

Trial Forge Guidance 5: ethical considerations in randomised Studies Within A Trial (SWATs).

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within a host trial, or several host trials, with the aim of evaluating or exploring alternative ways of delivering or organising a particular trial process. Although SWATs are recognised by funders, there are differences in how they are implemented, such as different consent requirements in the UK and Ireland. This complicates SWAT conduct, raises ethical considerations, and highlights the need for standardised, ethical approaches to SWATs. The purpose of the current study was to devise guidance to address this.

We used existing systematic reviews, searched PubMed and the SWAT register, and contacted SWAT teams known to the authors to identify relevant randomised SWATs to include in our literature review. We extracted information on SWAT descriptives and 19 outcomes of interest pre-identified by the authors as being potential ethical considerations. We themed our findings. We held three consensus building fora, all including representatives from eight key stakeholder groups representing a broad range of roles in trials. We presented participants with two SWATs to start conversation on perceived ethical issues. We also incorporated the findings of our literature review. Consensus building fora were recorded, transcribed, and analysed using NVivo, focusing on ethical principles, challenges, and solutions.

We developed guidance on ethical considerations applicable to randomised SWATs. There are 14 ethical considerations covering all stages of a SWAT, from development and SWAT team selection to communication of results. The considerations are posed as questions, so trial teams can easily answer these when designing their SWAT.

Studies Within A Trial are generally perceived to be low risk and low burden to participants. However, there are still varying ethical standards applied to these studies by researchers, sponsors, and ethics committees. These guidelines will be helpful to anyone planning or reviewing SWATs in understanding these differences and their ethical implications, and provide a practical guide for the ethical conduct of SWATs.

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Shiely Frances pmc-status-qastatus 0 pmc-status-live yes pmc-status-embargo no pmc-status-released yes pmc-prop-open-access yes pmc-prop-olf no pmc-prop-manuscript no pmc-prop-legally-suppressed no pmc-prop-has-pdf yes pmc-prop-has-supplement yes pmc-prop-pdf-only no pmc-prop-suppress-copyright no pmc-prop-is-real-version no pmc-prop-is-scanned-article no pmc-prop-preprint no pmc-prop-in-epmc yes pmc-license-ref CC BY-NC-ND issue-copyright-statement © BioMed Central Ltd., part of Springer Nature 2025 Background It is well known that randomised controlled trials are often inefficient in terms of recruiting to target and on time, as well as in retaining participants until the end of the trial [1 – 8]. A consequence of this is that it inevitably leads to delays, which can increase trial costs and delay potentially lifesaving treatments for patients [9]. Trialists are very aware of these inefficiencies and employ a number of strategies to improve them, particularly for recruitment and retention (e.g. giving conditional or unconditional vouchers, sending newsletters, or the inclusion of pre-paid envelopes for questionnaire return), but a lack of evaluation means that it is generally difficult to determine the impact of these steps [4 , 5 , 10].

Studies Within A Trial (SWATs) are a robust, cost-effective method of conducting primary methodological research in trials to provide evidence on how to improve trial processes, both through randomised and non-randomised evaluations [11]. A SWAT is a self-contained research study that is embedded within a host trial, or several host trials, with the aim of evaluating or exploring alternative ways of delivering or organising a particular trial process [12 , 13]. For the remainder of this manuscript, we will consider randomised SWATs only. SWATs are often constrained by the host trial in which they are embedded, which restricts the number of potential participants. Consequently, power calculations are not always done for SWATs [12]. The usefulness of findings of SWATs to future trials is only fully realised through replication (across clinical areas, participant groups, countries, etc.) and inclusion in meta-analyses [14]. In terms of evidence synthesis for SWATs, Cochrane systematic reviews exist only for recruitment [4] and

retention SWATs [5]. However, SWATs on any trial process, e.g. data collection and reporting, are possible. Despite SWAT-like trial methodology work from as far back as 1986 [4 , 15], progress on finding definitive answers to effectiveness has been slow. Nearly 40 years later, there is still limited high certainty evidence to support trial process decisions, even for recruitment and retention, which has been the focus of most randomised SWAT activity [4 , 5]. To increase SWAT activity, the PRESS (Protocol and Resources for Priority Recruitment and Retention SWATs) project recently worked with PPI (patient and public involvement) partners to prioritise recruitment and retention SWATs for evaluation. These include, for example, effectiveness and cost-effectiveness of a trial participant biography on participant recruitment rates; evaluation of a theoretically informed written trial invitation compared to a standard written invitation to improve recruitment; an evaluation of whether electronic reminders increase questionnaire completion rates compared to usual follow-up (retention); and an evaluation of whether offering flexibility in in-person follow-up visit location increases trial participant retention compared to not offering flexibility.

