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Studies Within A Trial (SWATs) to test recruitment and retention strategies: lessons learnt from the PROMETHEUS research programme

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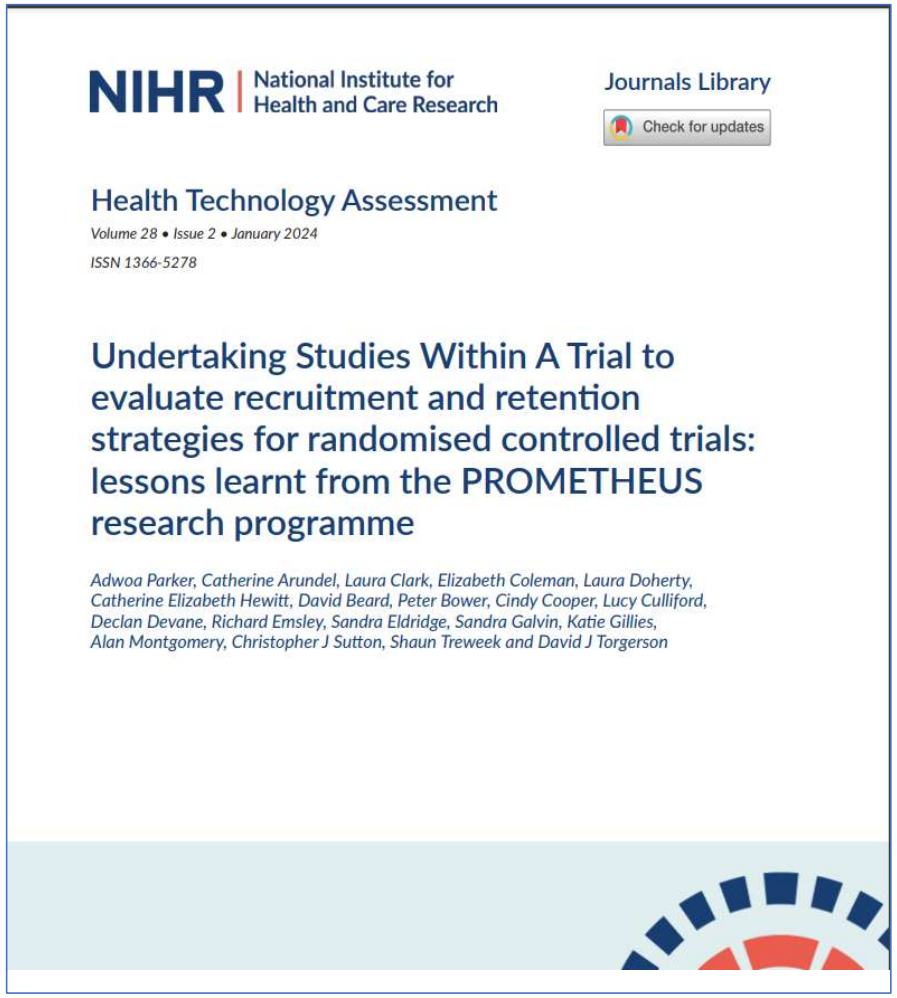
TRIAL FORGE

www.trialforge.org



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Undertaking Studies Within A Trial to evaluate recruitment and retention strategies for randomised controlled trials: lessons learnt from the PROMETHEUS research programme

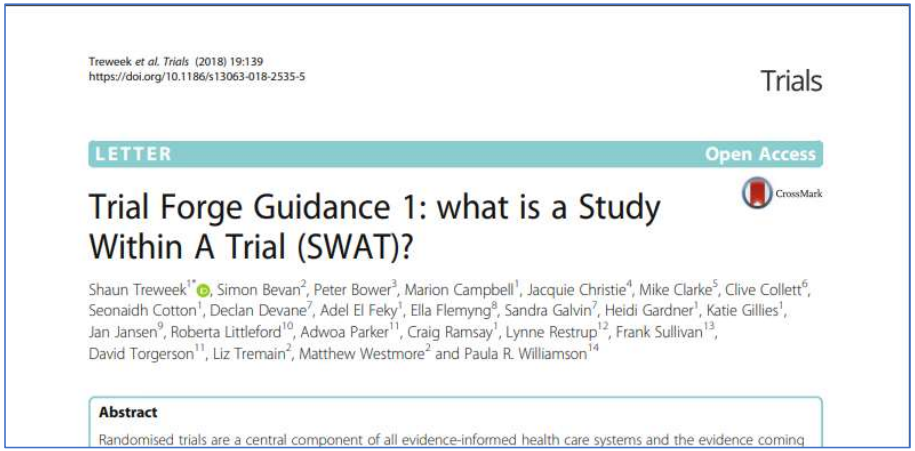
Adwoa Parker, Catherine Arundel, Laura Clark, Elizabeth Coleman, Laura Doherty, Catherine Elizabeth Hewitt, David Beard, Peter Bower, Cindy Cooper, Lucy Culliford, Declan Devane, Richard Emsley, Sandra Eldridge, Sandra Galvin, Katie Gillies, Alan Montgomery, Christopher J Sutton, Shaun Treweek and David J Torgerson

https://doi.org/10.3310/HTQW3107

What is a SWAT?

