Protocol for:

Trial Methodology Research Partnership project title:
Protocol and resources development for prioritised recruitment and retention strategies (PRESS-2)

This protocol will be complemented by the Protocol development for prioritised recruitment and retention strategies (PRESS-1) funded by the Health Research Board Trial Methodology Research Network in Ireland as part of the jointly funded project.

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Protocol registration

This protocol is a working document, it will be updated to reflect progress and findings as the project progresses. For transparency, versions of the protocol will be uploaded to https://osf.io/.

Plain English summary

Clinical trials are important, but recruiting and retaining participants is challenging. Fewer than half of all trials meet recruitment goals, wasting time, money, and effort for both researchers and participants. Poor retention, when participants drop out prematurely, weakens trial results. Recruitment and retention problems delay the timely development of effective treatments.

We have undertaken systematic reviews, which found a lack of high-quality evidence for guiding recruitment and retention decisions. To address this, we propose using Study Within A Trial (SWAT) methods. A SWAT is an evaluation done inside another trial and can test how effective strategies for recruiting and retaining participants are. We have identified priority recruitment and retention SWATs, based on frequency of strategy use, existing evidence, and research priorities.

Two of the priority questions focus on testing patient and public involvement (PPI) strategies for participant recruitment and retention. Our previous research highlights PPI's importance, yet more high-quality research is needed to understand its impact on recruitment and retention.

Our aim is to create clear plans, called protocols, for these PPI-focused questions. We will also develop resources to support researchers doing these and the other prioritised SWATs. These protocols and resources will be made available to other researchers. Each protocol will give clear guidance on the strategy being tested, outcome measures, and will be supported by resource packs to facilitate SWAT conduct.

Our work will speed up the evidence about what works and doesn't work for recruiting and retaining participants, leading to faster discoveries of better treatments.

Background

Recruiting and retaining participants to clinical trials is very challenging[1-4]. We know that fewer than 50% of trials meet their recruitment targets[5]. This leads to trial failure and wastes time and resources for trial teams, participants, and funders. Poor retention also causes research waste and can delay the implementation (or removal) of healthcare interventions[6] and increase trial costs[6, 7]. Missing primary outcome data resulting from attrition can lead to bias and also reduces the power of the study to detect clinically significant findings[8]. This is not just about slow process: poor recruitment and retention do real harm to patients and the public[9]. Data from the RECOVERY trial's dexamethasone arm[9] shows that every 50-day delay in completion of the trial due to, for example, slow recruitment or retention issues led to 450 additional deaths. Process efficiency matters.

Patient and public involvement (PPI) in research is fundamental to trials. However, a SWAT testing a PPI strategy (10), and a systematic review assessing PPI impacts on recruitment and retention (11) both highlighted a need for more high quality evaluations. As part of a James Lind Alliance Priority Setting Partnership, 20 research priority questions were generated to improve trial recruitment and retention(3, 12). Two priority questions were to investigate how PPI strategies could improve trial recruitment(12) and retention(3) through the use of SWATs.

The purpose of our study is to:

i) develop protocols for the two priority recruitment and retention SWATs focusing on PPI
ii) develop associated resources to support trialists to implement protocols for 11 priority questions. The support resources will include text for protocols, statistical analysis plans, intervention resources and ethical application templates.

Objectives:

1. Develop protocols for two prioritised recruitment and retention SWATs focusing on PPI, adopting a coordinated approach whereby the questions can be tested across multiple host trials simultaneously.
2. Develop accompanying practical resources for 11 top prioritised recruitment and retention strategies in Tables1,2 and 3 to support trial teams to ensure easy facilitation of SWAT implementation.
3. Register the final SWAT protocols, if appropriate, on the Northern Ireland (NI) SWAT Repository.
4. Publish the completed SWAT protocols (including those from the joint HRB-TMRN application) and accompanying resource packs, if appropriate, on the Trial Forge website with links to the Implement SWATs and NI SWAT Repository websites to ensure they are publicly available and therefore easy to implement for trial teams.
5. Facilitate communication with funding agencies in Ireland and the UK and their associated funding partners internationally to secure support and resources for the implementation of SWATs, and promotion of their adoption, ensuring the successful evaluation of recruitment and retention strategies.

TMRN Joint Application Objective
Develop five recruitment and four retention protocols to support trial teams to undertake the prioritised SWATs (Health Research Board TMRN complementary application).

