Project Identification: 2021-1-CZ01-KA220-HED-000023177

Investor/Program/Project type: European Union - Erasmus+ Key Action 2: Cooperation for innovation and the exchange of good practices; Strategic Partnerships in the field of education, training and youth

Curriculum Development of Human Clinical Trials for the Next Generation of PhD Students and Early Career Researchers in the Medical, Science, Pharmacy and Health Professions

CHAPTER 2

TRIALS METHODOLOGY RESEARCH

Authors: Frances Shiely
University College Cork, Cork, Ireland

Reviewers: Marta del Alamo, Christine Kubiak
European Clinical Research Infrastructure Network (ECRIN)

Date first created: 01/10/2022

Last revision: 07/05/2024

Content

Time required to complete this chapter

Core content:	35m
Additional/advanced content (yellow boxes):	1h 30m
Activities/practical exercises (blue framed boxes):	2h 45m
Total time:	**4h 50m**

Co-funded by the Erasmus+ Programme of the European Union

1 Introduction to the chapter

This chapter addresses trials methodology research (TMR) as an embedded feature of clinical trials training. Trials Methodology Research is about looking at the way trials are conducted, i.e., improving the tools and trade of clinical trial practice. Its purpose is to strengthen the methodology and reporting of clinical trials. There are specific challenges in clinical trials which affect the efficiency and internal and external validity of trials: recruitment, retention, patient and public involvement throughout the lifecycle of the trial, outcome selection, reporting and dissemination of trial results, to name but a few. This chapter will address these issues, and train the student on methods of addressing these challenges through evidence based research alongside, or within (SWATs - Studies Within A Trial) clinical trials. The students will learn about existing priorities in recruitment and retention, developed via a priority setting partnership, and how best to address incorporating these challenges in the design of their trial.

2 Introduction to Trials Methodology Research

What is Trials Methodology Research? This can be quite difficult to get your head around initially, but by the end of this chapter, it will all make sense. Trials Methodology Research is about looking at the way health research is conducted i.e., improving the tools and trade of research practice. It is conducted by researchers often referred to as Methodologists. These types of studies differ from doing things to/on patients – testing new drugs and treatments which can be described as Interventional Research. Yet, it is still research and needs to have a relevant question, an understandable proposal and lay summary along with all the other aspects of a study that can benefit from the patients' viewpoint, an external perspective and a grounding in reality.

Listening
In 2021, a team of researchers from the HRB TMRN (Trials Methodology Research Network, Ireland) and the MRC-NIHR-TMRP (Trials Methodology Research Partnership, UK) came together to produce a short animation to explain what trials methodology research is. Here is the product of the work, a short freely available video explaining it ("What is Trials Methodology?").[1]

2.1 Trials Methodology Research Definition

Research into the methods used in the design, conduct, analysis and reporting of clinical trials is essential to ensure that effective methods are available and that clinical decisions made using results from trials are based on the best available evidence, which is reliable and robust.[2]

In 2019, the HRB TMRN annual symposium was held in Dublin, Prof. Matthias Briel gave a really inspiring talk on "Increasing the Value of Clinical Trials", which sets the scene for trials methodology research. As you see from the definition, and as Matthias says, it is about research on research.

[1] https://www.youtube.com/watch?v=6sd7pV8XTRY
[2] Tudur Smith, C., Hickey, H., Clarke, M. et al. The trials methodological research agenda: results from a priority setting exercise. Trials 15, 32 (2014). https://doi.org/10.1186/1745-6215-15-32

Watch Professor Briel's inspiring presentation in a video ("Prof Matthias Briel - Increasing the value of clinical trials - evidence for progress?").[3]

3 The Trials Methodology Research Agenda

Reading
To begin this lesson, read the article mentioned above by Tudur Smith et al. for a good grounding on how priorities were set for the Trials Methodology Research agenda. This article is freely available from Trials.[4]


Tudur Smith et al. Trials 2014, 15:32
http://www.trialsjournal.com/content/15/1/32

TRIALS

RESEARCH Open Access

The trials methodological research agenda: results from a priority setting exercise

Catrin Tudur Smith[1*], Helen Hickey[1], Mike Clarke[2], Jane Blazeby[3] and Paula Williamson[1]

Abstract

Background: Research into the methods used in the design, conduct, analysis, and reporting of clinical trials is essential to ensure that effective methods are available and that clinical decisions made using results from trials are based on the best available evidence, which is reliable and robust.

