

4 Chapter 4: Invitation letters and patient recruitment (SWAT)

4.1. Introduction

Clinical trials depend on the willingness of healthcare professionals and patients or members of the public to dedicate their time and commitment to participate. Good recruitment and retention of patients are therefore essential to the adequate conduct of a trial (Fisher *et al.*, 2012). However, there are few evidence-based methods for increasing recruitment to a trial and retaining those who do enrol for the whole duration or until the completion of their final follow up (Treweek *et al.*, 2018a; Brueton *et al.*, 2013). If the required levels of patient recruitment are not met, this has implications for the trial's statistical power, likelihood of publication and internal and external validity (Glasgow *et al.*, 1996). Recruiting inadequate numbers of patients can place a financial strain on the research funder and the study might overrun, potentially influencing investments from research councils and governments for future research (Bower *et al.*, 2014). Most importantly however, it ultimately affects patients as important information directly surrounding their healthcare is left unanswered. Therefore, achieving appropriate numbers of participants is crucial. Recently the SWAT (Study Within A Trial) concept has been used to try and increase the evidence base on trial recruitment (Treweek *et al.*, 2018b). This chapter explores the concept of clinical trial recruitment, with a SWAT implemented within the CLEAR trial aimed at increasing participant recruitment.

4.1.1 Problem of clinical trial recruitment

Recruitment is frequently reported as a problem in trials. The same is true of retention, which is discussed in Chapter 5. A recent survey of clinical trial units showed that recruitment and retention are amongst the top three priorities for methodology research (Healy *et al.*, 2018). As a result, these have been prioritised for research funding under various national programmes (further outlined in section 4.1.3). The issue of poor recruitment to trials is not new and was mentioned, for example, as a problem within a key clinical trials text in 1986 (Meinert, 1986). Meinert stated that the likelihood of achieving the recruitment target is small, takes a major effort and is likely to take longer than planned. These issues have remained pertinent into the 21st century. More recently, empirical data from a review of large phase 3 randomised trials, funded in the UK by the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme from 2004 to 2016, found that the final recruitment target was met in only 56% (85 of 151) of trials (Walters *et al.*, 2017).

4.1.2 Previous research on trial recruitment

Currently, there are few evidence-based solutions to improving recruitment to trials. The bulk of research into recruitment was summarised in a 2018 Cochrane review (Treweek *et al.*, 2018a). It found 68 studies involving interventions or strategies aimed at increasing participant recruitment and was only able to draw three high certainty implications from this research. These were; the benefits of conducting open label trials as opposed to blinding participants, using telephone reminders for potential participants and using bespoke participant information leaflets. Although the absolute improvements in recruitment arising from these three methods were low, any increase to recruitment would positively impact other aspects of the trial. As the number of new trials registered is increasing year on year, with approximately 37,000 new registrations in 2020 in one register alone (ClinicalTrials.gov), having such scarce knowledge of effective ways to enrol participants is concerning and it is of no surprise that the Cochrane review concluded that future high-quality research is needed.

Since the increased awareness that poor recruitment of participants can negatively affect other trial aspects, several initiatives to encourage use of evidence-based methods and further explore recruitment research in large clinical trials have been started. Trial Forge is an online evidence base that aims to provide resources on how to make trials more efficient and includes information on recruitment (Trial Forge, 2020). In addition to providing information on SWAT, the platform has a section that summarises interventions for recruitment to trials based on low, moderate or high certainty evidence. More specific to recruitment is the Online Resource for Recruitment research in Clinical triAls (ORRCA) project that provides a searchable database for recruitment research, derived from systematic searches of general bibliographic databases (Kearney *et al.*, 2018).

4.1.3 The concept of SWAT

The SWAT approach for testing the effectiveness of trial methods, such as different recruitment interventions, is to ‘nest’ a methodology study within an ongoing trial. Recent guidance defines a SWAT as a “self-contained 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.*, 2018b). The SWAT concept aims to highlight and identify a variety of methodology strategies that would improve clinical research. Clinical trials evaluate the effectiveness of healthcare interventions whereas a SWAT evaluates the effectiveness of the methods used to conduct the trial. In other words, a SWAT explores how good the research methodology is. As there is little evidence on how best to run a clinical trial, SWAT can be used to generate high quality information that ensures the optimum methods are used in future trials. A key feature of the SWAT is that it does not affect the integrity of the host trial in relation to rationale or outcomes and can be ideally implemented independently in a variety of trials with a view to having future meta-analyses of the results

of multiple SWAT of the same topic. Ideas for SWAT and protocols are available on the website of the Northern Ireland Methodology Hub that maintains a repository of SWAT (Queen's University Belfast, 2020).

Growing awareness of the challenges of recruitment and of the SWAT concept, along with increased information, organisation and coordination, has led national health research funders in the UK and Ireland to actively encourage and financially support SWAT within clinical trials. The UK Medical Research Council's PROMETHEUS (PROMoting THE USE of SWATs) programme, initiated in 2018, is currently providing funding to 33 host trials for various SWAT (PROMETHEUS, 2020). They rank research questions on recruitment according to high, medium and low priority, determined by ease of implementation, cost and existing trials that have embedded the SWAT. Also, the NIHR HTA programme allows applicants to propose a SWAT within their trial to be funded for up to £10,000 (NIHR, 2020). Similarly, in Ireland, the Health Research Board Trials Methodology Research Network (HRB-TMRN) offers awards of up to €25,000 and had funded eight SWAT as of August 2020 (HRB-TMRN, 2020).

4.1.4 Rationale for this SWAT in the CLEAR trial

In many clinical trials outside of primary care, it is standard practice for patients who are potentially eligible to be sent or given an invitation letter by their clinician or hospital clinic. This is usually one of the first stages in recruitment for patients with bronchiectasis.

It is plausible that the invitation letter, associated participant information sheet (PIS) and other recruitment materials can influence whether a patient joins a trial, but whether and how these materials do so is uncertain because of the lack of robust research. Being at an early stage in a potential participant's trial journey, it is important that these materials are engaging as well as informative. The person who signed the invitation letter may act as part of the persuasion strategy to encourage someone to volunteer for the trial and different methods of personalisation, such as hand-written signatures from the lead clinician or a member of the clinical research team might have different effects on patient recruitment. Even if these effects are moderate, any boost in recruitment might shorten the trial, save resources and lead to a faster answer to the clinical question posed by the trial.

Another aspect in the design of the invitation letter is the inclusion of a photograph. For instance, patients might be influenced if a welcoming, friendly photograph of a doctor-patient interaction is shown on the invitation letter or a photograph of their local clinical team. There is a tendency for people to develop a preference for things that they are familiar with and seeing such a photograph with a familiar signature may lead to a positive response. This

psychological phenomenon is known as the mere-exposure effect or familiarity principle (Zajonc, 2001).

