisation. The audio guides have not yet been created, but the NIHR funding has enabled these to be planned in more detail, to be created at a later date. Very few pre-existing resources were identified to link to, highlighting the novelty of this work.

This new online resource will make the PeRSEVERE recommendations more easily findable and digestible for research professionals and patient contributors in the UK and beyond. The nature of the content means it is unlikely to go out of date, and processes are in place to add to the list of available resources as new, relevant work is done.

Anecdotally, there are signs that clinical trials units across the UK have been prompted by the PeRSEVERE project to review and amend their processes for managing participation changes in their trials. The new resource is likely to accelerate that process, ensuring the real-life complexities of participation changes in clinical trials are better managed, for the good of participants and the studies they take part in.

Dissemination

Dissemination of the resource will include the following:

- We will share the resource with relevant networks and individuals around the UK and internationally (for example, the UKCRC Registered Clinical Trials Unit Network and UK Trial Managers Network), highlighting its relevance to them and asking if they might share with colleagues and network members;
- We will contact custodians of other, relevant online resources to find out if they might link to our resource;
- Producing a peer-reviewed publication about the PeRSEVERE project and highlighting the resource;
- We may produce a short video to introduce the resource (for example, for sharing via social media);

- We will explore other routes for helping the guidance influence practice, for example via the work to develop guidance alongside the new clinical trials legislation in the UK;
- We will look for further opportunities to deliver presentations and training about PeRSEVERE and the issues it raises, for example at the International Clinical Trials Methodology Conference 2024.

We would welcome further feedback and suggestions for this resource. These can be submitted using contact details available on the website: https://perseverepprinciples.org/contact/.

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Appendices

None.

Conflict of interest declaration

There are no conflicts of interest to declare.