Workpackages

WP 1: Pre-initiation

Complementary joint HRB-TMRN Application: Design a master protocol template

1. *Review NI SWAT repository template and PROMETHEUS (Promoting the use of SWATs) template and conduct a needs assessment to identify areas of improvement. In addition, data points will be extracted from the data extraction forms from the Cochrane systematic review of recruitment strategies (update) and Cochrane systematic review of retention strategies to ensure the SWAT will be suitable for inclusion in any relevant meta-analysis. Other relevant guidance, e.g. TIDier for intervention description, will also be consulted for relevant sections. It will also be made clear in the protocol template why items are included.*
2. *Engage with relevant stakeholders, including researchers, trial coordinators, PPI colleagues and methodologists, to gather input and insights on essential components to be included in*

the master protocol template, ensuring it addresses a wide range of trial scenarios and complexities. These relevant stakeholders are members of the project group.

3. *Based on the feedback, develop a comprehensive master protocol template for effective SWAT replication and if deemed appropriate given the constraints of the repository, liaise with NI SWAT repository director to implement it there.*
4. *Validate the template through expert review and pilot testing with three existing SWAT protocols to ensure its applicability and practicality. Two experts per testing protocol will be recruited from the SWAT Network. Pilot testing will involve transferring existing protocol details and full completion (i.e. add any details not included in the existing protocol) of three SWAT protocols. The three existing protocols for testing will be selected by the study team members and will cover a range of SWAT types (e.g. pre-host trial consent, platform SWATs, host trial run as e-trial via SMS only) while not being included in the list of prioritised recruitment and retention SWATs.*

WP 2: Develop recruitment and retention SWAT protocols focused on PPI.

The two prioritised questions for PPI are:

• What is the most effective way of involving patients and the public in trials to improve participant recruitment?
• What is the most effective way of involving patients and the public in trials to improve participant retention?

We will firstly develop feasible SWAT recruitment and retention interventions to address these PPI questions. For the intervention (s), we will develop a protocol/protocols for evaluation via a simultaneous SWAT approach. A simultaneous SWAT is designed to answer the same question across multiple host trials in parallel, with findings combined (using a meta-analysis). This has been shown to be feasible and efficient(13, 14) because it uses one shared protocol, ethical approval, analysis, and write-up, generating evidence at both speed and scale.

The process for protocol development:

1. Using co-production methods(15) , we will work with our PPI collaborators and the wider SWATs PPI panel at The University of York to develop the PPI interventions and define outcomes of interest.
2. We will draft SWAT protocols using the HRB-TMRN complementary project's template (described in WP1, above) . We will adapt simultaneous SWAT protocols from PROMETHEUS (13, 14).
3. The protocols and resources will be shared with the experienced team members, including PPI members, for feedback, with the goal of enhancing clarity and robustness.
4. The protocols will be forwarded to SWAT Network members for comment.
5. Final protocols will be reviewed, including by PPI members, checked for language suitability (age 12)(16) and approved by the core team.
6. We will register the SWAT protocols, if appropriate, on the NI SWAT Repository.
7. Final protocols will be published on Trial Forge website, with links to the Implement SWATs and NI SWAT Repository websites.

Table 1. Prioritised recruitment and retentions PPI questions and examples of possible associated research questions

Recruitment and retention questions (general)	Examples of possible associated research questions
What is the most effective way of involving patients and the public in trials to improve participant recruitment	What is the effectiveness of involving patients and the public in planning targeted recruitment activities on recruitment rates, compared to usual patient and public involvement practice? Does involving patients and the public to co-develop patient facing materials increase recruitment rates, compared to usual practice? Does patient and public involvement in training trial recruiters using simulated recruitment sessions improve recruitment rates, compared to usual practice?
What is the most effective way to involve patients and the public in trials to improve participant retention?	What is the effectiveness of involving patients and the public in planning targeted retention activities on retention rates compared to usual PPI practice? Do PPI led follow-up strategies increase retention rates of under-represented groups, compared to usual PPI practice?