However, despite the importance of achieving high levels of patient recruitment, to date no clinical trials in patients with bronchiectasis have investigated the impact of recruitment strategies, meaning that specific challenges for recruiting these patients are uncertain. This SWAT contributes to filling this gap. Furthermore, regardless of any effect on overall response rates, the impact of the individual signing the invitation letter or the inclusion of a photograph on a person's willingness to join a trial might have an impact on the length of time that they participate in the trial.

The value of this SWAT is also apparent from the work of PRioRiT_y I (Prioritising Recruitment in Randomised Trials study) (Healy *et al.*, 2018), which was a large initiative to identify problems and solutions regarding recruitment to trials. The process involved multiple stakeholders and produced a top 10 list of questions that, if answered, would be likely to influence recruitment strategies. Question 4 was "What are the best approaches for designing and delivering information to members of the public who are invited to take part in a randomised trial?" The SWAT within the CLEAR trial will contribute to the answer for this question.

4.1.5 Previous research into the design of the invitation letter

Other studies have explored various aspects in the design of the invitation letter and PIS. A large ongoing SWAT is exploring whether a male, female or trial team signature on the invitation letter affects recruitment to a prospective cohort study (Maguire *et al.*, 2015). An interim analysis in 2015 of 8500 invitation letters revealed no significant differences between groups. Another study explored the use of bespoke invitation letters that had professional graphic design input (but no photographs) versus an original A4 letter (Cockayne *et al.*, 2017). After randomisation of 6900 invitations, there were no significant differences in recruitment. Two similar prospective studies found no significant differences with professionally developed invitation letters (Parker *et al.*, 2018; Man *et al.*, 2015). However, although these materials had various aspects of professional development and graphic design input, no photographs were included.

Another study explored if handwriting the patient's name on the invitation letter, rather than printing it, had an effect on recruitment. Despite 317 potential participants being given letters, only 12 were recruited into the host trial and the study found that handwriting patient's names decreased recruitment (McCaffery *et al.*, 2019). The authors noted this could be due to handwriting being perceived as less professional.

One study that investigated the impact on recruitment outside the setting of a clinical trial investigated the use of a personalised invitation letter compared to a generic letter for a NHS stop smoking service and found that the use of a personal letter significantly increased the proportion of those attending at 1 month (17.4% vs. 9.0%) and 6 months (9.0% vs. 5.6%). These results were obtained after randomisation of 4384 letters. The personalised letter detailed the patient's personal disease specific risks based on their age, gender and number of cigarettes smoked (Gilbert *et al.*, 2017).

4.1.6 Aim and objective

The aim of the study reported in this chapter was to explore the effects of methods used to optimise recruitment with the specific objective being:

- To determine if the nature of the signature and inclusion of a photograph on the invitation letter given to potential participants impacts on their recruitment to the CLEAR trial.

4.2 Methods

Two SWAT aimed at increasing recruitment were embedded within the CLEAR trial. They have been registered and published on the SWAT Repository Store of the Northern Ireland Methodology Hub (Queen's University Belfast, 2020).

4.2.1 SWAT implemented

For simplicity, these two recruitment SWAT will be referred to in this chapter as A and B. SWAT A is a variation of SWAT 3 on the repository store (Maguire & Clarke, 2014) and SWAT B is SWAT 53 (Anand & Green, 2017). These SWAT are focused on exploring recruitment to the CLEAR trial and were tested in a 2x2 factorial design.

4.2.1.1 SWAT A

SWAT A relates to the nature of the signature on the invitation letter in the trial recruitment pack that is given to potential participants. The interventions compared in this SWAT are:

1. Invitation letter is personally signed, using wet ink, by the local principal investigator (PI).
2. Invitation letter is generically signed and printed electronically as "The CLEAR Trial Team".

4.2.1.2 SWAT B

SWAT B relates to the inclusion of a generic doctor-patient photograph on the invitation letter. The interventions compared in this SWAT are:

1. Invitation letter includes a generic doctor-patient photograph.
2. Invitation letter does not include a doctor-patient photograph.

4.2.2 Outcome Measures

- The primary outcome is the proportion of recipients of each invitation letter who join the CLEAR trial.
- The secondary outcome is the proportion of recruited participants who had received each invitation letter who remain enrolled in the CLEAR trial.

4.2.3 Approvals

Details of the SWAT were incorporated into the CLEAR trial protocol (Bradley *et al.*, 2019; Appendix). All materials were submitted for ethical and governance approvals (granted on

30th November 2017 and 6th February 2018, respectively). These approvals are within the Appendix. In addition to the regulatory approvals, the four invitation letters received good feedback from a Public and Patient Involvement representative, full details of which are included in the Appendix.

4.2.4 Period for data collection

The SWAT is planned to continue until the completion of the CLEAR trial. The interim analysis presented here is based on data obtained from the beginning of the trial in June 2018 through to May 2020, but it should be noted that recruitment to the CLEAR trial and therefore to this SWAT was paused due to the COVID-19 pandemic on 12th March 2020.

4.2.5 SWAT A and B Participating Sites

Sites participating in the CLEAR trial pilot phase and the main trial were opted into participating in SWAT A and B and were informed of the procedures and protocol for implementation. All sites could withdraw from the SWAT at any time if they wished, for example because of site-specific feasibility. The participating sites are listed in the Appendix.

4.2.6 Overall CLEAR Trial Recruitment Strategy

The participating sites used common methods for the recruitment of potential participants to a clinical trial. This primarily involved directly approaching potential participants who were regularly attending their respiratory clinic or had been referred. When a potential participant was identified and approached, they were told about the CLEAR trial and given a recruitment pack that contained an invitation letter, PIS and informed consent form. Potential participants were also screened from databases and people identified in this way were sent the recruitment pack by post to their home address. This was also done for patients who had previously indicated that they were interested in the trial. After receiving the recruitment pack, the patient was able to assimilate the information and ask the study team any initial questions. In addition to this direct approach, patient electronic databases were screened for potentially eligible participants and followed up by the study team. If a patient wished to enrol in the CLEAR trial, they arranged a visit to a recruiting site, clarified any further queries and completed the informed consent form in the presence of a study staff member.

4.2.7 Design and Implementation of SWAT A and B

The 2x2 factorial randomised approach was used for SWAT A and B to allow simultaneous comparison of the interventions. The four possible combinations of invitation letter are shown in Table 34. Examples of the four different invitation letters are in the Appendix.