Funding to conduct SWATs is essential but many require small amounts, relative to the cost of the host trial. The value of SWATs is recognised by funding bodies in Ireland (www.hrb.ie) and the UK through the provision of dedicated SWAT funding (e.g. see <https://www.nihr.ac.uk/documents/methodological-sub-studies-studies-within-a-trial-or-project-swat-and-studies-within-a-review-swar/21512>). Canada also recently started to provide SWAT funding through their Accelerating Clinical Trials (ACT) consortium which is funded by the Canadian Institutes for Health Research (CIHR) (<https://act-aec.ca/funded-projects/>). Despite this, there are some systematic differences in how SWATs can be done within and across different jurisdictions. For example, in the UK, separate participant consent to take part in the SWAT is not usual, because doing so is often considered likely to undermine the evaluation. For example, if the SWAT is testing different recruitment materials, knowledge of the SWAT might impact behaviour if the SWAT participants are aware that different recruitment materials are being tested. Or if a host trial follow-up process is being evaluated, knowledge of the SWAT might change how potential participants interact with the SWAT intervention. In Ireland, it depends on the ethics committee, with separate consent likely to be required. For example, SWAT 107 [16] implemented at the pre-screening phase and SWAT 141 [17], both set in Irish-led host trials, required separate SWAT consent in addition to host trial consent. In comparison, a SWAT by Kho et al. [18] conducted in the UK did not need to collect consent for a SWAT that evaluated a similar intervention. From a research perspective, this can make conducting SWATs harder and potentially introduces differences into SWAT conduct, making their usefulness for meta-analyses more uncertain. The challenge facing ethics committees and trialists is how best to conduct a SWAT that is ethical, provides robust evidence on trial methodology, and does not impact the host trial, or the trial participants, negatively.

The purpose of the current study was to devise guidance documentation, Trial Forge Guidance 5 (TFG5), for ethics committees, trialists, methodologists, funders, approvals agencies, and others, to enable more harmonisation of SWAT conduct across borders, disciplines, and ethics committees. This guidance will support the ethically appropriate design, approval, and conduct of SWATs to address key inefficiencies in trial processes.

This work is part of a series of guidance on SWATs and how to improve clinical trials more generally, initiated by Trial Forge (<https://www.trialforge.org/>).

A multidisciplinary advisory group which consisted of trial methodologists, SWAT experts, ethicist, statistician, and research ethics committee members was established to advise the core project team.

To identify SWATs, either protocols or SWAT reports/publications, we used the Cochrane systematic reviews for strategies to improve recruitment and retention in randomised trials [4 , 5] and searched the literature via PubMed, the F1000 SWAT Collection, and SWAT register (the Northern Ireland SWAT Repository) (searches were conducted in August 2022). We contacted known SWAT teams with collections of SWATs (e.g. PROMETHEUS team in York, UK) to identify unpublished SWATs. Our eligibility criteria were as follows: (1) the SWAT intervention was

randomised; (2) the SWAT involved a real host trial (i.e. the host trial was not a mock/pretend trial); (3) if published, the SWAT was published in or later than 2010. If there was more than one record for a SWAT, the most recent was included.

We developed a data extraction form, piloted it on three SWATs by duplicate extraction (HB and FS), and decided on data categories as presented in Table 1 . Authors of included SWATs were not contacted for further information. Full data extraction was performed in duplicate by two reviewers (HB and GSH). Table 1 Data categories

- Patient and public involvement in SWAT development
- The justification for not needing ethical approval (if no)
- Whether SWAT participants or their legal guardians consented to participate
- Whether others consented to participate (e.g. health care staff)
- Description of the consent process and what participants consented to
- If consent was not collected the justification for this
- SWAT documentation for participants (e.g. participant information sheet, consent form)
- Who recruited and how were participants introduced and recruited to the SWAT
- Any steps taken in recruitment of vulnerable participants (e.g. any additional protections invoked, who consents on their behalf)
- Any statement regarding risk to participants
- Any description of confidentiality risks and steps taken to protect confidentiality
- Any description of ethical considerations or challenges
- Whether any ethical challenges were highlighted by the ethics committee and if there was a description of them
- Any challenges put forward by any other committee/review body other than the ethics committee and what it was
- Whether results of the SWAT were shared with participants (relevant to participant facing SWATs only)
- Any data sharing statement or text about the availability of the SWAT data
- SWAT using factorial design—yes or no because this design can cause SWATs to be excluded from meta-analyses due to possible contamination between interventions

Sixty invitation emails were sent directly to potential participants. Potential participants were identified by the project team and the opportunity to take part was advertised at the International Clinical Trials Methodology Conference 2022 and on social media, as well as with an established patient and public involvement (PPI) group in Ireland. We held three online meetings to build consensus on the ethical issues for inclusion in the guidance documentation and potential solutions

to those issues. In addition to two study team members (FS and ST), a total of 32 participants were involved, nine at meeting 1, 14 at meeting 2, and nine at meeting 3. Each meeting included representatives from eight relevant parties representing a broad range of roles in trials: sponsor representatives, clinical site members, other site members who approve study access, funders, PPI partners, research ethics committee members, trialists and methodologists, ethicists, and trial managers. The purpose was to elicit their views on processes, challenges, and ethical issues when conducting SWATs.

Attendees were sent a preparation pack 1 week before the consensus building forum. It contained educational materials to help attendees understand what a SWAT is and what an ethics review entails. We also provided a short description of two randomised SWATs, SWAT 13 [19] and SWAT 24 [20], from the Northern Ireland SWAT Repository, which we selected to use as a starting point to evoke discussion amongst the forum attendees. All these materials are provided in Supplementary File 1. Each meeting started with a recorded presentation by bioethicist and co-author, CW, which introduced ethical principles that guide the design and conduct of trials: respect for persons, justice, beneficence, and respect for communities [21]. In addition, the video highlighted how these principles are applied to SWATs. These four ethical principles are internationally accepted and encompass the World Medical Association Declaration of Helsinki principles [22]. Ethical issues in SWATs, starting with the case studies, were explored in an open discussion where participants also suggested solutions without prompting. The consensus fora hosts, ST and FS, also introduced the findings from our literature review in the discussion.