- A piece of methodological research nested into a 'host' trial.
- Can be randomised (i.e., trial within a trial) or non-randomised (e.g., qualitative, observational)

- *'A SWAT is a self-contained research study that has been embedded within a host trial with the aim of evaluating or exploring alternative ways of delivering or organising a particular trial process'.* (Treweek et al., 2018, Trials)



Treweek *et al. Trials* (2018) 19:139
https://doi.org/10.1186/s13063-018-2535-5

Trials

LETTER Open Access

Trial Forge Guidance 1: what is a Study Within A Trial (SWAT)?

Shaun Treweek[1*], Simon Bevan[2], Peter Bower[3], Marion Campbell[1], Jacquie Christie[4], Mike Clarke[5], Clive Collett[6], Seonaidh Cotton[1], Declan Devane[7], Adel El Feky[1], Ella Flemyng[8], Sandra Galvin[7], Heidi Gardner[1], Katie Gillies[1], Jan Jansen[9], Roberta Littleford[10], Adwoa Parker[11], Craig Ramsay[1], Lynne Restrup[12], Frank Sullivan[13], David Torgerson[11], Liz Tremain[2], Matthew Westmore[2] and Paula R. Williamson[14]

Abstract

Randomised trials are a central component of all evidence-informed health care systems and the evidence coming

Why do we need SWATs?

- The most rigorous method to test strategies to improve trial conduct
- They are useful
- Conceptually simple
- Generally cheap
- Help generate evidence to reduce research waste
- Great for extra publications
- We need more robust evidence! (and we need to use this evidence when we have it)

Key features of a SWAT

Aim to resolve uncertainties about how to do trials

Are embedded within a host trial, but do not affect the integrity of the host trial

Should have a formal protocol, just like the host trial

Individual SWATs can contribute to systematic reviews of SWATs

Can be evaluated in a single trial, but is preferably run across many trials

Will inform how we do future trials, and might inform decisions about the host trial

Treweek et. al., 2018; Trials

The recruitment & retention problem

Recruiting and retaining enough participants often very difficult

Only 43% of UK trials recruit to target & on time (Jacques, 2022)

Power & type II error; external validity

RECOVERY trial - dexamethasone arm: every 50-day delay in completion due to slow recruitment or retention led to ~450 more deaths in the UK alone (Knowlson & Torgerson, 2020)

Economic consequences: faster recruitment to RECOVERY dexamethasone arm (from 15% to 50%) could have generated an incremental net benefit to the UK of £17.2m (€20.1m / US$21.6m) (Gkekas, submitted)

Huge amounts of research waste & massive opportunity costs

Human cost: Delays evidence to improve treatments for patients & prolongs exposure to ineffective or dangerous treatments

PROMoting THE USE of SWATs (PROMETHEUS)

- Funded by UK NIHR (via MRC)
- led by Prof David Torgerson, University of York
- Co-applicants from 10 CTUs, a primary care centre, and HRB-TMRN
- PROMETHEUS aims to embed randomised SWATs to **test commonly used recruitment and retention strategies** for improving trial recruitment and retention
- Provided coordination of SWATs

PROMETHEUS aims

Pump prime and facilitate 25 recruitment & retention SWATs across multiple CTUs within 30 months

Test their effectiveness in the context of individual trials, and across different trial populations and contexts using meta-analyses

Aim to make SWATs routine when conducting trials

Methods

We created a priority list of recruitment and retention questions, with PPI input

Developed template SWAT protocols for testing priority questions

Advertised for trial teams to apply for funding of up to £5,000 to test one of our prioritised questions or their own

Independent peer review

Successful applicants given funding, methodological and process support to embed and report the SWAT

TABLE 1 List of key recruitment and retention questions in priority order

Recruitment strategies
What is the effect of adding a pen printed with the trial/university logo to the trial invitation on recruitment rates (SWAT 37)?
What is the impact of recruitment sites receiving an extra trial co-ordinator visit on recruitment rates (SWAT 27)?
What is the effectiveness of a brief PIL vs. standard length PIL on participant recruitment rates (SWAT 137)
What is the impact of a training workshop for staff recruiting patients into trials on recruitment rates (SWAT 111)?
What is the effect of offering financial incentives to potential trial participants on recruitment rates (SWAT 59)?
What is the effect of mentioning scarcity of trial places in invitation letters on recruitment of trial participants (SWAT 60)?
What is the effectiveness of telephoning people who do not respond to a postal invitation on recruitment to randomised trials (SWAT 61)?
Retention strategies
What is the effect of adding a pen printed with the trial/university logo to the trial invitation on retention rates (SWAT 37)?
What is the effectiveness of a theoretically informed cover letter on improving response rates to annual postal questionnaires (SWAT 24)?
What is the effect of a text message notification vs. no text message on questionnaire response rates (SWAT 25/SWAT 31)?
What is the effectiveness of a personalised text message vs. a standard text message for promoting response to postal questionnaires (SWAT 35)?
What is the effect of timing text message prompts to increase trial participant response to postal questionnaires (SWAT 44)?
What is the effectiveness of sending pre-notification cards (letters/e-mail) to trial participants 1 month (2 weeks) before outcome measurement to improve retention (SWAT 76/SWAT 86)?
What is the impact of receiving a social incentive strategy cover letter compared with a standard covering letter on response rate to postal questionnaires (SWAT 144)?
Do courtesy telephone calls to trial participants following enrolment increase future retention rates (SWAT 114)?