Table 34: Factorial design of SWAT A and B as implemented in the CLEAR trial.

| 2x2 factorial design | | Photograph | |
|----------------------|----------|---------------------------------------|--|
| | | With Photograph | Without photograph |
| Nature of Signature | Personal | <i>Personal wet signature + photo</i> | <i>Personal wet signature + no photo</i> |
| | Generic | <i>generic signature + photo</i> | <i>generic signature + no photo</i> |

SWAT A and B were implemented for recruitment packs handed to potential participants at clinics and those posted to patients. Sites were asked to estimate their expected recruitment numbers and the local PI signed a number of invitation letters using wet ink. The recruitment packs were prepared per site based on recruitment estimates, with each pack having a unique Pack Identifying Number on the envelope. These Pack Identifying Numbers were randomly generated for each site using mixed block sizes, with an excessively large list created to accommodate over recruitment at all sites. Packs were then prepared into bundles, so that each bundle of eight contained two of each type of invitation letter. The bundles were then distributed to sites with instructions, along with other site initiation materials. Instructions were given to sites not to alter the sequence of the packs in the bundles or the order of the bundles. When giving recruitment packs to a potential participant in person, site staff took the topmost pack from the bundle so that they were handed out in the correct sequence. Before the recruitment pack was given to a patient, the Pack Identifying Number was recorded against the relevant Patient Identification Number on the CLEAR trial screening log. If a site used more than one member of staff to recruit at a time, the packs were split into two or more piles, with packs then being tracked for sequential use from the bundles in each of these piles. The unique Pack Identifying Numbers were used to link individuals on the screening log who

did or did not enrol into the CLEAR trial with the type of recruitment pack they had been given. When posting a recruitment pack to the patient, sites addressed the envelope containing the recruitment pack to the potential participant. If a site had limited numbers of recruitment packs left, they requested further packs and if they exhausted their supply, they would use the standard CLEAR trial invitation letters until they received further packs. Any such interim use of standard invitation letters was not logged and related data are not used in the SWAT analysis. If a site did not participate in the SWAT, they would have used the standard invitation letter throughout the duration of the CLEAR trial. The process is summarised schematically in Figure 35.

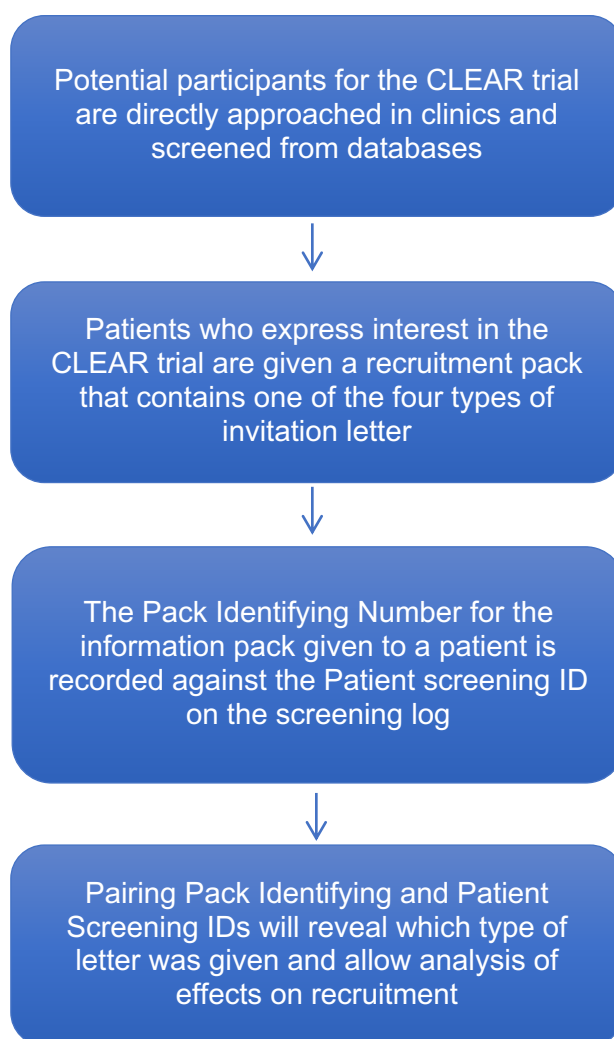


Figure 35: Schematic Diagram of the SWAT A and B process.

4.2.8 Analysis

The primary analysis compares the proportion of participants recruited to the CLEAR trial depending on the type of recruitment pack they received. Secondary analyses will examine retention in the CLEAR trial and the extent/duration of the recruited person's participation. Subgroup analyses would have been conducted according to age, gender, disease severity and ethnicity if sufficient data were available but these data were not recorded on the CLEAR screening log so these variables are only available for patients who enrolled in the CLEAR trial and not for those who were randomised into the SWAT but did not join the CLEAR trial. All analyses and data manipulation were done using the statistical software R (www.rstudio.com) with the exception of the comparative analysis which was done on www.medcalc.org using their odds ratio calculator to calculate the odds ratio, its 95% confidence interval (CI) and test for significance, where the threshold for statistical significance was set to $p=0.05$. The full R script of the analysis is shown in the Appendix. The datasets imported for the analysis were the CLEAR trial screening log and SWAT randomisation list that contained the Pack Identifying Numbers. Both datasets contained data collected from June 2018 to May 2020. Various manipulations and transformations were performed but the key steps for the primary analysis were matching the Pack Identifying Numbers between the two datasets in order to establish the total numbers and types of letters that were distributed and the subsequent number of patients who enrolled into the trial, and what type of letter they received. This created a new dataset. For the secondary outcome, an additional dataset, the CLEAR trial patient visit tracker was matched, by the CLEAR trial Subject ID, to the new dataset that had been created for the primary outcome. The number of patients who had withdrawn from the CLEAR trial at any point in each of the letter groups was determined.

4.3 Results

All CLEAR trial sites participated in this SWAT. These results contain data from 14 sites including the 10 sites that participated in the 8-month pilot phase of the CLEAR trial.

4.3.1 Pilot feasibility assessment

After the pilot phase, each site was contacted on 18 February 2019 and asked if they had encountered any difficulties when implementing SWAT A and B. Each site commented on the how successful the SWAT were and that they could implement the protocol fully. All sites implemented SWAT A and B as per protocol. Communications from each site are summarised in Table 35.