WP 3: Development of resource pack to support routine embedding of SWAT protocols

We will develop a supporting resource pack for the eleven priority questions across the HRB-TMRN and MRC-NIHR-TMRP co-funded studies (Tables 1, 2 and 3), to support trial teams to implement the SWATs. The primary researcher will collaborate with the core team to draft this resource pack to comprise of:

1. Standardised text for trial teams to use when embedding the SWATs in grant applications.
2. Guidance for costing models for trial teams to embed the SWATs in grant applications (with input from the project Health Economist).
3. Ethics application wording and templates for trial teams in both the UK and Ireland (with input from experienced study team members in the UK and Ireland).
4. A Statistical Analysis Plan (with input from the project Statistician).
5. Guidance on assessing cost-effectiveness of SWATs (with input from the project Health Economist).
6. Documents will be sent to the Trial Forge SWAT Network and PPI members to gather comments.
7. Final protocols will be reviewed, including by PPI members, checked for language suitability (age 12)(16) and approved by the core team.
8. Randomised SWAT publication guidelines for reporting SWATs, will also be included in the resource pack (17).

Table 2. Prioritised recruitment strategies and examples of possible associated research questions.

Priority Recruitment Question	Example questions
What is the most effective way to use video(s) to support trial recruitment?	Do video(s) providing information about a trial together with written information increase recruitment compared to written information only? Do video(s) providing information about a trial together with written information increase recruitment of under-represented groups important for the trial compared to written information only?
What is the most effective way of sending potential trial participants invitation letters by post to optimise recruitment rates?	Do posted trial invitation letters with a follow-up postal reminder letter increase recruitment rates, compared to usual practice? Does a posted trial invitation letter with a follow-up electronic reminder (text message or email) increase recruitment, compared to usual practice? Does a behavioural theory-informed trial invitation letter increase recruitment rates, compared to a standard letter? Is sending a full trial-invitation pack containing all relevant information (including an invitation letter, the participant information sheet, reply slip and pre-paid envelope) as a first postal approach more cost-effective for recruiting participants, compared to sending a single-page invitation letter?
What is the most effective way of using qualitative research to optimise recruitment rates?	Does undertaking embedded qualitative research in feasibility studies to identify potential barriers and facilitators to recruitment in the main trial increase recruitment rates, compared to not undertaking qualitative work to identify potential barriers and facilitators to recruitment? Does pre-trial qualitative research to identify and address potential recruitment issues increase recruitment rates, compared to no pre-trial qualitative research? Does undertaking qualitative research using the QuinteT Recruitment Intervention (QRI) improve recruitment rates, compared with not using the QRI?

Table 2. Prioritised recruitment strategies and examples of possible associated research questions (continued).

Priority Recruitment Question	Example questions
What are the most effective strategies to recruit underserved groups?	Do video(s) providing information about a trial increase recruitment of particular under-represented groups important for the trial compared to written information only? Does asking for verbal consent improve the recruitment of particular under-represented groups, compared to asking for written consent? Does providing 'easy access' study information materials increase recruitment rates, compared to standard study materials? Does translating trial materials and providing interpreters improve the recruitment of non-English speakers, compared to standard practice?
What is the most effective way to use financial incentives to support recruitment?	Do financial incentives increase recruitment compared to no financial incentive? Do cash-based financial incentives increase recruitment rates compared to vouchers with the same face value? Do higher-value financial incentives increase recruitment rates compared to lower-value incentives? Do cash-based financial incentives increase recruitment of people experiencing socioeconomic disadvantage compared to vouchers with the same face value?

Table 3. Prioritised retention strategies and examples of possible associated research questions

Priority retention question	Example questions
What is the most effective way of offering flexibility to support participant retention?	Does offering trial participants flexibility in follow-up visit location increase retention rates, compared to not offering flexibility? Does offering trial participants flexibility in follow-up visit location increase retention of people experiencing socio-economic disadvantage compared to not offering flexibility? Does offering trial participants flexibility for method of follow up (e.g., postal, telephone or email) compared to not offering flexibility increase retention rates? What is the effectiveness of asking participants to complete a diary on retention rates, compared to not asking participants to complete a diary?
What is the most effective way of using participant reminders to support retention?	Do electronic (text message or email) reminders increase retention rates, compared to usual follow-up? Is sending an electronic (text message or email) reminder more cost-effective than sending a postal reminder? Do telephone-call reminders increase retention of digitally excluded participants, compared to usual follow-up?
What is the most effective way to use financial incentives to support retention?	Do financial incentives increase retention compared to no financial incentive? Do higher-value financial incentives increase retention compared to lower-value incentives? Do cash-based incentives increase retention rates compared to vouchers with the same face value? Do cash-based financial incentives increase retention of people experiencing socioeconomic disadvantage compared to vouchers with the same face value?
What is the most effective way of using routine data collection to support retention?	Does using routinely-collected data (*e.g., ONS/HES/GP/Hospital data*) improve retention rates, compared to using participant-reported data? Does using routinely-collected data (*e.g., ONS/HES/GP/Hospital data*) increase the retention of under-served groups, compared to using participant reported data?