Descriptive statistics (frequencies) were used for quantitative data. Analysis was carried out using IBM SPSS Statistics, version 29.0.1.0 (171). Qualitative data extracted from the SWATs were content analysed using descriptive codes. Findings are presented as a narrative summary.

The online consensus building fora were audio recorded and transcribed verbatim. Written comments made by attendees during the fora were also saved and included in the analysis. All transcripts and written comments were analysed using NVivo (version 12; QSR International) for data management. Consensus building fora were content analysed using a directed approach [23], by initially identifying the relevant ethical principle(s) (deductive coding) and then further sub-categorised using descriptive labels for both challenges and suggested solutions (inductive coding).

Eighty-nine sources of randomised SWATs were eligible for inclusion. We use the term 'sources of SWATs' because one publication may report multiple SWATs, and not all included SWATs have been published. Of 182 registrations on the Northern Ireland SWAT Repository, 140 were randomised SWATs (others were not randomised and some registrations were blank (repository accessed August 2022)). None was found to contain ethical information relevant to this study, so this SWAT source was excluded (Fig. 1). Fig. 1 PRISMA flow diagram

One hundred and three SWATs from sources other than the Northern Ireland SWAT Repository were included and Table 2 presents their characteristics, categorised by the stage of the SWAT in relation to ethical review. Fifty percent (n = 52) of SWATs had registration details. The host trials spanned a wide range of medical conditions and health areas. For example, of the 103 SWATs, the single most frequent condition was cancer (n = 12, 12%), followed by mental health (n = 9; 9%) and smoking (n = 5; 5%). Of the SWATs that were successfully embedded and evaluated (n = 92; 90%), the number of trial participants randomised to the SWATs ranged from 14 to 20,759 (the large number of participants stems from a recruitment SWAT sending different length invitations for host trial screening visits) while other SWATs randomised PPI partners, recruitment or intervention sites, or doctors. Table 2 List of SWATs included according to stage of ethical review

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

b <https://f1000research.com/collections/swat>

We identified eight themes: reporting of SWATs, primary outcomes, ethical approval, SWAT consent, SWAT randomisation, ethical considerations, patient and public involvement, communication of results. Each are presented below.

In the 103 included SWATs, the sponsor was mostly not listed (n = 85, 83%). When reported (n = 18; 17%), sponsors were mainly higher education institutions (n = 15; 83%), NHS and higher education co-sponsorship (n = 2; 11%), or solely NHS (n = 1; 6%). Of 92 evaluated SWATs, 31 (34%) did not report sex or gender. Of the 61 that did, none reported both and none reported non-binary genders or intersex. One study reported transgender identity. Amongst SWATs reporting gender (n = 8; 13%), three included women only, none men only, and five included both. Amongst those reporting sex (n = 52), six (12%) included females only, none males only, 41 (79%) included both females and males, one reported parent sex (2%), and four (8%) included numbers of females, males, and missing/unknown.

Out of the 92 evaluated SWATs, 30 (33%) did not report participant age. Where reported, age ranged from 4 days to 80 years and was summarised mostly by the mean. Nineteen SWATs (21%) reported ethnicity or race, using 13 different classification systems (e.g. African American, White, other; White race; White, non-White, missing; White, Black, Asian, other, unknown).

Ninety-two percent of SWATs had retention (n = 56, 54%) and recruitment (n = 39, 38%) as their primary outcome. Examples of other primary outcomes were adherence, understanding, and quality of consent. For the SWATs with recruitment as the primary outcome, interventions most frequently targeted host trial postal invitations (n = 21; 54%). For SWATs with retention as the primary outcome, interventions most frequently targeted host trial questionnaire follow-up (n = 44; 79%) in various modes (e.g. postal, email, online, telephone).

Of the 103 SWATs, 90 (87%) reported requiring ethical approval, three (3%) said it was not needed, and nine (9%) gave no detail. The three SWATs not needing approval were from Denmark and the UK; one Danish SWAT provided justification that it was classified as a survey.

Amongst the 90 requiring approval, the detail provided varied: two (2%) referred only to host trial approval, 47 (52%) gave generic statements that approval had been obtained, 15 (17%) were submitted as amendments to the host trial, nine (10%) were submitted alongside host trial applications, and eight (9%) indicated seeking separate ethics committee approval. Five (6%) SWATs involved multiple host trials and received programme-level or amended approvals. One (1%) SWAT reported approval indirectly in the author contributions section. Finally, three (3%) SWATs did not proceed after receiving ethics committee feedback.

Of the 90 SWATs reported needing ethical approval, 12 (13%) reported collecting consent from participants and/or legal guardians, 16 (18%) described indirect consent (e.g. via host trial PIL, consent for SMS contact, or return of questionnaires), and two (2%) included consent for both SWAT arms after ethics review (SWAT 107 and 141). Most (50, 56%) did not collect consent, and 12 (13%) did not report on consent. Two (2%) SWATs, as well as collecting SWAT participant consent, collected additional consent from doctors or volunteer community health advisors.