Methods: An on-line Delphi survey of 48 UK Clinical Research Collaboration registered Clinical Trials Units (CTUs) was undertaken. During round one, CTU Directors were asked to identify important topics that require methodological research. During round two, their opinion about the level of importance of each topic was recorded, and during round three, they were asked to review the group's average opinion and revise their previous opinion if appropriate. Direct reminders were sent to maximise the number of responses at each round. Results are summarised using descriptive methods.

Results: Forty one (85%) CTU Directors responded to at least one round of the Delphi process: 25 (52%) responded in round one, 32 (67%) responded in round two, 24 (50%) responded in round three. There were only 12 (25%) who responded to all three rounds and 18 (38%) who responded to both rounds two and three. Consensus was achieved amongst CTU Directors that the top three priorities for trials methodological research were 'Research into methods to boost recruitment in trials' (considered the highest priority), 'Methods to minimise attrition' and 'Choosing appropriate outcomes to measure'. Fifty other topics were included in the list of priorities and consensus was reached that two topics, 'Radiotherapy study designs' and 'Low carbon trials', were not priorities.

Conclusions: This priority setting exercise has identified the research topics felt to be most important to the key stakeholder group of Directors of UKCRC registered CTUs. The use of robust methodology to identify these priorities will help ensure that this work informs the trials methodological research agenda, with a focus on topics that will have most impact and relevance.

Keywords: Trials methodology, Priority setting

3.1 The Delphi Method

You will have noticed the methodology used in the Tudur Smith et al. article, thus it is important to learn a little about it. The Delphi method was first introduced in 1950. The Delphi method is a process used to arrive at a group opinion or decision by surveying a panel of experts. Experts respond to several rounds of questionnaires, and the responses are aggregated and shared with the group after each round. The technique can also be adapted for face-to-face. The Delphi survey method is popular in many disciplines. Originally developed as a means of forecasting future scenarios, this method has been used to determine the range of opinions on particular matters, to test questions of policy or clinical relevance, and to explore (or achieve) consensus on disputed topics. The ultimate mentioned here is how it is best used in trials methodology research.

Discussion board
Look at Figure 1 and Figure 2 below. Think of a research question. Could you use the Delphi method to answer it? If not, what question do you have on trials methodology that could be answered by the Delphi Method?

[3] https://youtu.be/x7pvz_Efm-k
[4] https://trialsjournal.biomedcentral.com/articles/10.1186/1745-6215-15-32