Table 35: Feedback on SWAT invitation letters from pilot sites.

| Site | SWAT invitation letters | | |
|---------------------------|-------------------------|--|---|
| | Using SWAT? | How is it being implemented? | Any issues/comments from site |
| Ninewells Dundee | Yes | Generally, staff speak to patients first at clinic, then give them the SWAT packs. They did send out 29 and have had a few declines from this. | None. Site wondered if this defeated the purpose of SWAT packs as they are speaking to the patient first rather than sending out. |
| Belfast | Yes | As per protocol | None. Staff can't leave any packs at chest clinic as then they wouldn't know who got what, however they get around this. If a medic refers a patient, they will post out a pack. One patient didn't receive pack, so gave new pack number. |
| Craigavon | Yes | As per protocol | None. The PI will also give out packs at clinic and he writes down the pack number for the study coordinator. |
| Altnagelvin | Yes | As per protocol | None. Only thing is if posting the pack, I have to use specific Trust envelopes or else it won't be posted, therefore I have to open the pack and insert in Trust envelope. However, I don't look at the contents before putting in envelope, and also the SWAT pack number has already been allocated to the patient and the address put on the envelope before the pack has been opened. |
| Edinburgh | Yes | As per protocol. | None |
| Princess Alexandra | Yes | As per protocol. | None |
| Freeman | Yes | As per protocol | No issues and happy with process. Staff put address on envelope and post. |
| Royal Free | Yes | As per protocol | No issues. Staff state easy to use |
| Brompton | Yes | As per protocol | No issues currently/keeping track. |
| Southampton | Yes | As per protocol | None |

Following the site feedback on the SWAT, any issues that had been identified were resolved on a site-by-site basis and it was decided to continue the SWAT at the pilot sites and to implement them in all additional sites for the main phase of the CLEAR trial.

4.3.2 Primary Outcome (Recruitment)

In total, the screening logs contained data for 1253 individuals and when matched with the SWAT randomisation list, a total of 368 packs were handed out across all sites. The types of invitation letter distributed are summarised in Table 36.

Table 36: The types of invitation letters handed out (n=368) with the number and proportion of participants that enrolled.

| Type of Letter | Number Distributed | Number Declined | Number Enrolled | Proportion Enrolled |
|--------------------------------|--------------------|-----------------|-----------------|---------------------|
| Generic Signature and No Photo | 88 | 55 | 33 | 37.5% |
| Generic Signature and Photo | 88 | 60 | 28 | 31.8% |
| Wet-ink Signature and No Photo | 91 | 65 | 26 | 28.6% |
| Wet-ink Signature and Photo | 101 | 67 | 34 | 33.7% |
| Overall Total | 368 | 247 | 121 | 32.9% |
| | | | | |
| Photo | 189 | 127 | 62 | 32.8% |
| No photo | 179 | 120 | 59 | 32.0% |
| Wet signature | 192 | 132 | 60 | 31.2% |
| Generic signature | 176 | 115 | 61 | 34.7% |

Of the 368 potential participants given an invitation pack, 121 individuals enrolled onto the CLEAR trial. The types of invitation letters that they received are summarised in Figure 36, alongside the numbers of letters distributed. Figure 37 shows enrolment according to photo and type of signature.

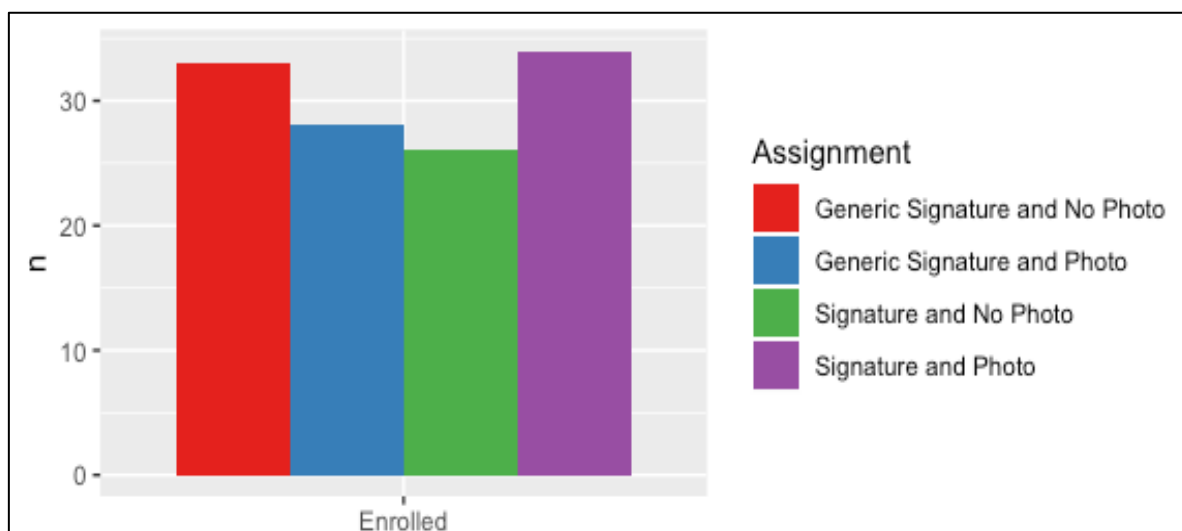


Figure 36: The number of invitation letters that resulted in enrolment for the four randomisation groups (n=121).

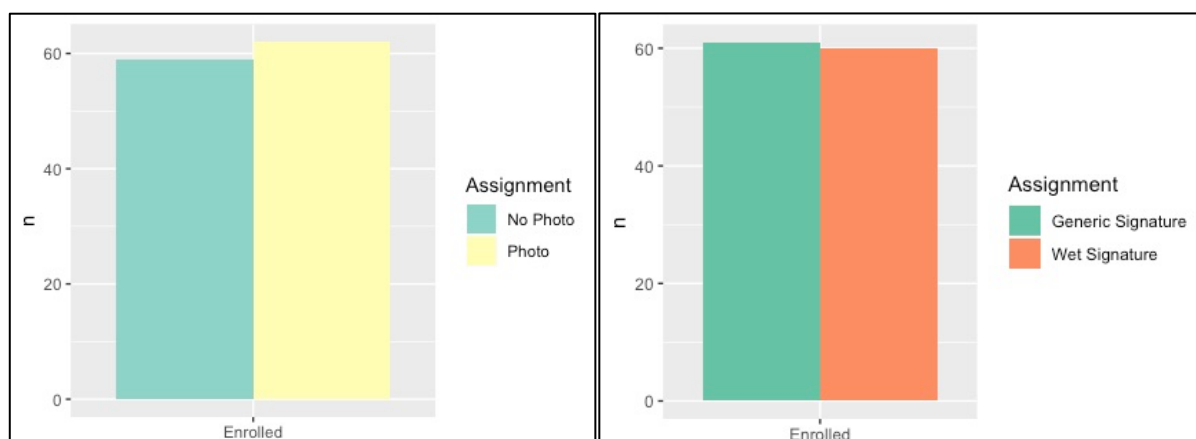


Figure 37: The number of invitation letters that resulted in enrolment for Photo vs No photo and Wet signature vs Generic signature.

4.3.2.1 Recruitment comparative analysis

The separate pairings of SWAT A and B in relation to recruitment were compared using odds ratios. Overall, no significant differences were found across the comparisons as shown in Table 37 and Table 38.

