Protocol for:

TMRN joint project title: Protocol development for prioritised recruitment and retention strategies (PRESS-1)

TMRP joint project title: Protocol and resources development for prioritised recruitment and retention strategies (PRESS-2)

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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 http://osf.io/.

Plain English summary

Clinical trials are important, but recruiting and retaining participants is challenging. Fewer than half of trials meet their recruitment goals, leading to wasted time, money, and effort for research teams and participants. Additionally, poor retention, when participants drop out before the study ends, can limit the strength of the trial's results. Recruitment and retention problems therefore delay the identification and implementation of effective new treatments.

We have undertaken systematic reviews that found that there is little high-quality evidence to guide recruitment and retention decisions. One way of filling these gaps is to use a Study Within A Trial (SWAT). A SWAT is an evaluation done within a 'host' trial and can, for example, test whether a new retention strategy is better than an existing strategy. We have created lists of priority recruitment and retention SWATs based on how often the strategy is used, existing evidence and recruitment and retention research priorities.

We now aim to create clear plans, called protocols, for these priority SWATs. These protocols can then be used by other researchers and promoted to researchers by funders. Each protocol will give clear guidance on the recruitment or retention strategy to be tested and the test outcomes to be measured and will be supported by a resource pack (described in our complementary project, PRESS 2) providing help on how to do the SWAT.

Our work will make speed up the evidence about what works, and what 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 due to, for example, slow recruitment or retention issues, led to 450 additional deaths. Process efficiency matters.

To address these issues, three pieces of work have been completed:

1. Two Cochrane systematic reviews of strategies to improve recruitment[5] and retention[10]. The Review on recruitment identified only three things, with high certainty evidence, that improved recruitment rates to trials, but these improved recruitment by just 10%, 6% and 1% respectively[5]. The review on retention identified 52 comparative retention strategies, none of which were supported by high-certainty evidence as determined by GRADE assessment[10]. A systematic review of SWAT economic evaluations found no cost effective strategies with statistical certainty[11].
2. PRioRiTy study I and II, identified 20 research priority questions to improve trial recruitment[12] and retention[3] process as part of a James Lind Alliance Priority Setting Partnership.
3. A SWAT testing a PPI strategy [13], and a systematic review assessing PPI impacts on recruitment and retention [14] both highlighted a need for more high-quality evaluations.
4. Over the last year the current applicants have, as part of the Trial Forge SWAT Network, a network of more than 40 institutions[15], identified and prioritised recruitment and

retention strategies[16] that can be evaluated using randomised SWATs (Appendix 1). Prioritisaiton was done by combining frequency of strategy use in National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme trials, evidence from the Cochrane recruitment[5] and retention reviews[10], the cost-effectiveness review[11] and the findings of PRioRiTY I and II [3, 12].

While we know that SWATs are an effective means of evaluating recruitment and retention strategies, convincing trial teams to undertake this 'extra' work while simultaneously getting a trial up and running, can be challenging. Interviews with institutions involved in the Trial Forge SWAT Network have frequently noted that availability of resources to support SWATs (e.g., protocols, statistical analysis plans, intervention resources, ethical applications etc.) could help colleagues undertake SWAT research.

Our study will develop SWAT protocols (this application) and associated resources (the process of developing these is described in a separate protocol) for the prioritised recruitment (n=5) and retention strategies (n=4) in Appendix 1. This will make it easier for trial teams to adopt and implement evaluations of priority SWATs. This will focus trialists attention on specific evidence gaps, leading to faster generation of evidence to improve recruitment and retention strategies.

Aim: To develop SWAT protocols for prioritised trial recruitment and retention strategies.

Workpackages

1. Design a master protocol template
2. Develop SWAT recruitment and SWAT retention protocols
3. Dissemination

WP 1: Pre-initiation

1. Protocol for this study written.
2. Appoint researcher.
3. Establish core committee with responsibility for the work programme (Chair (PI), appointed researcher, PPI member, at least two members of the SWAT Network (two from Ireland and two from UK).