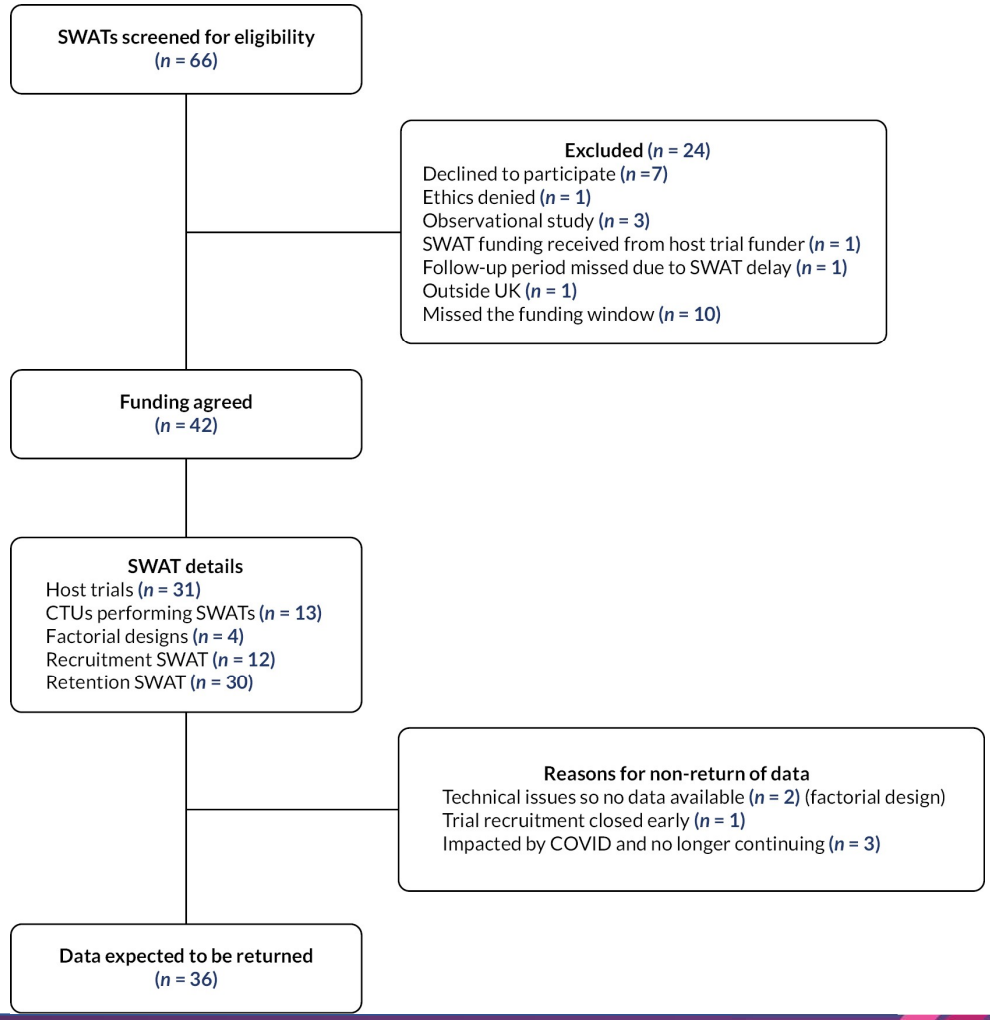
Methods

To allow meta-analyses, we developed a standardised protocols for the SWATs, alongside a Statistical Analysis Plan

Each SWAT obtained approval from the host trial's research ethics committee, and institutional governance committees as needed

Anonymised, individual patient-level data on recruitment and/or retention were shared securely with the PROMETHEUS team

Results: SWATs



Results

- Mean cost per SWAT = £3535
- 12 tested the same SWAT across multiple host trials using a co-ordinate, simultaneous SWAT design
- Two recruitment and five retention questions were tested in more than one host trial
- COVID-19 pandemic had a negative impact: 2 terminated, 10 SWATs delayed
- PROMETHEUS will add 18% more SWATs to the Cochrane review of recruitment strategies, and 79% more SWATs to the Cochrane review of retention strategies.

Findings from PROMETHEUS SWATs

Recruitment: No evidence of a significant difference for any of the strategies tested

Retention:

- Pre-notifying participants by card prior to sending questionnaires was effective [risk difference 3.3%, 95% CI −3.0% to 9.6%]
- Pre-notifying participants by letter or e-mail was effective (risk difference 3.8%, 95% CI −6.1% to 13.6%).
- Sending personalised text messages was more effective for improving the return of postal questionnaires vs non-personalised text messages (risk ratio 1.16, 95% CI 1.00 to 1.33); and resulted in fewer completions via telephone [adjusted OR 0.44, 95% CI 0.22 to 0.87].
- Including a pen with a questionnaire probably increases retention and response rate (pooled OR 1.21, 95% CI 1.09 to 1.35).

What not to do: evidence from PROMETHEUS

If you want to improve retention, don't post Christmas cards to participants:

- Pooled odds ratio 0.96, 95% CI 0.71 to 1.29, p = 0.77 (8 SWATs)
- Costs money and staff resources and is bad for the environment (average of 140g of CO_2 equivalent per card sent).