Table 37: Comparative analysis between Photo vs No photo and Wet signature vs Generic signature, and the overall effect on recruitment. An odds ratio greater than 1 indicates that recruitment is more likely to occur in the first group listed in the comparison.

| Comparison | Odds ratio | 95% CI interval | Z statistic | P value |
|--|------------|-----------------|-------------|---------|
| 1. Photo versus No Photo | 0.99 | 0.64 to 1.53 | 0.032 | 0.9745 |
| 2. Wet Signature versus Generic Signature | 0.86 | 0.55 to 1.32 | 0.695 | 0.4870 |

Table 38: Comparative analysis between the different types of letter and the overall effect on recruitment. An odds ratio greater than 1 indicates that recruitment is more likely to occur in the first group listed in the comparison.

| Comparison | Odds ratio | 95% CI interval | Z statistic | P value |
|--|------------|-----------------|-------------|---------|
| 3. Generic Signature and No Photo versus Generic Signature and Photo | 1.29 | 0.69 to 2.49 | 0.791 | 0.4288 |
| 4. Generic Signature and No Photo versus Wet-ink Signature and No Photo | 1.50 | 0.80 to 2.81 | 1.268 | 0.2050 |
| 5. Generic Signature and No Photo versus Wet-ink Signature and Photo | 1.18 | 0.65 to 2.15 | 0.550 | 0.5825 |
| 6. Generic Signature and Photo versus Wet-ink Signature and No Photo | 1.17 | 0.62 to 2.21 | 0.473 | 0.6362 |
| 7. Generic Signature and Photo versus Wet-ink Signature and Photo | 0.92 | 0.50 to 1.69 | 0.269 | 0.7876 |
| 8. Wet-ink Signature and No Photo versus Wet-ink Signature and Photo | 0.79 | 0.43 to 1.46 | 0.759 | 0.4476 |

4.3.3 Secondary outcome (retention)

16 patients who joined the CLEAR trial and whose invitation letter had been randomised in SWAT A and B, subsequently withdrew from the trial. Eleven patients withdrew their consent under their own decision. This analysis only used data for these 11 patients and not those who were withdrawn for reasons outside the patient's control such as adverse events or decisions by their responsible clinician. The distribution of these 11 patients by type of invitation letter is shown in Table 39 and Figure 38. Figure 39 shows enrolment according to photo and type of signature.

Table 39: The types of invitation letters handed out (n=121) with the number and proportion of participants that withdrew n=11).

| Type of Letter | Number enrolled | Number remained | Number withdrew | Proportion withdrew |
|--------------------------------|-----------------|-----------------|-----------------|---------------------|
| Generic Signature and No Photo | 33 | 28 | 5 | 15.1% |
| Generic Signature and Photo | 28 | 27 | 1 | 3.6% |
| Wet-ink Signature and No Photo | 26 | 22 | 4 | 15.4% |
| Wet-ink Signature and Photo | 34 | 33 | 1 | 2.9% |
| Total | 121 | 110 | 11 | 9.1% |
| | | | | |
| Photo | 62 | 60 | 2 | 3.2% |
| No photo | 59 | 50 | 9 | 15.3% |
| | | | | |
| Wet signature | 60 | 55 | 5 | 8.3% |
| Generic signature | 61 | 55 | 6 | 9.8% |

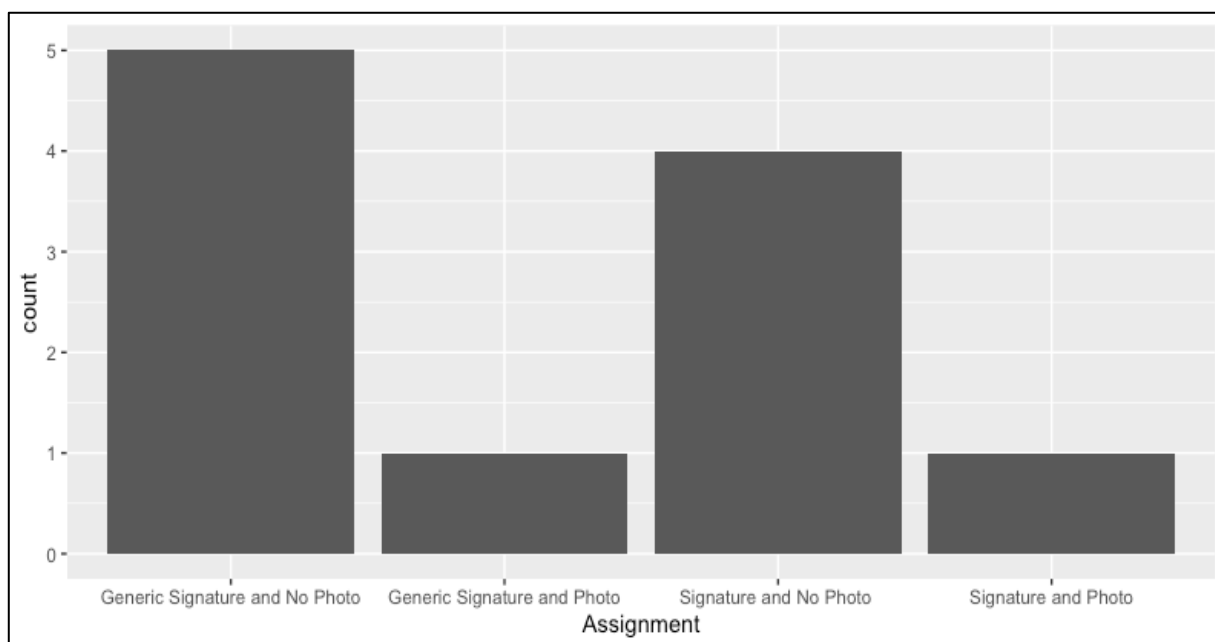


Figure 38: The numbers of patients that withdrew from the trial and their assigned letter at enrolment (n= 11).