Of the 12 SWATs that collected consent, nine (75%) described recruitment: in two, pre-host trial consent was required and the SWAT was introduced by host trial clinical/recruiting staff and SWAT staff consented participants; in four, recruiting physicians/host trial staff consented participants; one used participant expression of interest; one counted site agreement as consent; and one appeared to confuse host trial consent with SWAT consent. In SWATs without formal recruitment, some introduced the intervention indirectly (e.g. mentioning a voucher in a cover letter). SWAT documentation varied across the 12 SWATs, from not reported (n = 5; 42%) to detailed PILs and consent forms (7; 58%). One SWAT included a signed agreement to view an animation.

Amongst the 50 SWATs that did not collect consent, 27 (54%) provided justification: nine (33%) had consent waived by ethics committees, six (22%) were described as low risk, three (11%) stated they were not withholding information, seven (26%) had participants unaware of the SWAT, and two (7%) described host trial consent as covering the SWAT. SWATs without consent were seen across many countries.

No SWAT described participants as vulnerable. However, for one SWAT it was reported that the parents of the child participant provided consent, and the children provided assent. It should be noted that the consent and assent for host trial and SWAT were integrated in the same process and materials.

Randomisation was described in 97 (94%) SWATs. Of the 6 SWATs (6%) for which randomisation was not available, two SWATs were completed, three were abandoned after ethics review, and one was abandoned before ethics review. A total of 14 (14%) SWATs were described explicitly as using factorial design.

One (1%) SWAT from the total 103 noted possible harm (feeling pressured to participate) but did not measure it; the rest did not mention risks, apart from seven described as low risk and exempt from ethical approval. Three (3%) SWATs reported steps to protect confidentiality: avoiding voicemail in reminder calls, emailing vouchers rather than posting, and discussing confidentiality at first contact when a community health advisor volunteer was involved.

Eight SWATs (8% of 103) reported ethical considerations or challenges (unrelated to review committees) affecting or addressed within the SWAT. The same consideration was extracted for three SWATs from a single source. Reported considerations included data confidentiality, fairness in access to information, participant confidentiality, staff protection regarding returned incentives, fairness around monetary incentives, and justification for not collecting consent when host trial consent covered mode of contact.

Five SWATs (5%) reported ethics committee challenges: two which were completed and three abandoned after ethics review. (1) SWAT 141 tested guided self-reflection to boost recruitment; the ethics committee requested more detail in the intervention PIL and written consent for control participants. (2) SWAT 107 tested an animation; the ethics committee requested more protocol detail, PILs, and consent for the intervention arm. (3) SWAT 91 used a theoretically informed newsletter and was asked to send a newsletter to the control group too, affecting the outcome measurement. (4) Two SWATs intended as replications of SWAT 24 were affected by ethics committee concerns: one single-host trial replication was abandoned after a committee described intervention materials as coercive, and another involving three host trials saw two ethics committees request changes for coercive language and one for aggressive language.

Challenges were also raised by bodies other than the research ethics committee for three SWATs (3%). One SWAT 24 replication saw a local PI refuse participation, citing concerns about damaging participant relationships. In SWAT 13, two sites rejected the amendment: one due to confidentiality concerns around incentive reporting and another because participants were not informed about randomisation to the SWAT. In the third SWAT, the host trial's Data and Safety Monitoring Board recommended stopping the SWAT due to lack of efficacy. Some other SWATs also had non-participating sites without reported reasons.

Out of the 103 included SWATs, 17 (17%) reported PPI involvement.

Seven (7%) SWATs reported informing (n = 4) or planning (n = 3) to inform participants of the SWAT results. Forty-two (41%) SWATs included a data sharing statement. Conditions for data sharing varied, ranging from unconditional sharing, Creative Commons licencing with attribution, to requiring data sharing agreements and specifying time-limited availability and conditions.

Of 60 invitations sent, 39 (65%) people expressed an interest in attending the online consensus building fora and 32 (53%) attended. Table 3 describes the number of stakeholder types attending the meetings. Although many had several roles, Table 3 shows the role for which they were invited to the consensus building forum. Table 3 The number of stakeholder types that attended the three consensus building fora and the countries where stakeholders were based

e.g. university sponsor representative, NHS sponsor representative

e.g. Clinical Research Facility/Clinical Research Centre Ireland, National Institute for Health and Care Research Clinical Research Network (NIHR CRN), UK

e.g. government funding bodies, charities, industry

PPI partners/organisations to approach to invite PPI partners

e.g. experienced PPI partners, trial participants, research ethics committee lay members

e.g. National Health Service (NHS) REC members, university REC members

There are four ethical principles that govern trials: respect for persons, beneficence, justice, and respect for communities [24]. The ethical principle of respect for persons requires researchers to obtain the informed consent of prospective research participants (unless conditions for a waiver of consent applies) and to preserve the confidentiality of private information. The ethical principle of beneficence means that researchers must maximise the benefits of research participation while minimising risks. The ethical principle of justice obliges researchers to select research participants fairly and to ensure they have reasonable access to any beneficial treatment identified. Finally, the ethical principle of respect for communities calls on researchers to respect communal values, protect and empower social institutions, and, where applicable, abide by the decisions of the legitimate communal authority [24].