Don't print follow-up questionnaires on pink paper:

- Pink versus white paper for printing the primary outcome showed evidence of a decreased response in the pink paper group [risk ratio, 0.92 (95% CI 0.80, 1.06)], and that it was also more burdensome to collect postal data in this group.

Lessons learnt from PROMETHEUS: guidance for undertaking SWATs

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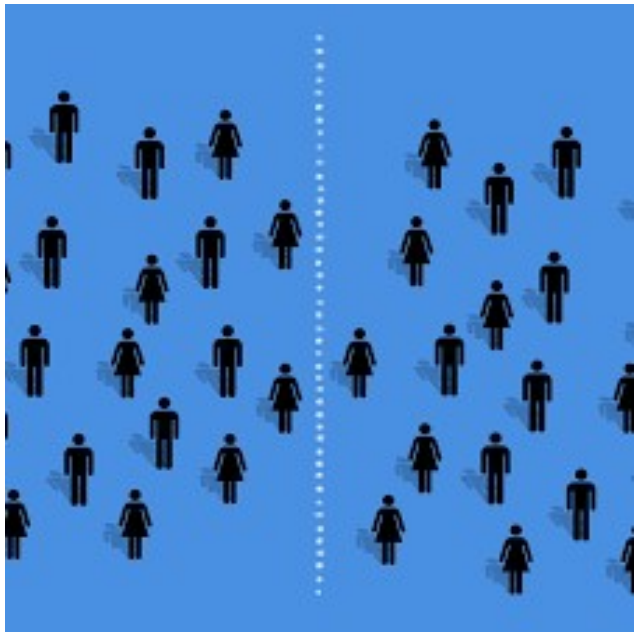
You will need a ‘host’ trial

- Often this is pragmatic: usually your own trial or that of a collaborator or colleague



Guidance on costs & funding

Costs vary

- Can be ~€3.5-35k+ for a single randomised SWAT
- Will cost a lot more for a programme of SWATs
- Need for transparent costs of SWATs
  - Funding from HRB-TMRN: Trial Forge Guidance 2 Extension: Reducing research waste by considering the cost-effectiveness of undertaking further SWATs on interventions (PI: F. Shiely)

Funding SWATs

Health Research Board
TMRN
Trials Methodology Research Network

MRC | Medical Research Council

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NIHR | National Institute for Health Research

CIHR IRSC | Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

ACT AEC | Accelerating Clinical Trials / Accélérer les Essais Cliniques

CCCTG
Canadian Critical Care Trials Group

Guidance on involving patients & the public in SWATs

- Include PPI when planning SWATs, same as for the main trial
- Include those who would potentially be impacted by the strategy being tested
- PPI members can include potential or enrolled trial participants
- Especially useful to identify novel or adapt existing strategies to your trial
- Finding PPI partners:
  - For SWAT strategies targeting participants/potential participants, approach the PPI members for the host trial
  - For strategies targeting staff, approach staff undertaking the recruitment at sites

Guidance on SWAT development

- Need for clear SWAT research priorities (which are updated)
- Priorities should be presented alongside estimated costs, resource use and, if possible, a protocol
  - HRB-TMRN & MRC-NIHR cofounded project: Protocol and resources development for prioritised recruitment & retention strategies (PRESS) (PIs: Shiely; Parker)
- Tools to help trial teams identify strategies suited to their host trial and patient group needed
- Communication as to when no further SWAT replications are needed
  - Trial Forge (inc. Trial Forge Guidance 2 update); Implement SWATs

Choosing your SWAT question

"The literature on interventions to improve recruitment to trials has plenty of variety but little depth"

Important to replicate existing SWATs

- Power & generalisability

Choosing your SWAT question

- We have prioritised 11 recruitment and retention questions to be tested using randomised SWATs:
  - https://www.trialforge.org/2024/02/a-list-of-11-priority-recruitment-and-retention-swats/
- The Prioritising Recruitment in Randomised Trials study (PRioRiTy)
  - https://priorityresearch.ie
- PRioRiTy II: Prioritising Retention in Randomised Trials study
  - https://www.trialforge.org/priority-two
- There is a repository of SWATs to help you link with the work others are doing
- For specific advice about which SWAT might work for your trial, you can contact the Trial Forge SWATs Centre at York

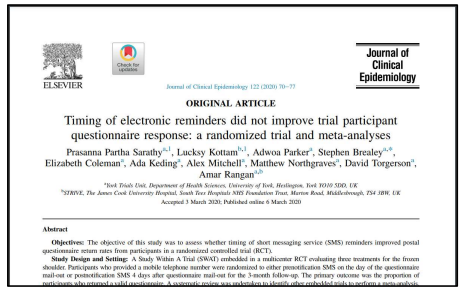
Guidance for SWAT funders

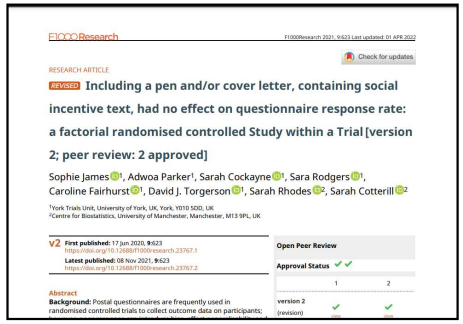
- Trial teams want to know that they were doing a SWAT that is necessary and relevant to increase the evidence base. More funding is needed to develop these types of resources