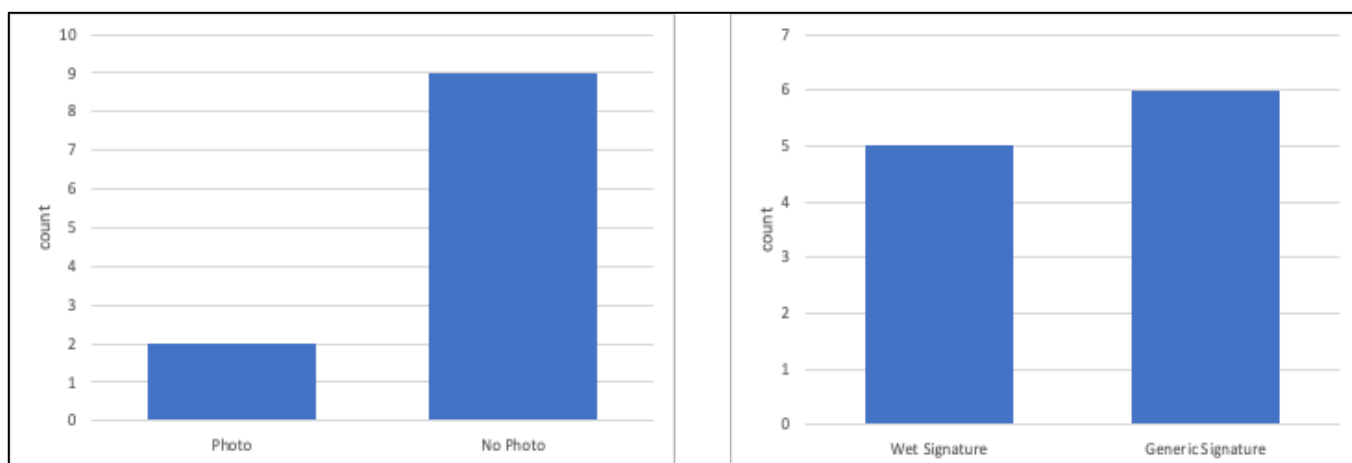


Figure 39: The number of patients that withdrew from the trial for Photo vs No photo and Wet signature vs Generic signature.

4.3.3.1 Retention comparative analysis

Patient withdrawals in the different invitation letter groups were compared using odds ratios and a test for significance. Overall, the one statistically significant difference was for using an invitation letter with a photo versus a letter with no photo, with significantly lower loss if a photo had been used (with photo: 2 withdrawals; without photo: 9 withdrawals), with the odds of a patient leaving the trial being 5.4 times greater (95% CI 1.12 to 26.15, $p=0.04$) if a photo was not used (Table 40 and Table 41). However, this finding is of borderline statistical significance, based on small numbers and does not take account of the possibility of multiplicity affecting the likelihood of statistically significant results.

Table 40: Comparative analysis between Photo vs No photo and Wet signature vs Generic signature and the overall effect on retention. An odds ratio greater than 1 indicates that withdrawal is more likely to occur in the first group listed in the comparison.

| Comparison | Odds ratio | 95% CI interval | Z statistic | P value |
|--|------------|-----------------|-------------|---------|
| 1. Photo versus No Photo | 0.19 | 0.04 to 0.90 | 2.095 | 0.036 |
| 2. Wet Signature versus Generic Signature | 0.83 | 0.24 to 2.89 | 0.287 | 0.774 |

Table 41: Comparative analysis between the different types of letter and the overall effect on retention. An odds ratio greater than 1 indicates that withdrawal is more likely to occur in the first group listed in the comparison.

| Comparison | Odds ratio | 95% CI interval | Z statistic | P value |
|--|------------|-----------------|-------------|---------|
| 3. Generic Signature and No Photo versus Generic Signature and Photo | 4.82 | 0.53 to 44.00 | 1.394 | 0.163 |
| 4. Generic Signature and No Photo versus Wet-ink Signature and No Photo | 0.98 | 0.24 to 4.10 | 0.025 | 0.980 |
| 5. Generic Signature and No Photo versus Wet-ink Signature and Photo | 5.89 | 0.65 to 53.47 | 1.576 | 0.115 |
| 6. Generic Signature and Photo versus Wet-ink Signature and No Photo | 0.20 | 0.02 to 1.96 | 1.378 | 0.168 |
| 7. Generic Signature and Photo versus Wet-ink Signature and Photo | 1.22 | 0.07 to 20.47 | 0.140 | 0.889 |
| 8. Wet-ink Signature and No Photo versus Wet-ink Signature and Photo | 6.00 | 0.63 to 57.31 | 1.556 | 0.120 |

4.4 Discussion

This is the first implementation of SWAT 53 and of this variation of SWAT 3. The analysis did not reveal a significant difference in recruitment when using wet signatures compared to generic signatures or when using or not using a photograph on the invitation letter. Based on the primary outcome, with an anticipated enrolment of 32.9% of patients joining when given any invitation letter, a sample size of 3840 letters would need to be distributed to detect meaningful differences. This larger sample would be able to detect a difference of 5%, with 90% power at the 5% significance level. For the secondary outcome, assuming a withdrawal percentage of 9.1%, a sample size of 1470 would detect a difference of 5% at the same power and significance. This interim analysis explored a cohort of 368 patients who were randomised to one of four recruitment packs and amongst whom, 121 joined the CLEAR trial. On this basis, if the CLEAR trial achieves its sample size of 380 patients, more than 1200 recruitment packs will be distributed, which will provide more data towards the required sample size that can be pooled with future research to provide a definitive answer. For the secondary outcome exploring retention, one significant association was found. If patients got a letter that contained a photo, as opposed to no photo, they were more likely to remain within the trial. However, as noted above this result is unstable and more definitive answers for all the comparisons need to await further recruitment and follow-up in the CLEAR trial.

There are several factors to consider in relation to these interim findings from these two SWAT. Firstly, in the broad view, each SWAT tested minor changes to a small part of the overall recruitment pack. The CLEAR trial recruitment packs contained the 1-page invitation letter, an 11-page PIS and a 2-page Informed Consent Form. The signature and photograph may not have had any conscious influence whilst potential participants focused on all the information and deliberated whether to join the trial. Other factors, such as the actual trial medication interventions (HTS and carbocisteine), trial specific risks, the number of study visits and time required within the trial are likely to have had much greater influence on the decision made. The changes on the invitation letter may have more influence in less complex trials or non-interventional studies with shorter documentation, or any influence may be too small to detect in these SWAT. For instance, an earlier study found that including an invitation letter, addressed directly to the patient by using their name, did not affect recruitment compared to sending no invitation letter at all (Tworoger *et al.*, 2002). This suggests invitation letters are not as important as commonly thought. Secondly, the nature of this SWAT intervention is non-verbal, while a large part of recruitment to trials is verbal, with face-to-face communication between trial staff and potential participants. It is possible that verbal discussions about the trial carry more influence than the documentation given to the patient, especially since many people with bronchiectasis are long-term patients at recruiting sites and

already had relations with trial staff. This was the case, in particular, with one site that largely spoke with their patients before giving them a pack. Related to this, an earlier study found that direct contact with potential participants to join a breast cancer screening program was more successful than just posting out invitation letters (Segura *et al.*, 2001). Thirdly, the social psychological aspects of the mere-exposure effect described previously (section 4.1.4) can also work in a negative way. For instance, rather than a patient having a positive preference for the familiarity of the personal signature and doctor photograph, they may not be happy with past experience of their clinical environment or care. Lastly, it is important to note the clinical characteristics of this population, a primarily older population with a chronic disease within the UK which might influence the potential impact of the SWAT interventions. For instance, an early review by Linsky (1975) highlighted this complexity of recruitment methods used and their context.