Co-funded by the Erasmus+ Programme of the European Union

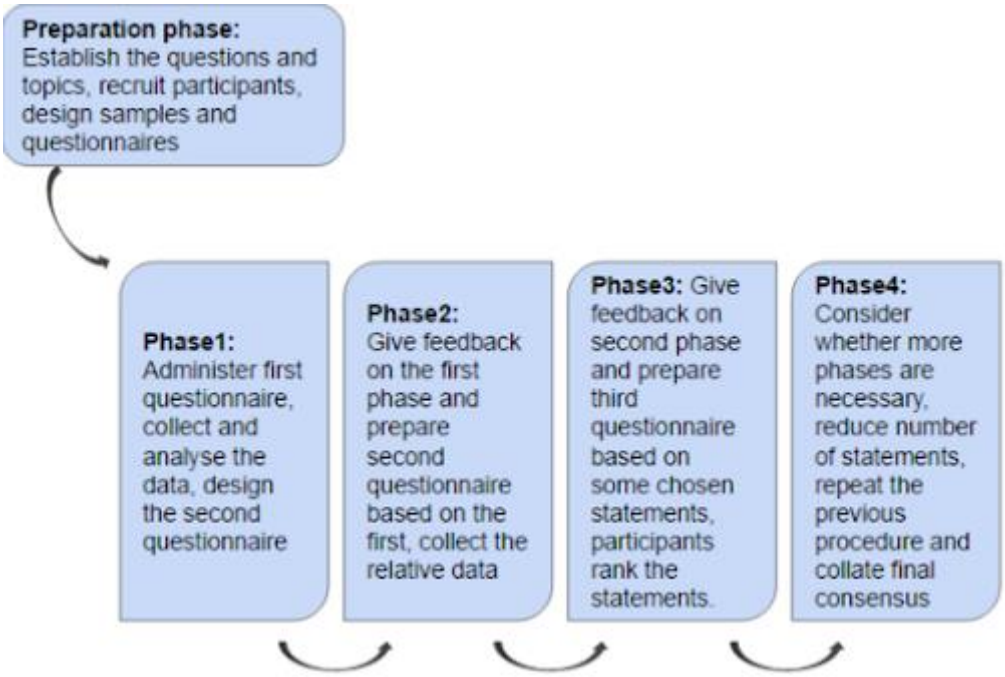


Figure 1: Delphi Phases

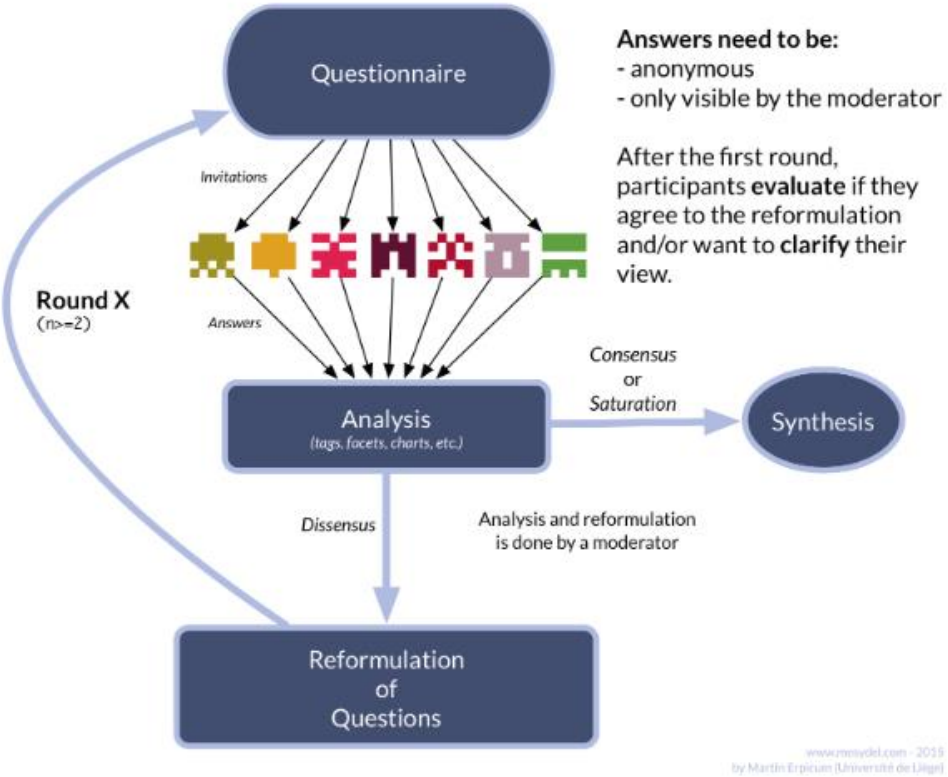


Figure 2: The Delphi Cycle

Co-funded by the Erasmus+ Programme of the European Union

3.2 Key Characteristics of the Delphi Method

1. **Anonymity** of experts, which assures free expression of opinions provided by the experts. This method helps to avoid social pressure from dominant or dogmatic individuals or even from the majority or minorities,
2. **Iteration** – at any point, experts can change their opinions or judgments without fear of being exposed to public criticism,
3. **Controlled feedback** – experts are informed about views of other experts who participate in the study,
4. Some form of **statistical aggregation** permits a quantitative analysis. Thus, though qualitative, the Delphi method can provide quantitative results.

3.3 What happens when the findings of our research are not published?

Listening
When we conduct research, we have an expectation that we will produce results, and that these results will be published. Would you believe, sometimes results are not published. Why does that happen?