Our consensus building fora participants were given a presentation on these principles to provide a framework for our discussion on the ethical issues in SWATs. We present this discussion as results using the same framework, divided into the five key parts of the trial: design/planning/protocol development; recruitment; data collection; analysis; and dissemination. When synthesising the recordings of the consensus fora, as ethical considerations/themes unique to SWATs arose, we labelled them, beginning at no. 1. A full list of the considerations, along with proposed solutions, is presented in Table 4 in Trial Forge Guidance 5. Note that not all themes from the literature review emerged as focused discussion in the consensus fora. Table 4 Ethical issues in SWATs and actions to address them (excerpt from Trial Forge Guidance 5, Supplementary File 2)

1. Is there resource waste due to developing interventions for groups who will not benefit?

2. Is there resource waste as the intervention is not appropriate, e.g. causes unintended harm/upset or is not accessible to all?

3. Is the integrity of the host trial protected?

4. Does the SWAT intervention meet equality, diversity, and inclusivity criteria?

- Involve PPI partners in SWAT design as early as possible. Getting PPI partners' views on the SWAT intervention early will help ensure it is acceptable to SWAT participants. It will also reassure ethics committees that people with lived experience have been involved in the development of the SWAT

- Earlier studies have linked factorial designs to potential research waste [5]. If a factorial design is proposed, ask if it is the correct choice for a SWAT. Is it likely to be excluded from future reviews due to potential intervention interactions and therefore represent research waste?*

- Consider whether the SWAT intervention choice may disproportionately undermine the autonomy of one or more groups within the host trial by limiting their ability to take part in the SWAT more than others

- Are checks of acceptability of the SWAT intervention with potential participants needed? Do participants need a choice regarding whether they receive the SWAT intervention or not? PPI can help to answer this question

- Are potential participants likely to meet/know each other and discuss the SWAT intervention? What might happen if they find out they are treated differently (e.g. one receives a monetary incentive and the other does not). Consider whether the intervention is appropriate for the population*

- Is the REC that provided the approval for the SWAT listed in the SWAT protocol on the SWAT Repository Store? Although not all SWATs on the SWAT Repository Store will have gone through the approval process, it should be added as an update when appropriate

- All SWAT websites (e.g. PROMETHEUS, Implement SWATs, Trial Forge) should provide a list of ethics committees that are familiar with SWATs*

- o PROMETHEUS <https://www.york.ac.uk/healthsciences/research/trials/swats/prometheus/>

- o Implement SWATs <https://www.implementswats.org/>

- o Trial Forge <https://www.trialforge.org/>

- If possible, choose a REC that is familiar with SWATs. If the REC is familiar with SWATs, you may not need to provide much background information about SWATs in your submission

- If the REC is not familiar with SWATs, we suggest including general SWAT information text, including the purpose of SWATs, the potential benefit of SWATs (including to the host trial), and the principle that SWATs should never affect the implementation of the host trial. This text is provided in TFG5*

9. Is it ethical to randomise trial participants to a SWAT without informing them?

10. Will informing participants about the SWAT risk influencing the findings?

- Reassure the REC that the SWAT intervention poses a minimal risk to participants and might even be done without ethical approval (e.g. newsletters might already be sent from the trial office to participants) and why this would be a proportionate approach. Reassure the ethics committee that the secure data collection and storage arrangements in keeping with data protection regulations will be followed

- Explain to the REC that knowledge of the SWAT is likely to change actions in relation to the target behaviour and therefore any results may not be reliable

For participants (only relevant if SWAT participants also are participants in the host trial):

- Include a generic description of SWATs in the host trial participant information leaflet. Ensure to include that a low-risk SWAT might be conducted and while they cannot be fully informed about their participation, they will receive the results (if they wish to)
- Consider giving participants the possibility of opting out of taking part in SWATs and instructions on how they do this?*
- Who is included in the SWAT? In order to establish generalisability of any intervention, we need to know who was included in the study. Collect and report appropriate information to describe the SWAT participants in terms of equity, diversity, and inclusion (EDI) characteristics, e.g. age, sex, gender, race, ethnicity and ancestry, socioeconomic status and location of the trial, and trial and SWAT coordination sites. This will also allow later subgroup analyses to be done
- Be prepared to share SWAT data to enable subgroup analyses, e.g. using any of the EDI characteristics listed above
- If your participants are 'blinded' to their participation in a SWAT, they should be fully informed at the end of the SWAT or host trial, whichever is appropriate for your SWAT. A description of the SWAT as well as the results of the SWAT, if participants want to receive it, should be sent to them. This can be included when participants are sent the results of the host trial
- In the UK, the Health Research Authority (HRA) recommends sending trial results to trial participants: <https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/research-transparency/informing-participants/communicating-study-findings-participants-guidance/>

*Issues and solutions added by the study authors on reflection after the consensus building fora. All other issues and solutions were suggested by participants in the consensus-building forum