WP 2: 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 3: Develop SWAT recruitment and SWAT retention protocols

1. The primary researcher will draft the SWAT recruitment and retention protocols. Emphasis will be given to clear and concise instructions to facilitate easy adoption by trial teams. The protocols to be drafted will be selected from the prioritised recruitment and retention strategies listed in appendix 1. Specifically, PPI partners will be asked to select nine strategies from appendix 1. In order to support PPI partners and give them a basis for how to select, they will be provided with background information for each possible strategy including evidence to date and its context. PPI partners will be requested to provide reasons for their selections/non-selections.
2. The researcher will share the drafted protocols with the co-applicants and collaborators, for internal review and feedback. The team will provide constructive comments and suggestions to enhance the clarity and robustness of the protocols.
3. The protocols will be forwarded to SWAT Network members for comment. To avoid large workloads, each protocol will be sent to two SWAT Network members.
4. The final protocols will be reviewed, checked for language suitability as recommended for health literature, age 12[17] and signed off by the core team. The final methods will be informed by another project involving AI in writing plain English summaries.
5. Once signed off, the final SWAT protocols may, if appropriate, be registered on the NI SWAT Repository.
6. The final SWAT protocols will be registered on the NI SWAT repository, Trial Forge website and Implement SWATs website and linked to the Trial Forge website.
7. Three to four completed SWAT protocols may also be used to test the UK HRA SWAT ethics system.

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 Ireland and the UK 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.

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 2024, the annual HRB-TMRN Trial Methodology Symposium 2024, etc.).

Distribution through Trial Forge and existing networks

Availability of the protocols (this TMRN application) and resource packs (TMRP complementary application) will be distributed widely through the networks of the PI, co-applicants and collaborators. Trial Forge, hosted in Aberdeen, will provide a link to the published document on their website, and provide a short video description of the project and its findings to complement the publication. The HRB CRF-UCC, host institution of the PI Dr Frances Shiely is a HRB TMRN partner and also a Trial Forge Site, as well as the University of York, and will do the same. Knowledge of the existence of the readily available protocols will be disseminated widely through the HRB TMRN, MRC-NIHR-TMRP, HRB, HRB NCTO, UKTMN, PROMETHEUS and Accelerating Clinical Trials Canada. The established Trial Forge SWAT network, which includes the PI, co-applicants and collaborators will also disseminate the SWAT protocols. We will also work with funders including NIHR and HRB to build reference to the extended suite of available SWAT protocols into their SWAT and Definitive Intervention funding calls. This will benefit ongoing research between members of the HRB TMRN and MRC-NIHR-TMRP and trial methodological researchers around the world.

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 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/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

To ensure meaningful PPI for our SWAT interventions and protocols, we will employ co-production methods[18], as outlined by Goldsmith (2019). Our PPI collaborators from the UK and Ireland will play a substantial role in shaping the interventions and protocols at every stage. These collaborators will actively engage in the core committee and contribute throughout the research process.

Our PPI colleagues will offer insights during the development of interventions, protocols and related resources. Their input will include the types of PPI strategies to be tested, comparators, outcomes, and considerations around equality, diversity, inclusion, as well as the accessibility and acceptability of the SWAT intervention.

Utilising existing PPI networks in the UK and Ireland, we will gather perspectives from diverse backgrounds to ensure matters of under-representation, such as ethnicity, culture, and socioeconomic status, are addressed in the protocols. This will also be supported by input from colleagues with expertise in PPI and inclusion of these under-represented groups in research. When relevant, broader PPI input will be sought from the larger SWAT PPI group at the University of York and the permanent PPI groups at the University of Aberdeen's School of Medicine and Health Services Research Unit.

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 Aberdeen University.

Project management
The study will be coordinated by a Study Management Group, consisting of Dr Frances Shiely (lead investigator) and Professor Shaun Treweek (University of Aberdeen) and an appointed researcher (HB). The group will meet regularly to discuss progress of the study. The researcher will undertake and oversee the day to day running of the study and will be accountable to the lead investigator.

Ethical considerations
Ethical 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
NIHR HTA	National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (UK research funder)
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
PRioRiTy I	The Prioritising Recruitment in Randomised Trials study
PRioRiTy II	The Prioritising Retention in Randomised Trials study
QuinteT	QuinteT Recruitment Intervention [from Qualitative Research Integrated within Trials (QuinteT) and involves understqanding how recruitment is done and where the issues are and developing a plan for how to address the issues.]
SWAT	Study Within A Trial
TFG	Trial Forge Guidance
UCC	University College Cork
UK	United Kingdom
WP	Work package

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Appendix 1

Table 1 List of prioritised recruitment and retention strategies respectively

Prioritised recruitment strategies and example questions	
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 not sending a reminder letter? Does a posted trial invitation letter with a follow-up electronic reminder (text message or email) increase recruitment, compared to not sending a reminder? Does a behavioural theory-informed trial invitation letter increase recruitment rates, compared to a standard letter? Is sending an initial full trial-invitation pack containing all relevant information (including an invitation letter, the participant information sheet, reply slip and pre-paid envelope) 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?[19]
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?
Prioritised retention strategies and example questions	
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 groups1, compared to using participant reported data?
PRESS 2 **Prioritised PPI recruitment and retention strategies and example 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 of involving 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?