- When applying for funding, trial teams need to say whether the question they are addressing is a priority SWAT question & give a clear rationale for choosing that question

Guidance on SWAT design choices

- Individual randomised design often straightforward and efficient
- Factorial designs
  - 2x2 factorial SWATs can test the effectiveness of two strategies at the same time
  - Even more efficient
  - Test for interaction effects
  - *OTIS retention SWAT*: Including a pen or no pen, with or without cover letter containing a social incentive text
- Cluster randomisation
  - May be more feasible for practical/logistical reasons
  - Minimises 'contamination' and dilution bias between intervention and control participants





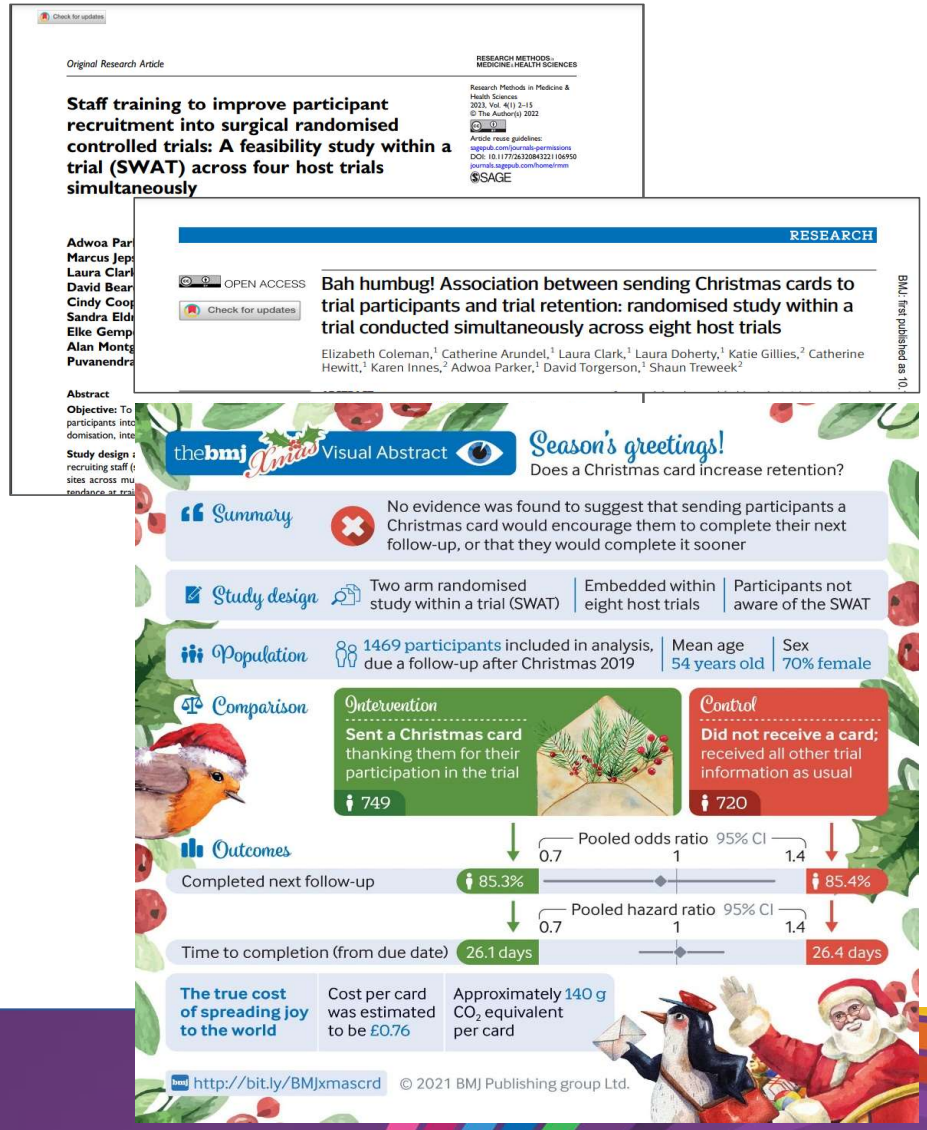
Multiple SWATs can be undertaken simultaneously

Bigger, better, faster: rapid, high-quality evidence at scale

Training workshop for staff recruiting participants - demonstrated feasibility of simultaneous SWATs

Simultaneous SWAT testing effectiveness of sending Christmas cards to participants on retention

Significant coordination needed



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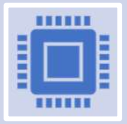
When to embed the SWAT