Watch this TED talk by Síle Lane from All Trials where she discusses the ramifications of this ("The hidden side of clinical trials | Sile Lane | TEDxMadrid").[5]

4 Priority Setting Partnerships (Priority I – unanswered recruitment priority research questions)

Once Tudor-Smith et al. demonstrated the benefit of a PSP (Priority Setting Partnership) to establish a research agenda, the necessity to use the same methodology to prioritise the challenges of recruitment to randomised trials became clear. We know that 50% of trials fail because they fail to recruit to target, so tackling the priorities for research in this area are important. The PSP on recruitment was led at the University of Galway, Ireland and involved members from the UK and Ireland and included patient representatives also. The PSP for recruitment is called PRIORITY (or since there have been sequels to it, sometimes it's called PRIORITY 1).

4.1 About PRioRiTy I

The PRioRiTy study identified research priorities for how to improve the process of how people are recruited to (PRioRiTy I study) randomised trials i.e., what are the most important things

[5] https://youtu.be/-RXrGLolgEc

we need to know take part in trials. If lots of people don't take part in the trial, then the trial results may become unreliable or unstable, which wastes vital research time and money.

The study involved people across the UK and Ireland who are, or have been, involved directly, in designing, running, analysing, or taking part and/or staying involved in randomised trials. We used a priority setting partnership (PSP) approach based on the methods of the James Lind Alliance (JLA). The JLA (UK) brings patients, carers and healthcare professionals together in Priority Setting Partnerships. These partnerships identify and prioritise unanswered questions about healthcare that the public, carers and professionals jointly agree are the most important. The aim of this is to help ensure that those who fund health research are aware of what future research will really matter in everyday use.

The PRioRiTy PSP was focused on methodological uncertainties rather than on treatment uncertainties and therefore a modified JLA approach was developed and used.

The PRioRiTy study where the first time a modified JLA approach was used to address methodological uncertainties within randomised trials. This was an Ireland and UK initiative and was funded by several funders, including: the Health Research Board (Ireland), Chief Scientist Office of the Scottish Governments Health and Social Care Directorate, and the Medical Research Council.

4.2 PRioRiTy I Methods – The Workshop

Listening
Watch this short 3 minute summary of the workshop process ("PRioRiTy PSP Workshop 2016").[6]

4.3 PRioRiTy I Methods and Results

Reading
Read the modified JLA PSP process and the conclusions of the research published in the open access journal, Trials.[7] The Priority Study is used to inform us in our research and is widely cited and referred to when designing clinical trial methodological questions.


Healy et al. Trials (2018) 19:147
https://doi.org/10.1186/s13063-018-2544-4

Trials

METHODOLOGY Open Access

Identifying trial recruitment uncertainties using a James Lind Alliance Priority Setting Partnership – the PRioRiTy (Prioritising Recruitment in Randomised Trials) study

Patricia Healy[1,2*], Sandra Galvin[1,2], Paula R. Williamson[3], Shaun Treweek[4], Caroline Whiting[5], Beccy Maeso[5], Christopher Bray[6], Peter Brocklehurst[7], Mary Clarke Moloney[8], Abdel Douiri[9], Carrol Gamble[3], Heidi R. Gardner[4], Derick Mitchell[10], Derek Stewart[11], Joan Jordan[10], Martin O'Donnell[1,12], Mike Clarke[1,13], Sue H. Pavitt[14], Eleanor Woodford Guegan[15], Amanda Blatch-Jones[15], Valerie Smith[1,16], Hannah Reay[17] and Declan Devane[1,2]

4.4 Top 10 Research Priorities in Recruitment

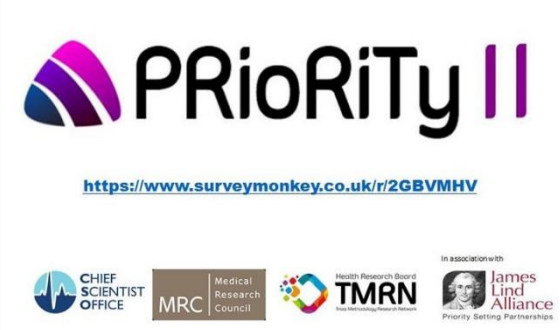
The conclusion of the priority study was to establish the top 20 priorities for methodological research on clinical trials. Here is a table of the top 10.