We will publish the supporting resource pack on the Trial Forge website and link to the Implement SWATs and NI SWAT Repository websites, if appropriate.

Websites:
-NI SWAT repository
https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/
-Trial Forge
https://www.trialforge.org/
-Implement SWATs
https://www.implementswats.org/#

WP 4: Dissemination

Protocols for Trial Teams and Funders
We will produce an open access academic publication in the journal Trials, summarising our work for this project with details of where the protocols can be accessed on the Trial Forge website. This will be co-produced with our PPI colleagues. The title will be: PRESSing Need for Evaluation of Recruitment and Retention Strategies in Trials: Results from the PRESS project. All contributors to the research will be appropriately acknowledged. We will open communication with funding agencies in the UK and Ireland and their associated funding partners to ensure their continued support and resource allocation for the implementation of SWATs, and explore new avenues for funding opportunities to ensure the successful evaluation of recruitment and retention strategies. We will consider submitting a funding application to undertake simultaneous SWATs to evaluate the effectiveness and cost-effectiveness of the PPI strategies.

Ongoing Support
We will offer ongoing support and assistance to trial teams implementing the SWAT recruitment and retention protocols, fostering a collaborative learning environment and facilitating their successful adoption. In order to receive support, researchers will be instructed to contact York Trial Forge SWAT centre (trial-forge-swat-centre@york.ac.uk).

Conferences
The findings will be presented as oral presentations at national and international trial methodology conferences (e.g. the International Clinical Trials Methodology Conference, the annual HRB-TMRN Trial Methodology Symposium, etc.).

Public Engagement
Public-facing dissemination will include talks orientated towards a general audience. This will be done in collaboration with the HRB TMRN and MRC-NIHR-TMRP whose members regularly engage in public engagement activities and as a webinar which has capacity to reach more than 2000 people. We will use social media outlets to support communication to the general public. In addition, CRF/CRC/NIHR-RSS (formerly CTU) websites will be used to communicate results from this study, to support public access to these protocols and promote wider public engagement with clinical trials.

Public and Patient Involvement

Our PPI colleagues will play a pivotal role in ensuring the final protocols are comprehensible to lay members, not just those with scientific expertise. They will review, provide feedback, and approve the final protocols and resources, and we will invite them to co-author the protocols.
We have allowed for remuneration of their time in the budget.

Data management

As no personal or sensitive data will be collected for this project, file sharing between study team members will be via email.

A secure project-specific shared folder will be used for audit and storage purposes with access restricted to the study management group members at York University.

Project management

The study will be coordinated by a Project Management Group, consisting of Dr Adwoa Parker (lead investigator), Dr Frances Shiely (lead investigator complementary HRB-TMRN project, University College Cork), co-investigators; Professor Shaun Treweek (University of Aberdeen), Catherine Arundel (University of York), Dr Chris Sutton (The University of Manchester) and co-investigator and appointed researcher for the HRB-TMRN project Dr Hanne Bruhn (University of Aberdeen); and Research Assistant - Jackie Wilkinson (University of York). The group will meet regularly to discuss progress of the study. The lead investigator and research assistant will undertake and oversee the day-to-day running of the study and will be accountable to the Project Management Group.

Ethical considerations

Ethics approval will not be required to conduct this research.

There will be ethical considerations associated with each protocol developed which will be dependent on the recruitment or retention strategy proposed. This will be considered by the team developing the protocols, and reviewed by the core committee, on a case basis.

List of abbreviations

HRB TMRN	Health Research Board Trials Methodology Research Network (Ireland)
MRC-NIHR-TMRP	Medical Research Council and National Institute for Health and Care Research Trials Methodology Research Partnership
NI	Northern Ireland
PPI	Patient and Public Involvement
PRESS 1	Protocol development for prioritised recruitment and retention strategies
PRESS 2	Protocol and resources development for prioritised recruitment and retention strategies
SWAT	Study Within A Trial
UK	United Kingdom
WP	Work package

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