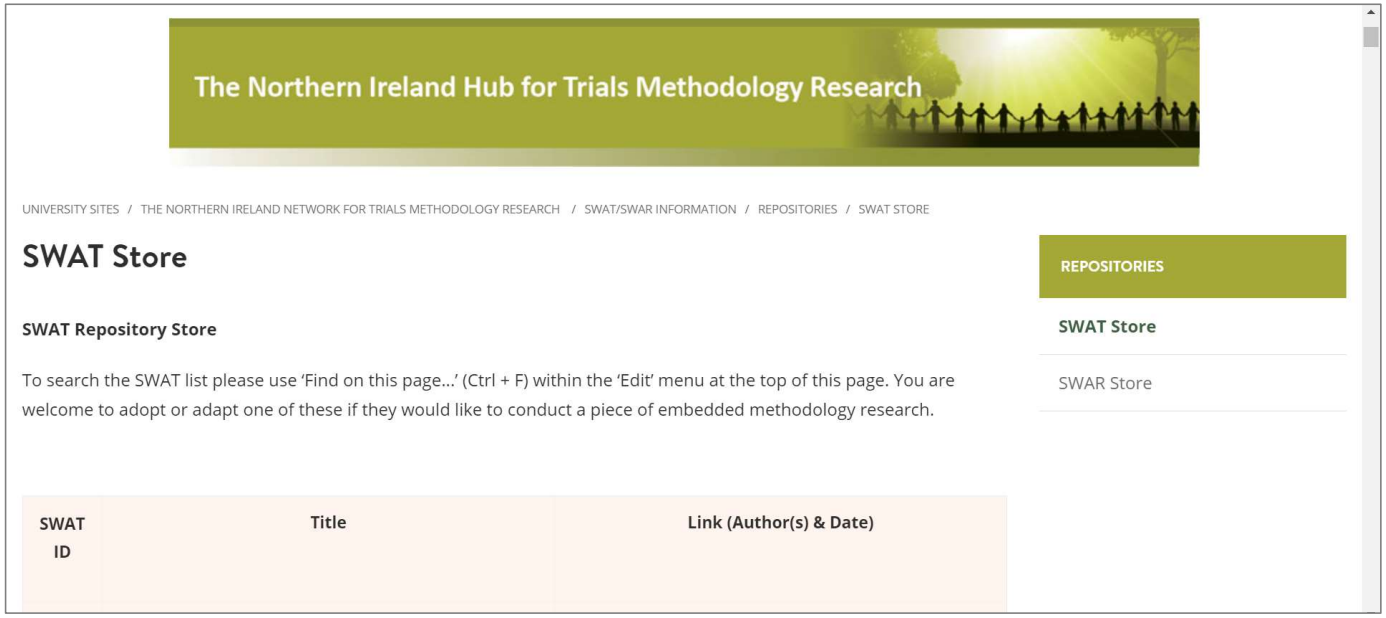
The earlier the better (and easier): we often plan SWATs at the design stages of our trials



But it is never too late to implement a SWAT.

E.g., A randomised SWAT testing a retention strategy can be implemented up until the last follow-up time-point.

Register your SWAT



https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/

Guidance for governance approvals for SWATs

- SWATs are low risk studies
- Most SWATs will need ethical approval
- For recruitment and retention SWATs, patients are not usually informed about being included in a SWAT
  - This is because it is not be possible to get individual consent from patients as it may confuse them as to what they are consenting to and may impact on their behaviour
  - Useful to get PPI input on this
  - Journal reviewers should consider the need to query this type of informed consent
- We have worked with the Health Research Authority in the UK to develop a streamlined approvals process and guidance for SWATs

Guidance on sample sizes

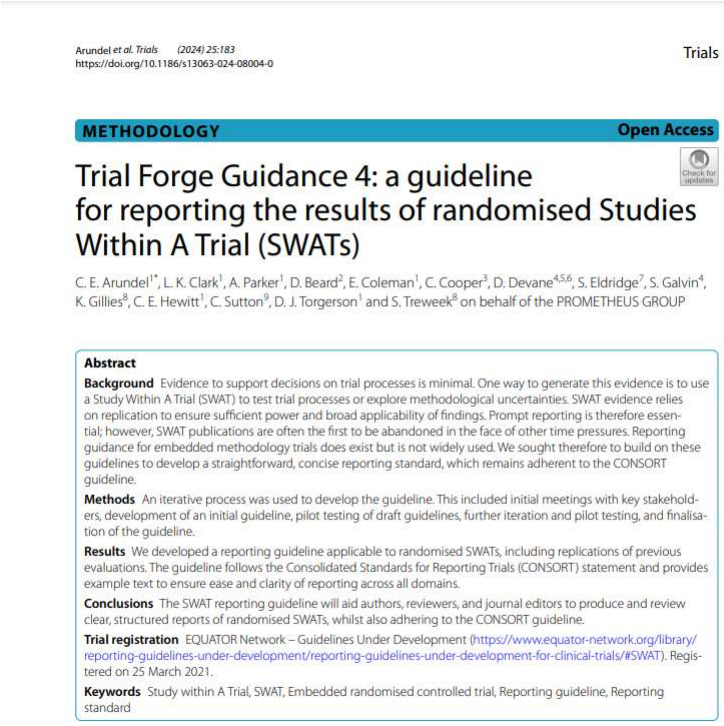
- For some SWATs (such as recruitment SWATs), the sample for the SWAT will actually be much larger than the host trial
- Other SWATs are constrained by host trial size - a separate power calculation may not be useful
- Meta-analysis of several SWATs testing the same intervention can provide powerful evidence

Guidance on randomisation & analysis

- Randomisation
  - Randomisation can be separate to that used for the host trial randomisation
  - Individual randomisation is preferable but may not always be practical. Cluster randomisation can be used.
- Analysis
  - The analysis will be simple for primary outcome (comparison of two proportions)