[6] https://youtu.be/x8w6oc6O2Zo
[7] https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2544-4

Table 1: Top 10 Research Priorities in Recruitment

Overall ranking	Uncertainty as research question
1	How can randomised trials become part of routine care and best utilise current clinical care pathways?
2	What information should trialists communicate to members of the public who are being invited to take part in a randomised trial in order to improve recruitment to the trial?
3	Does patient/public involvement in planning a randomised trial improve recruitment?
4	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?
5	What are the barriers and enablers for clinicians/healthcare professionals in helping conduct randomised trials?
6	What are the key motivators influencing members of the public's decisions to take part in a randomised trial?
7	What are the best approaches to ensure inclusion and participation of under-represented or vulnerable groups in randomised trials?
8	What are the best ways to predict recruitment rates to a randomised trial and what impact do such predictions have on recruitment?
9	What are the best approaches to optimise the informed consent process when recruiting participants to randomised trials?
10	What are the advantages and disadvantages to using technology during the recruitment process?

5 Priority Setting Partnerships (Priority II – unanswered retention priority research questions)



The PRioRiTy II study identified research priorities for how to improve the process of how people are retained in (PRioRiTy 2 study) randomised trials i.e., what are the most important things we need to know to stay involved in randomised trials. If lots of people drop-out of the trial, then the trial results may become unreliable or unstable, which wastes vital research time and money. Both PRioRiTy studies involved people across the UK and Ireland who are, or have been, involved directly, in designing, running, analysing, or taking part and/or staying involved in randomised trials. We used a priority setting partnership (PSP) approach for both studies based on the methods of the James Lind Alliance (JLA). The JLA (UK) brings patients, carers and healthcare professionals together in Priority Setting Partnerships. These partnerships identify and prioritise unanswered questions about healthcare that the public,

carers and professionals jointly agree are the most important. The aim of this is to help ensure that those who fund health research are aware of what future research will really matter in everyday use.

Listening
Watch this short summary of the activity that goes on in a PSP workshop ("PRioRiTy II Reaching Consensus").[8] As you will notice, initial phases were remote, then the final phase was a face-to-face workshop.

5.1 PRIORITY II Methods and Results

Reading
Read the published paper from 2019.[9]


Brunsdon et al. Trials (2019) 20:593
https://doi.org/10.1186/s13063-019-3687-7

Trials

METHODOLOGY Open Access

What are the most important unanswered research questions in trial retention? A James Lind Alliance Priority Setting Partnership: the PRioRiTy II (Prioritising Retention in Randomised Trials) study

Dan Brunsdon[1], Linda Biesty[2], Peter Brocklehurst[3], Valerie Brueton[4], Declan Devane[5], Jim Elliott[6], Sandra Galvin[5], Carrol Gamble[7], Heidi Gardner[1], Patricia Healy[2], Kerenza Hood[8], Joan Jordan[9], Doris Lanz[10], Beccy Maeso[11], Amanda Roberts[1], Imogen Skene[12], Irene Soulsby[1], Derek Stewart[1], David Torgerson[13], Shaun Treweek[1], Caroline Whiting[11], Sharon Wren[14], Andrew Worrall[1] and Katie Gillies[1*]

5.2 The Priorities in Retention in Trials

The findings, similar to the Priority I study, were twenty priority questions for retention in randomised trials. Here is the list of the top 10.

Table 2: Top 10 research questions prioritised

Overall ranking	Research question
1	What motivates a participant's decision to complete a clinical trial?
2	How can trials make better use of routine clinical care and/or existing data collection to improve retention?
3	How can trials be designed to minimise burden on staff and participants and how does this affect retention?
4	What are the best ways to encourage trial participants to complete the tasks (e.g. attend follow-up visits, complete questionnaires) required by the trial?
5	How does involvement of patients/the public in planning and running trials improve retention?
6	How could technology be best used in trial follow-up processes?
7	What are the most effective ways of collecting information from participants during a trial to improve retention?

[8] https://youtu.be/bXbIjDg3MAQ
[9] https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3687-7

8	How does a participant's ongoing experience of the trial affect retention?
9	What information should trial teams communicate to potential trial participants to improve trial retention?
10	How should people who run trials plan for retention during their funding application and creation of the trial (protocol development)?

6 Priorities for Methodological research on patient and public involvement in clinical trials

6.1 The Patient's Perspective

Trials Methodology Research is not just about the researchers. A critical part is the involvement of patients and the public, or what we term (PPI).

Listening
Professor Derek Stewart is a well known patient advocate and works with many trials methodology researchers to improve the conduct of clinical trials. He was conferred with an honorary Professorship at NUI Galway, Ireland, for his PPI work.