The ethical principle of beneficence emerged in what is a fundamental issue prevalent in SWATs—the absence of equipoise. Equipoise relates to the uncertainty principle, i.e. that participants and researchers are unsure about which intervention will confer most benefit to participants. There is no recognised process to identify when equipoise is or is not present in SWATs. As SWATs often evaluate modifications to approaches that may already be in use (e.g. infographics for presenting information to potential participants, trial newsletters, different ways of collecting participant data), it is not unusual for trial teams and others to have views on effectiveness prior to evaluation. Moreover, evidence of effectiveness in SWAT interventions is dependent on replication, which means some evidence often exists ahead of a SWAT. This makes equipoise hard to achieve, or be certain of, in many cases. SWAT teams may face challenges in selecting interventions for testing and in potentially making recommendations to trial teams about strategies that will not be used while the SWAT evaluation is running. This is also a risk for trials in general. However, the authors and consensus building forum participants concluded that the choice of interventions for testing may be less evidence-informed than for trials in general. This may lead to evaluations of intervention that may not always be the most suitable (ethical consideration 1):

So trying to determine equipoise I think is really difficult [...]. You might want to for example, look at the process of what's the best way to see people for visits in a clinical trial, and you might do for example, face to face visits versus telephone visits. But by doing that you then don't offer the other things, that maybe lots of patients prefer video consultations and they don't like either face to face visits or telephone. But because there's a real lack of data to guide selection of interventions, I think that's one of the big challenges, one of the big ethical dilemmas of SWATs how to overcome that problem is challenging (...) . (Participant 14; trialist/methodologist, meeting 2).

Also, regarding ethical consideration 1, and the principle of respect for communities, there was also a consideration of PPI partners being helpful in preventing resource waste and ensuring that the

SWAT will provide a benefit to society:

I suppose the other one is the perceived balance of... kind of the opportunity cost of the finance and thinking about Charles' [CW, Bioethicist on project team] principle of respect for communities, which communities are we thinking about and who, or what, activities don't get this money if it's invested in trying to persuade a few more people to return a questionnaire . (Participant 4, ethicist, meeting 1).

Ethical consideration 2 addressed concerns around causing unintended harm/upset by the proposed intervention:

.. I wonder if sometimes assumptions might be made about harm where actually we don't have evidence of harm and some of these could be sort of reframed as research questions . (Participant 7, sponsor representative, meeting 1).

A further issue highlighted at the consensus fora was the issue of proportionality. Although the primary aim of research ethics committees (RECs) is to safeguard research participants against undue risks and burdens, there is a tendency to err on the side of caution when there is a lack of evidence regarding potential risk or burden associated with an intervention. This cautious approach can sometimes lead to a loss of perspective on the appropriate level of concern. Recognising this issue, the authors sought to emphasise the importance of proportionality in the guidance materials. This was supported during the consensus building meeting.

Also the idea of proportionality that underpins all of this doesn't it, so is it a proportionate approach to require ethical approval, is it proportionate to require individual consent to take part in the SWAT as well as the study, and how you might justify whether your approach is proportionate or not, and that's the role often of perhaps qualitative research to explore whether a SWAT is feasible and also whether the approach you're proposing is proportionate or not, and also the role of a public involvement contribution in that. (Participant 9, trialist/methodologist, meeting 2).

The safeguarding of the host trial(s) was discussed extensively, and several ethical considerations were raised, governed by the principle of beneficence. This was discussed in relation to the case study involving monetary incentives. It was noted that what researchers perceive as an incentive might not necessarily be perceived as such by SWAT participants. This mismatch in perception could lead to unintended consequences for the host trial, for example a lower return rate for questionnaires:

(...) but the bit that strikes me most about this is that there is an assumption that this is an incentive [£5 voucher], and that... I'd be curious to know if there's ways in which you can measure whether this is a disincentive. (Participant 10, patient and public involvement partner, meeting 1).

Another aspect concerning the protection of host trial(s) highlighted how the SWAT intervention could intersect with ongoing societal issues, such as the general cost-of-living. This context may render certain incentives, like monetary rewards, more appealing to specific participant demographics rather than being universally attractive, potentially leading to biased questionnaire responses:

Then, my final thought is really that particularly in the current economic climate if you were rewarding people who returned their questionnaire with a voucher, would you be skewing the data in the sense that some people might... much more incentivised to do that who really, really... that £5 would make a big difference to them than other people? (Participant 8, PPI partner, meeting 1).

I was just going to say from a practical experience of delivering SWATs when we talk to our participants, my work is done with the elderly and I think we do we have to be really mindful about this being coercive because I know with this group of people they'll often ring up and they'll say they

want to withdraw from a study, but they'll do it in such a nice way, they'll say, "If it's not too much trouble dear, I'd really like to... if I could come out", and it would be so easy to coerce them and say, "Well actually..." and cajole them into it, and obviously we don't. But I think just have to be mindful that some people are really very vulnerable, and I have seen some letters on this nudge theory, or whatever else you want to call it, where it has been pretty heavy handed and I wasn't really happy about that. (Participant 6, trialist/methodologist, meeting 2).

In terms of the ethical principle of respect for communities, there was a general call to educate RECs and other review bodies about SWATs in the consensus building fora and to help other SWAT teams by letting them know which RECs have experience of a specific SWAT protocol to achieve consistency in the review process. As educating RECs and other review committees about SWATs is not quickly achievable, we have developed this general information about SWATs as part of this guidance. SWAT teams can then submit this text at the time of review (see TFG5 guidance). Participants in the consensus building fora also suggested updating the SWAT registry entry to show which RECs had approved SWAT evaluations.