The findings presented in this chapter are consistent with the limited previous research into invitation material design. For instance, SWAT 3, 4 and 5 are currently embedded using a 3x2x2 factorial design in the recruitment phase for a large longitudinal study (Maguire *et al.*, 2015). An interim analysis found that the gender of the person's signature on the invitation letter did not affect recruitment. Similarly, SWAT 23 tested the design of an optimised recruitment pack versus a generic pack for recruitment to a lung cancer trial and an analysis of 2262 letters found minimal differences in recruitment (Parker *et al.*, 2018). That study had made widespread changes across the invitation materials including photographs and shortening the overall content. Earlier studies exploring optimisation of patient recruitment materials also found limited differences in recruitment when compared to original controls (Cockayne *et al.*, 2017; Man *et al.*, 2015). While another study, involving 1050 participants, found that the addition of an audio-visual DVD to the paper invitation material had no impact on patient recruitment (Rogers *et al.*, 2019). The 2018 Cochrane analysis found that using bespoke recruitment materials had little or no effect, based on three studies available up to 2017 (Treweek *et al.*, 2018a), but identified an ongoing study exploring invitation letter design on recruitment for people with schizophrenia (Grønbech, 2018).

On the other hand, the aforementioned study by Gilbert (2017) which did not recruit to a trial but aimed to enrol patients in NHS Stop Smoking Services, did find that letters personalised to include an individual's numerous risk factors significantly increased participation. This suggests that it would be worth evaluating a more personalised approach for recruiting patients to clinical trials and that this may have more impact than generic changes. This line of research may need to be extended, especially into different disease areas, as the emerging evidence shows that impersonalised modifications to the invitation letters make little or no difference to recruitment and that evaluations of such changes may no longer be worthwhile

(Treweek *et al.*, 2018b). Again, this is further evidenced by the aforementioned study by McCaffery (2019) where handwriting the patient's names decreased recruitment in a falls' prevention trial for people over 65 years of age. However, using a heavily personalised approach as by Gilbert (2017) in a clinical trial is likely to require careful regulatory and ethical considerations.

Separate to the design of the recruitment materials, behavioural change techniques may have an important role in trial recruitment. A study exploring the reasons why patients decline to join a trial found that most are due to self-judged ineligibility or not needing the intervention (Hughes-Morley *et al.*, 2016). Therefore, it may be best to highlight to patients the community benefit of their participation and for trialists to design trials with greater therapeutic intent (Miller and Brody 2003).

Important strengths of this study are that it is the first to implement SWAT 3 and 53 in a large clinical trial and its use of allocation concealment and randomisation of the recruitment packs. Another strength is that this analysis adopted a 2x2 factorial design and so allowed for simultaneous investigation of two separate modifications to the design of the letter. Overall, there were no major issues in implementing this SWAT. All sites that participated in the initial pilot for the host CLEAR trial were happy to continue with the SWAT for the duration of the whole trial. A general advantage to sites was that they received pre-prepared packs from the Northern Ireland Clinical Trials Unit so did not need to prepare packs at site, the only caveat being that sites needed to store their packs appropriately in order to maintain the randomisation. This SWAT did not encounter any of the issues regarding approvals, costs and site uptake, that have been experienced in some other SWAT (Martin-Kerry *et al.*, 2019). The key limitation for this study is that it is an interim analysis of around one third of the total anticipated data that will be included in the final analysis and, as such, is substantially under-powered compared to that main analysis.

4.4.1 Conclusion

This study did not detect any significant effect on recruitment based on the type of signature used or the inclusion of a photograph in an invitation letter for a randomised, clinical trial in bronchiectasis. Given that other studies that tested various adjustments to recruitment materials have found similar results, such simple changes to the recruitment materials are unlikely on their own to have a major impact on increasing clinical trial enrolment. Other methods to increase recruitment should be explored, such as the use of pragmatic designs (e.g. open label trials) and the use of different methods for the verbal interaction with potential participants, as are investigated in several SWAT (e.g. SWAT 6, 17, 43, 106 and 120). For the trial proposed in Chapter 7 (section 7.2), a recruitment intervention directed towards patients

would not be feasible due to the nature of critically ill patients. Therefore, a SWAT intervention aimed at site investigators would be more feasible. These might include SWAT 66, which explores site visits to initiate recruitment in sites that fail to recruit, or SWAT 99 that explores site initiations conducted with a comprehensive recruitment action plan.

4.5 References

- Anand R, & Green N. SWAT 53: Including a photograph on the invitation letter for a prospective study. *The Northern Ireland Network for Trials Methodology Research*. Apr 15, 2017. Available at: <https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/FileStore/Fileupload,758669,en.pdf>
- Bower P, Brueton V, Gamble C, Treweek S, Smith CT, Young B, Williamson P. Interventions to improve recruitment and retention in clinical trials: a survey and workshop to assess current practice and future priorities. *Trials*. 2014 Dec;15(1):1-9.
- Bradley JM, Anand R, O'Neill B, Ferguson K, Clarke M, Carroll M, Chalmers J, De Soyza A, Duckers J, Hill AT, Loebinger MR. A 2×2 factorial, randomised, open-label trial to determine the clinical and cost-effectiveness of hypertonic saline (HTS 6%) and carbocisteine for airway clearance versus usual care over 52 weeks in adults with bronchiectasis: a protocol for the CLEAR clinical trial. *Trials*. 2019 Dec;20(1):1-0.
- Brueton VC, Tierney J, Stenning S, Harding S, Meredith S, Nazareth I, Rait G. Strategies to improve retention in randomised trials. *Cochrane Database of Systematic Reviews*. 2013;(12):MR000032.
- ClinicalTrials.gov. 2020. Trends, charts, and maps. Available from: <https://clinicaltrials.gov/ct2/resources/trends#RegisteredStudiesOverTime>
- Cockayne S, Fairhurst C, Adamson J, Hewitt C, Hull R, Hicks K, Keenan AM, Lamb SE, Green L, McIntosh C, Menz HB. An optimised patient information sheet did not significantly increase recruitment or retention in a falls prevention study: an embedded randomised recruitment trial. *Trials*. 2017 Dec;18(1):1-0.
- Fisher L, Hessler D, Naranjo D, Polonsky W. AASAP: a program to increase recruitment and retention in clinical trials. *Patient Education and Counseling*. 2012 Mar 1;86(3):372-7.
- Gilbert H, Sutton S, Morris R, Petersen I, Wu Q, Parrott S, Galton S, Kale D, Magee MS, Gardner L, Nazareth I. Start2quit: a randomised clinical controlled trial to evaluate the effectiveness and cost-effectiveness of using personal tailored risk information and taster sessions to increase the uptake of the NHS Stop Smoking Services. *Health Technology Assessment (Winchester, England)*. 2017 Jan;21(3):1.
- Glasgow RE, Eakin EG, Toobert DJ. How generalizable are the results of diabetes self-management research? The impact of participation and attrition. *The Diabetes Educator*. 1996 Dec;22(6):573-85.
- Grønbech, B. E., Recruitment of Patients Through Invitation Letters. [Internet]. 2018 [cited 10 Aug 2020]. Available from: <https://clinicaltrials.gov/ct2/show/NCT03590015>
- Healy P, Galvin S, Williamson PR, Treweek S, Whiting C, Maeso B, Bray C, Brocklehurst P, Moloney MC, Douiri A, Gamble C. Identifying trial recruitment uncertainties using a James Lind Alliance priority setting partnership—the PRioRiTy (Prioritising recruitment in randomised trials) study. *Trials*. 2018 Dec;19(1):1-2.
- HRB-TMRN: Study Within A Trial (SWAT). [Internet]. 2020 [cited 5 Aug 2020]. Available from: <https://www.hrb-tmrn.ie/research-and-innovation/funding-opportunities/studies-within-a-trial-swats/>