Listen to Professor Derek Stewart in this short video clip ("Derek Stewart - HRB-TMRN Symposium 2020")[10] which he delivered to the HRB Trials Methodology Research Network Symposium on what patient and public involvement in trials methodology research means. Derek had throat cancer 25 years ago.

Here are Derek's wise words on **Why Trials Methodology Research is Important for Patients**

It seems to me (and I would really welcome other opinions) that the value for research participants are…

- to see that the most effective research methods are being used to gather and understand evidence,
- to be assured that trial methods are being reviewed, evaluated and progressing,
- to know that improvements and innovation are being discussed and implemented,
- to be certain that the methods themselves have been evaluated using highest quality research.

Trials Methodology Research, therefore, increases the likelihood that quicker and better answers might be found; data is used more effectively and efficiently; and, the way research is carried out is advanced. As a former teacher, it is the equivalent of having a thorough understanding about learning as well as the subjects we teach – the subtle difference between an educationalist and a teacher.

As patients, we have come to expect health research that rigorously tests out new drugs, treatments and care as part of a constant search for improvement of patient care. We are actively involved with

[10] https://youtu.be/Tmd85CVYjXs

Co-funded by the Erasmus+ Programme of the European Union

researchers in these interventional studies. Such evidence that is gathered matters as much to us as the researchers.

It is, in many respects, unsurprising that the same thoroughness is used to test the research methods themselves. It is ultimately, in our interests as patients, that we better understand why people choose to take part in studies, whether one method be better than another, and what are the best ways of analysing the data.

Involving patients and the public in the sphere of Trials Methodology Research is increasing and we, as patients, may need to consider how to make this meaningful for research, for us and future trial participants.

Involvement with Methodologists feels like another stage in our learning about research. It is a bit like going to college after school (even if only part time). It becomes more about questioning the picture on the jigsaw box as well as the individual pieces. It is about helping to make research itself more effective and efficient to the benefit of patients.

Patient, public involvement with Trials Research is described by Alice Biggane (2), as helping “to increase both the value, integrity and quality of research”. These seem to be vital components for all research but particularly important for Trials Methodology Research especially as we look towards the greater the use of data, digital technologies and artificial intelligence.

I believe that our involvement with Trials Methodology Research also helps us to be more capable partners and advocates. It helps us step slightly away from our personal experience of health and think more of the concept of ‘patient’. Though our personal experience remains the driver for change, we begin to think in the abstract to make it better for all. It also assists with our knowledge of research practice and the things we don’t know.

Patient experience, our voices and presence are needed to ensure the compass points in the right direction and that the realities of people’s lives are taken into account.

6.2 The METHODICAL Study

PPI in Clinical trials is seen as increasingly important and many UK funders now require researchers to provide evidence of how it has and will inform their studies. Traditionally PPI tends to involve a small number of patients or members of the public (known as PPI contributors) to offer a distinctive perspective to researchers or clinicians on the design and conduct of a trial. Some PPI contributors will have direct personal experience of the condition being investigated, whilst others bring general experience of being a patient or service users.

Despite the emphasis on PPI in the UK and internationally, there are uncertainties about how best to implement it, about the purpose of PPI and whether it actually does improve research.

Conducted in the UK, it was a national priority setting exercise to determine the methodological research priorities for addressing these uncertainties. 237 people from across the UK registered to take part in an online two round Delphi survey, representing a wide range of PPI stakeholders such as PPI contributors, funders, chief investigators, trial managers, researchers, PPI coordinators and PPI advisors.

A face to face meeting of 25 randomly chosen representatives from across the stakeholder groups was used to discuss the online survey results and decide on future research priorities. Sixteen topics were voted as critically important and should form the basis for future research.

The METHODICAL results have recently been published in the journal Health Expectations and the next step in the process is to facilitate the start-up of collaborative working groups on each of these critically important topics. The aim is that these groups will generate future grant proposals in order to develop the evidence base for PPI.