I know the REC that had reviewed the SWAT initially had a bit of pushback and it was then that we had to go back and say, "Well, this has been approved before." That was a point that I'd scribbled down at the start, you know, if the SWAT repository or whatever... it would always be quite good to know what ethics committees had actually reviewed what SWATs. I think if I was putting an application in now for a SWAT, I'd want to reference that because that's happened, I'd want to say, "This has actually been approved by X, Y, Z." If I see that sometimes in a REC, I'm like, "Well, okay, that's how many people have thought that this was all right previously." (Participant 2, trial manager, meeting 3).

In relation to respect for communities, the suggested solution was also to include PPI partners on the SWAT team for the REC to be confident that someone similar to SWAT participants has been consulted about all aspects of the SWAT and the intervention.

In summary, in terms of the guidance, the solution offered at the consensus building fora was to include public and patient partners in the SWAT team to help identify and avoid these issues. Of 103 included SWATs in our literature review, just 17 (17%) reported PPI involvement.

Respect for persons emerged in our consensus building fora and was debated at length, primarily when discussing informed consent. The ethical principle requires the informed consent of prospective research participants, unless conditions for a waiver of consent apply. However, requiring informed consent can cause problems for many, if not most, SWATs. SWATs are typically about trial processes that will happen in one form or another regardless of the SWAT, are low risk, and knowledge of participation in a SWAT might influence how participants interact with it, undermining the evaluation. SWAT investigators typically request that host trial participants are not consulted or informed about the SWAT.

Our consensus building forum participants had differing views on this. In one of the fora there was a desire to give SWAT participants a choice about whether to accept or refuse an intervention. Of course, this is likely to result in the intervention changing, because providing knowledge of the intervention is likely to change behaviour, and this is problematic from a SWAT design and implementation perspective. This discussion originated around the use of monetary incentives (shopping vouchers) to enhance retention:

Offering payment doesn't mandate that people accept it. (...). Again, it's very paternalistic. (Participant 10, PPI partner, meeting 2, chat).

... making you feel respected, trusted... and not (e.g.) taken for a cheapskate or someone who would only be motivated by money, and not inclined to do something that is socially valuable unless there was money involved. (Participant 4, ethicist, meeting 1, chat).

The discussion highlighted that not all incentives will be perceived in the same way by everyone. One forum participant suggested that offering a choice either in whether to receive the incentive, or the type of incentive, would give SWAT participants some autonomy of their participation:

(...)is there any way that people could have a choice over what gift voucher they receive or what... if we're calling it an incentive (inaudible) it might not be, whatever incentive they receive, I'm thinking that if it was a large trial, you might also get the additional information about which is the best way of... you know, what type of voucher or what type of financial reward, or if it may not even be financial, it might be something completely different, is most likely to result in people... I don't know, completing the questionnaires. (Participant 8, PPI partner, meeting 1).

Three solutions emerged from the consensus building fora, two by the forum participants and one by the authors. Firstly, it was suggested to include a blanket consent at the time of host trial consent, i.e. a general description of SWATs and that when taking part in the host trial, participants might also take part in a SWAT:

I just think there's the risk of making research so laborious that this kind of work doesn't get done [...]In the States they did update the common rule in 2018 exactly because RECs were totally overwhelmed... with all these kind of research requests and they introduced the concept of broad consent. [...] But I think it's important that people are aware, that they're informed you know, it might not be an individual consent, I'm thinking of one trial in particular, but there was a notification given to patients and they were all told that their particular facility may or may not be randomised to an intervention and the IRB's [Institutional Review Board which is a research ethics committee in the US]) approved that. Individual consent wasn't obtained but... there was notifications provided to everybody about a pragmatic cluster randomised trial. (Participant 4, funder, meeting 2).

The second suggestion was to fully debrief SWAT participants about the purpose of the SWAT and what was involved when the SWAT is completed:

(...) it's no different, really, to a blinded clinical trial where you might tell people what arm they're on at the end and which IMP [investigational medical product] they received. I suppose in that sense it is justifiable ethical, as long as you're transparent at the end of the study. (Participant 6, sponsor representative, meeting 3).

The authors added to this the best time to inform participants of the SWAT findings would be together with information about the host trial results, as it is current best practice to do so [25 , 26]. Additionally, the authors suggested having public and patient partners on the SWAT team as an essential part of working towards a solution to the concerns raised, to ensure SWAT participants' right to autonomy is respected.

In summary, taking the literature review and our consensus building discussions, practices vary, but our consensus building fora participants were open to host trial consent without the need for separate SWAT consent from participants, with the caveat that they are informed at some point that their data has been included in a SWAT.

In terms of the principle of justice, there was a discussion around whether SWAT interventions target the parts of the host trial population that they need to target:

(...)... so you're deliberately trying to incentivise people who are not responding to the survey, (...), maybe there are certain groups who the financial incentive doesn't have a big impact for, so this question of looking at who's responding, I think it's particularly important, because (...) those principles that get reviewed at the ethics committees, justice is maybe one of the ones that doesn't get as much attention as the consent or the risks and benefits, [...]. (Participant 2, trialist/methodologist, meeting 1).