Guidance on reporting SWATs

- The findings should be published as soon as possible
- Reporting guidelines for randomised SWATs



Arundel *et al. Trials* (2024) 25:183
https://doi.org/10.1186/s13063-024-08004-0

Trials

METHODOLOGY Open Access

Trial Forge Guidance 4: a guideline for reporting the results of randomised Studies Within A Trial (SWATs)

C. E. Arundel[1*], L. K. Clark[1], A. Parker[1], D. Beard[2], E. Coleman[1], C. Cooper[3], D. Devane[4,5,6], S. Eldridge[7], S. Galvin[4], K. Gillies[8], C. E. Hewitt[1], C. Sutton[9], D. J. Torgerson[1] and S. Treweek[8] on behalf of the PROMETHEUS GROUP

Abstract

Background Evidence to support decisions on trial processes is minimal. One way to generate this evidence is to use a Study Within A Trial (SWAT) to test trial processes or explore methodological uncertainties. SWAT evidence relies on replication to ensure sufficient power and broad applicability of findings. Prompt reporting is therefore essential; however, SWAT publications are often the first to be abandoned in the face of other time pressures. Reporting guidance for embedded methodology trials does exist but is not widely used. We sought therefore to build on these guidelines to develop a straightforward, concise reporting standard, which remains adherent to the CONSORT guideline.

Methods An iterative process was used to develop the guideline. This included initial meetings with key stakeholders, development of an initial guideline, pilot testing of draft guidelines, further iteration and pilot testing, and finalisation of the guideline.

Results We developed a reporting guideline applicable to randomised SWATs, including replications of previous evaluations. The guideline follows the Consolidated Standards for Reporting Trials (CONSORT) statement and provides example text to ensure ease and clarity of reporting across all domains.

Conclusions The SWAT reporting guideline will aid authors, reviewers, and journal editors to produce and review clear, structured reports of randomised SWATs, whilst also adhering to the CONSORT guideline.

Trial registration EQUATOR Network – Guidelines Under Development (https://www.equator-network.org/library/reporting-guidelines-under-development/reporting-guidelines-under-development-for-clinical-trials/#SWAT). Registered on 25 March 2021.

Keywords Study within A Trial, SWAT, Embedded randomised controlled trial, Reporting guideline, Reporting standard

Dissemination: Cochrane reviews

- Share your findings with me, so I can include them in future updates of the Cochrane recruitment & retention reviews
- As evidence builds, these reviews will be modified into ‘living reviews’

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implement SWATs

Using IMPLEMENTation science and Studies Within A Trial to improve evidence-based participant recruitment and retention in randomised controlled trials.