Reading

Read the publication.[11]

Accepted: 9 May 2017
DOI: 10.1111/hex.12583

ORIGINAL RESEARCH PAPER

WILEY

Priorities for methodological research on patient and public involvement in clinical trials: A modified Delphi process

Anna Kearney BSc (Hons), PGCert, Research Associate[1] | Paula Williamson BSc, PhD, Professor[1] | Bridget Young BA (Hons), PhD, Professor[2] | Heather Bagley BA (Hons), MPhil, Patient and Public Involvement Co-ordinator[1] | Carrol Gamble Bsc (Hons), PhD, Professor[1] | Simon Denegri BA (Hons), NIHR National Director for Patients and the Public in Research and Chair[3] | Delia Muir BA (Hons), Wellcome Trust Engagement Fellow[4] | Natalie A. Simon BSc (Hons), Public Involvement & Engagement Manager[5] | Stephen Thomas MBA, Patient and Public Involvement partner | Jim T. Elliot Bsc (Hons), PhD, Patient and Public Involvement partner | Helen Bulbeck BA (Hons), PGCert, MA (Hons), MA, PhD, Patient and Public Involvement partner | Joanna C. Crocker MBiochem, PhD, Research Fellow[6] | Claire Planner BA (Hons), MSc, Research Associate[7] | Claire Vale PhD, Senior Research Scientist[8] | Mike Clarke DPhil, Professor[9] | Tim Sprosen BSc (Hons), DPhil, Associate Professor[10] | Kerry Woolfall BA (Hons), MA (Hons), PhD, Research Fellow[2]

7 Studies within a Trial (SWATs)

7.1 What is a SWAT

SWAT stands for a 'Study Within A Trial' and it is a research study that is embedded within a larger host trial. The aim of a SWAT is to evaluate or investigate different methods of organising or delivering a specific trial process such as recruitment or retention.

7.2 Why Do We Need SWATs?

Randomised trials are central to providing health care evidence that helps patients, clinicians and policy-makers to make evidence informed choices about treatments and therapies. However, when it comes to making decisions about the design, conduct and reporting of randomised trials themselves, there is scant evidence to support them. This means that trial process decision-making is largely based on instinct and experience, not evidence. Sometimes this is fine, sometimes it isn't. Without evidence it's hard to spot the difference before it's too late. One way of building an evidence-base to support trial process decisions is to do a SWAT because they provide an opportunity to evaluate alternative options when conducting a trial process (e.g. patient recruitment, patient retention, reporting the findings) to provide much needed evidence about how the trial process can be improved.

[11] https://pubmed.ncbi.nlm.nih.gov/28618076/

7.3 What Are the Key Features of a SWAT?

1. It seeks to resolve important uncertainties about process.
2. It is embedded within a host trial.
3. It must not affect the scientific integrity of the host trial.
4. It should have a formal protocol, just like the host trial.
5. It can be evaluated in a single trial but is well-suited for running across more than one host trial.
6. It will provide data to inform the design and conduct of future trials but might also provide data to inform decisions about the ongoing host trial.

7.4 How Can We Encourage People to Do SWATs?

The structures to encourage SWATs are constantly being developed. First, there was the recognition that this type of research was valuable. Second, was the need for guidance on what a SWAT is and how to do one (Trial Forge Guidance). Third then was the need for funding. Key funders have provided separate SWAT funding (a ring fenced pocket of funding) within grants for trials, e.g., HRB (Ireland), NIHR (UK).

Listening
Watch in the three and a half minute presentation from Hywel Williams, Director of the NIHR Health Technology Assessment Programme here he talks about SWATs ("SWAT - Studies within a trial").[12]

He mentions Trial Forge, the Northern Ireland SWAT repository, PROMETHEUS and the James Lind Alliance Priority Setting. Note how he says, to access the funding, you must register the SWAT on the Northern Ireland SWAT repository. This SWAT repository, though available on an Irish website, is an international repository, first set up by Professor Mike Clarke at the Queens University of Belfast, and more than 95% of SWATs conducted are registered here. The protocols available on the repository are freely available for anyone to use. You will note that much of the Trials Methodology research conducted and published, and similarly SWATs, are done in the UK and Ireland. Actions such as this are really important because this prevents duplication of work.

Here is the link to check out the NI SWAT repository.[13]

Professor Williams also says that you must make the results of the SWAT available as soon as it is complete. This also is important. Another really important point is that he says the SWAT may not be powered to be conclusive about the research questions, but the real value in a SWAT is the ability to combine the results of multiple SWATs together. It took a while for funders to realise this because as we know, one of the first things we ensure in a RCT is that the study is 'powered' appropriately for the primary outcome.