Additionally, the overall issue of the inclusivity and appropriateness of SWATs for the population being investigated emerged. Issues can involve, e.g. whether all participants have a mobile phone (or a particular brand of mobile phone) or whether the theory underlying the SWAT intervention is generalisable to all or only some of the population:

(...) whether there are, then, any implications or concerns about fairness, equality of respect, which I would also include as justice, by the way. I wouldn't just see justice as a purely distributive matter. I think we should be attending to more relational understandings of justice as well – are people treated as equals, are people related to as equals. You know, it's unlikely that there's a huge problem here, but if the behavioural theory that has informed the thing had been developed in one very narrow population, then there might be concerns. (Participant 4, ethicist, meeting 1).

The authors have tackled this issue in the guidance document for SWATs, recognising that the generalisability of evidence relies on the representativeness of the sample of participants involved.

Protection of the host trial was discussed extensively at the consensus building fora, with many issues arising for the design and data collection stage. However, protection of the host trial also emerged at the analysis stage. In terms of justice, it was highlighted that in other countries subgroup analysis is becoming a requirement:

In Canada there is now increasing requirement to include Sex and Gender-Based Analyses (SGBA +). I wonder how often studies look at sub-analyses? (Participant 2, trialist/methodologist, meeting 1, chat).

However, due to the generally restricted sample size in SWATs, any subgroup analysis will probably have to be done at the pooling stage. In Trial Forge Guidance 4, the authors suggest SWAT teams make their data available for subgroup analysis and to describe who took part in the SWAT [27].

The issue of progress reviews was discussed, and it was decided that a statistician should be consulted to determine the need for a review point for the SWAT. It was agreed that this should be done prospectively when the SWAT is being designed.

The principle of justice prevails here. Justice requires that when the host trial is complete research participants have reasonable access to any beneficial treatment identified. In SWATs, it may appear convenient to overlook the principle of justice when participants are unaware of their involvement and because SWATs provide evidence on trial processes, rather than on treatment benefit. However, such behaviour is neither ethical nor in line with best practice. During consensus building fora, there was a proposal to treat SWAT participants similarly to those in host trials where participants are provided access to the SWAT intervention treatment. In SWATs, this intervention could be a monetary incentive, supplementary information through a newsletter, or something entirely different. Only seven (7%) of the SWATs we identified reported to have ($n = 4$) or plan ($n = 3$) to inform SWAT participants of the SWAT results. The authors included this point as a final step in the process of a SWAT/host trial and dissemination.

(...), much like giving patients with placebo/standard of care, the opportunity/access to intervention treatment that is done in many drug treatment trials. (Participant 14, trialist/methodologist, meeting 2, chat).

In summary, the agreed solution was to ensure that no-one should be disadvantaged when participating in a SWAT. Thus, if there was some benefit in the intervention arm, e.g. a monetary incentive, which the comparator arm did not get, it should be provided to the control arm when the SWAT is concluded. Additionally, it was strongly voiced in the fora that it was okay not to seek separate SWAT consent. However, all participants should be informed of their participation, and the results, when the SWAT has concluded.

Our full guidance document, Trial Forge Guidance 5, is presented in Supplementary File 2. Here we present the ethical considerations derived from the data extraction as well as the consensus building fora. We also provide suggested solutions to the concerns raised. The guidance has been written in collaboration with PPI co-author PH. In addition, the guidance includes text providing background information on SWATs, which is intended to educate the reader about the purpose of SWATs, how they can be used to inform design choices in the host trial, and how SWATs are different from other types of studies. This text was written by the authors based on consensus building forum attendees' request for education of ethics committees about SWATs.

Our study drew on systematic reviews, database searches, and unpublished SWATs via direct contact with known teams, thus ensuring thorough coverage. The consensus building fora included many people with a variety of roles in trials from a reasonably large number of countries, increasing the representativeness and relevance of the guidance. The consensus fora included patient and public involvement contributors, and this guidance is co-produced with a PPI partner also, ensuring relevance for all trial teams and participants. This is reflected in the guidance document also. There are also some limitations. This guidance has been developed for randomised SWATs as these constitute the majority of SWATs (NI SWAT Repository). While this does not mean the guidance is not relevant to SWATs using other designs, it will likely exclude ethical challenges specific to these designs. Consensus building forum participants were based exclusively in the global north; in addition, the majority were based in either Ireland or the UK. However, this also reflects the literature where all 103 SWATs included were conducted in the global north and most in either Ireland or the UK. Hence, this reflects a limitation of the area of research rather than a study-specific limitation per se.

Although SWATs are generally low risk and low burden to participants, this does not mean ethical standards for research do not apply. While similar in many ways to other research studies, SWATs have important differences that have implications for their ethical conduct. We anticipate this guidance will not only guide all relevant parties in the ethical conduct of SWATs but also provide education about SWATs, their purpose, limitations, and the need for these studies in making clinical trials more efficient, particularly making replication of SWATs possible so the evidence for target interventions can increase.

Supplementary Material 2. Trial Forge Guidance

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All materials are available in supplementary files in this paper. The transcripts of the consensus building fora generated and analysed during the current study are not publicly available due to their containing information that could compromise participant consent (but are available from the corresponding author on reasonable request).

Ethical approval was given by the Clinical Research Ethics Committee of the Cork Teaching Hospitals, Ireland (ECM 4 (m) 20/09/2022). Verbal consent was collected from all attendees at the start of each consensus building forum.

All research participants consented to the publication of their data for this publication.

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