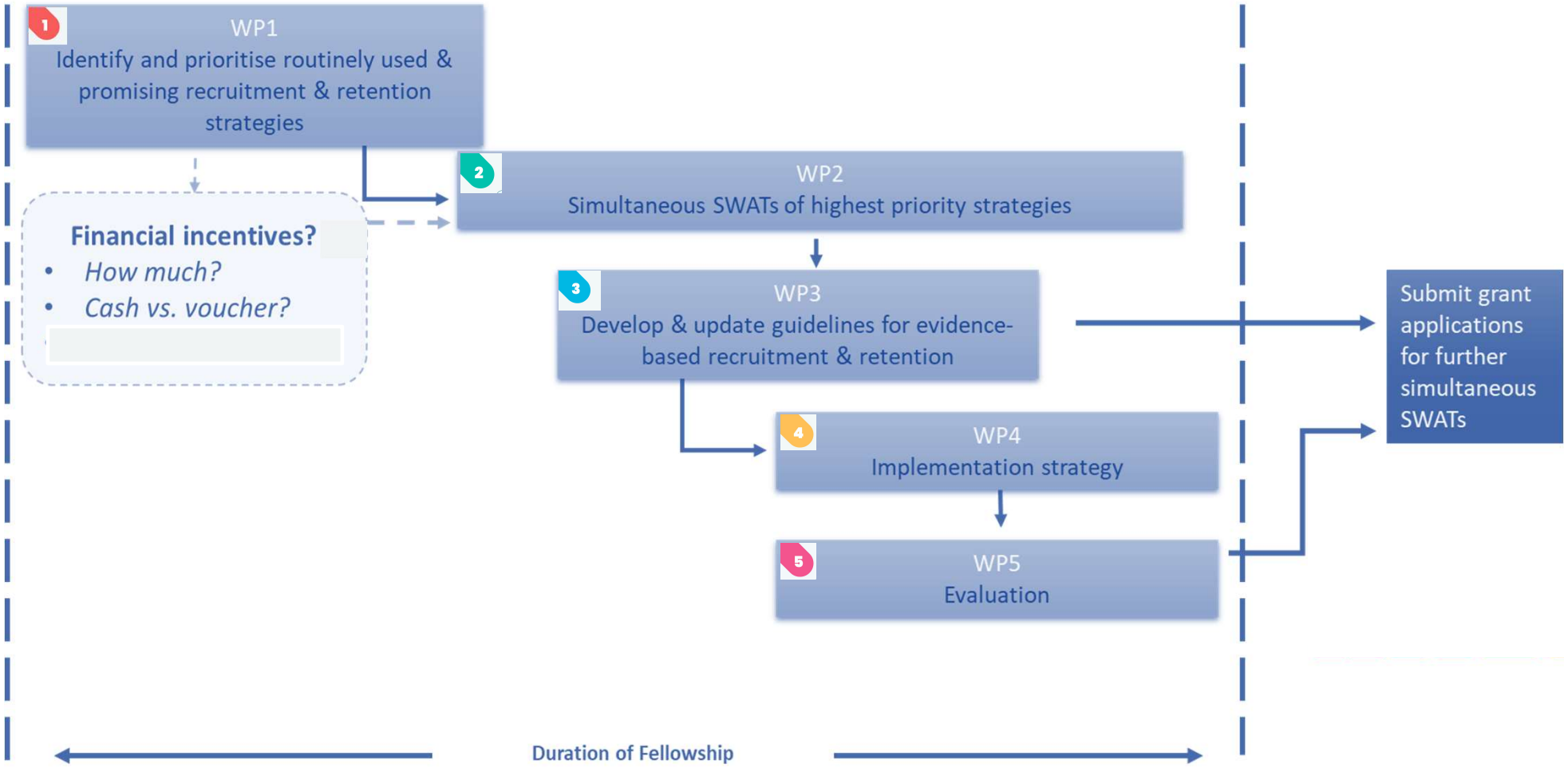
https://www.implementswats.org

Implement SWATs: overarching aims

1. To test the effectiveness and cost-effectiveness of routinely used and promising trial recruitment and retention strategies, using simultaneous SWATs

2. To develop, implement, and test guidelines for evidence-based recruitment and retention in trials

Overview of methods



2

Test high-priority strategies using coordinated SWATs

WP2: Simultaneous SWATs of monetary incentives

Aims: rapidly build the evidence-base for the effectiveness and cost-effectiveness of monetary incentives for recruiting and retaining trial participants by undertaking simultaneous SWATs, alongside a process evaluation.

Uncertainties around the use of monetary incentives include:

- What are the optimal values of incentives for recruitment and retention?
- What is the optimal format (cash *vs.* payment card *vs.* voucher)?
- Incentives will likely range between £10 and £50

2

WP2: Methods

Adaptive design

Strategies that show promise will be retained for further testing. Strategies shown to be not effective will be dropped

Type of SWAT	Initial SWAT strategy arms
Implement SWATs funded host trials: Recruitment & Retention	1.£10 cash 2.£10 voucher 3.£10 payment card 4.No incentive
Host trials with incentives already funded: Recruitment or Retention	1.Cash – amount as funded 2.Voucher– amount as funded 3.Payment card – amount as funded
Host trials with incentives already funded: Recruitment or Retention	1.Lower amount voucher 2.Higher amount voucher 3.Lower amount cash 4.Higher amount cash 5.Lower amount payment card 6.Higher amount payment card

Outcomes

- **Recruitment SWATs**: Primary outcome is recruitment rate. Secondary outcomes include cost-effectiveness.
- **Retention SWATs**: Primary outcome is retention rate. Secondary outcomes include number of reminders sent to participants and cost-effectiveness.
- We will explore where possible the effects of the strategies in different patient populations: sex, age, ethnicity, geographic location and deprivation.

2

Monetary incentive SWATs

implement SWATs

- Host trial eligibility
  - Recruitment: host trials will be eligible if using individual randomisation
  - Retention: host trials will be eligible if using individual randomisation and participants have at least one follow-up remaining
- If host trials have incentives costed in, we will randomise (potential) participants to the existing incentives. £5,000 to cover costs of SWAT
- If the trial does not have any incentives costed in, up to £10,000 to also take into account the cost of the incentives
- UK funder or recruiting participants in the UK
- If you're putting in a trial funding application in Ireland, consider putting in this SWAT

Resources

- Parker A., et al. Undertaking Studies Within A Trial to evaluate recruitment and retention strategies for randomised controlled trials: lessons learnt from the PROMETHEUS research programme. Health Technol Assess 2024;28(2). https://doi.org/10.3310/HTQW3107
- Interested in doing a recruitment or retention randomised SWAT? Here's our 2024 priority list of questions to test: Parker, A., et al. (2024, February 8). WP1: Identifying and prioritising trial recruitment and retention strategies. https://doi.org/10.17605/OSF.IO/CZ829
- Interested in collaborating to test the effectiveness and cost-effectiveness of monetary incentives for recruiting and retaining participants in trials? Further information here: https://docs.google.com/document/d/1LNHxvUyhxKSexLvboiSHCpm5ySuqJOjO/edit?usp=sharing&ouid=117279899757688883871&rtpof=true&sd=true
- SWAT resources: videos and documents on doing SWATs: https://www.york.ac.uk/healthsciences/research/trials/swats/swatresources/
- SWAT funding Ireland: https://www.hrb-tmrn.ie/research-innovation/study-within-a-trial-swat-funding/
- SWAT funding UK NIHR: https://www.nihr.ac.uk/documents/trial-forge-additional-guidance/32778
- The Prioritising Recruitment in Randomised Trials study (PRioRiTy) https://priorityresearch.ie
- PRioRiTy II: Prioritising Retention in Randomised Trials: https://www.trialforge.org/priority-two
- There is a repository of SWATs to help you link with the work others are doing
- For specific advice about which SWAT might work for your trial, contact the Trial Forge SWATs Centre

Thank you for listening!

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