Hughes-Morley A, Young B, Hempel RJ, Russell IT, Waheed W, Bower P. What can we learn from trial decliners about improving recruitment? Qualitative study. *Trials*. 2016 Dec;17(1):1-3.

Kearney A, Harman NL, Rosala-Hallas A, Beecher C, Blazeby JM, Bower P, Clarke M, Cragg W, Duane S, Gardner H, Healy P. Development of an online resource for recruitment research in clinical trials to organise and map current literature. *Clinical Trials*. 2018 Dec;15(6):533-42.

Linsky AS. Stimulating responses to mailed questionnaires: A review. *Public Opinion Quarterly*. 1975 Jan 1;39(1):82-101.

Maguire L & Clarke M. SWAT 3: Gender of the person signing an invitation letter for a prospective study. *The Northern Ireland Network for Trials Methodology Research*. Jan 21, 2014.

Maguire L, Burns F, Clarke M. The NICOLA recruitment trial (NICOLA-RT): can you improve recruitment by making zero cost amendments to the invitation letter?. *Trials*. 2015 Dec;16(2):1-.

Man MS, Rick J, Bower P. Improving recruitment to a study of telehealth management for long-term conditions in primary care: two embedded, randomised controlled trials of optimised patient information materials. *Trials*. 2015 Dec;16(1):1-1.

Martin-Kerry J, Parker A, Bower P, Watt I, Treweek S, Torgerson D, Arundel C, Knapp P. SWATted away: the challenging experience of setting up a programme of SWATs in paediatric trials. *Trials*. 2019 Dec;20(1):1-6.

McCaffery J, Mitchell A, Fairhurst C, Cockayne S, Rodgers S, Relton C, Torgerson DJ, OTIS Study Team. Does handwriting the name of a potential trial participant on an invitation letter improve recruitment rates? A randomised controlled study within a trial. *F1000Research*. 2019;8.

Meinert CL. Clinical Trials: design, conduct and analysis (Vol. 39). 1986. OUP USA.

Miller FG, Brody H. A critique of clinical equipoise: therapeutic misconception in the ethics of clinical trials. *Hastings Center Report*. 2003 May 6;33(3):19-28.

NIHR: National Institute for Health Research HTA Stage 1 guidance notes . [Internet]. 2020 [cited 5 Aug 2020]. Available from: <https://www.nihr.ac.uk/documents/hta-stage-1-guidance-notes/11743>

Parker A, Knapp P, Treweek S, Madhurasinghe V, Littleford R, Gallant S, Sullivan F, Schembri S, Rick J, Graffy J, Collier DJ. The effect of optimised patient information materials on recruitment in a lung cancer screening trial: an embedded randomised recruitment trial. *Trials*. 2018 Dec;19(1):1-8.

PROMETHEUS: PROMoting THE USE of SWATs. [Internet]. 2020 [cited 4 Aug 2020]. Available from: <https://www.york.ac.uk/healthsciences/research/trials/research/swats/prometheus/#tab-2>

Rogers A, Flynn RW, Mackenzie IS, MacDonald TM. Does the provision of a DVD-based audio-visual presentation improve recruitment in a clinical trial? A randomised trial of DVD trial invitations. *BMC Medical Research Methodology*. 2019 Dec;19(1):1-6.

Queen's University Belfast: Studies Within A Trial (SWAT) [Internet]. 2017 [cited 10 May 2018].

Available from:

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

Segura JM, Castells X, Casamitjana M, Macià F, Porta M, Katz SJ. A randomized controlled trial comparing three invitation strategies in a breast cancer screening program. *Preventive Medicine*. 2001 Oct 1;33(4):325-32.

Treweek S, Altman DG, Bower P, Campbell M, Chalmers I, Cotton S, Craig P, Crosby D, Davidson P, Devane D, Duley L. Making randomised trials more efficient: report of the first meeting to discuss the Trial Forge platform. *Trials*. 2015 Dec;16(1):1-0.

Treweek S (a), Bevan S, Bower P, Campbell M, Christie J, Clarke M, Collett C, Cotton S, Devane D, El Feky A, Flemyng E. Trial forge guidance 1: what is a study within a trial (SWAT)? *Trials*. 2018 Dec;19(1):1-5.

Treweek S (b), Pitkethly M, Cook J, Fraser C, Mitchell E, Sullivan F, Jackson C, Taskila TK, Gardner H. Strategies to improve recruitment to randomised trials. *Cochrane Database of Systematic Reviews*. 2018(2); MR000013.

Trial Forge. [Internet]. 2020 [cited 6 Aug 2020]. Available from: <https://www.trialforge.org/>

TwoRoger SS, Yasui Y, Ulrich CM, Nakamura H, LaCroix K, Johnston R, McTiernan A. Mailing strategies and recruitment into an intervention trial of the exercise effect on breast cancer biomarkers. *Cancer Epidemiology and Prevention Biomarkers*. 2002 Jan 1;11(1):73-7.

Walters SJ, dos Anjos Henriques-Cadby IB, Bortolami O, Flight L, Hind D, Jacques RM, Knox C, Nadin B, Rothwell J, Surtees M, Julious SA. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. *BMJ Open*. 2017 Mar 1;7(3):e015276.

Zajonc RB. Mere exposure: A gateway to the subliminal. *Current Directions in Psychological Science*. 2001 Dec;10(6):224-8.