7.5 What Would Make Doing SWATs Easier?

Conducting research should be as simple a process as possible, and so too should the conduct of SWATs. So what are the important factors that would make it easier?

[12] https://youtu.be/PoIE6xxK-pA
[13] https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/

1. If we had a list of priorities (and we do now, Priority Study 1 and Priority Study 2).
2. Research infrastructure changes to make SWATs easier (we can see from Hywel Williams that this is changing).
3. Collaboration.

Now collaboration is key to most research, but with competing priorities, competing against colleagues for grants etc. this is not always easy to see. However, if you look at most good pieces of research, they involve collaboration. We have to think as trialists and "together we are better". This does not just mean working with other researchers. It includes working with patients and the public, ethics committees, funders etc.

If you'd like to read more about "What is a SWAT", go to Trials (Trial Forge Guidance 1: what is a Study Within A Trial (SWAT)?).[14]

7.6 Case Study of a successful SWAT, i.e. when another SWAT is not needed

In 2021, the British Medical Journal published an article titled, "Bah humbug! Association between sending Christmas cards to trial participants and trial retention: randomised study within a trial conducted simultaneously across eight host trials".

You can read the full article, which we would highly recommend.[15] In fact, there was an editorial associated with this publication also.[16] Please read it and see the visual abstract below (*Figure 3*).

7.6.1 The Christmas Card SWAT

The objective of the study was to determine the effectiveness of sending Christmas cards to participants in randomised controlled trials to increase retention rate at follow-ups, and to explore the feasibility of doing a study within a trial (SWAT) across multiple host trials simultaneously. The participants were 3223 trial participants who were still due at least one follow-up from their host randomised controlled trial. The main outcome measure was the proportion of participants completing their next follow-up (retention rate) within their host randomised controlled trial. The results were: 1469 participants (age 16-94 years; 70% (n=1033) female; 96% (813/847) white ethnicity) across the eight host randomised controlled trials were involved in the analysis (cut short owing to covid-19). No evidence was found of a difference in retention rate between the two arms for any of the host trials when analysed separately or when the results were combined (85.3% (639/749) for cards versus 85.4% (615/720) for no card; odds ratio 0.96, 95% confidence interval 0.71 to 1.29; P=0.77). No difference was observed when comparing just participants who were due a follow-up in the 30 days after receiving the card (odds ratio 0.96, 0.42 to 2.21). No evidence of a difference in time to complete the questionnaire was found (hazard ratio 1.01, 95% confidence interval 0.91 to 1.13; P=0.80). These results were robust to post hoc sensitivity analyses. The cost of this intervention was £0.76 (€0.91; $1.02) per participant, and it will have a carbon footprint of approximately 140 g CO_2 equivalent per card. One benefit of this approach was the need to

[14] https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-2535-5
[15] https://www.bmj.com/content/375/bmj-2021-067742
[16] https://www.bmj.com/content/375/bmj.n2870

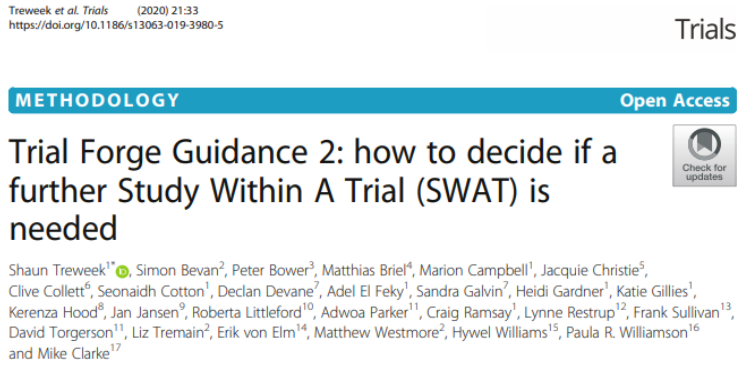
only submit one ethics application. The conclusions were: Sending Christmas cards to participants in randomised controlled trials does not increase retention. Undertaking a SWAT within multiple randomised controlled trials at the same time is, however, possible. This approach should be used more often to build an evidence base to support selection of recruitment and retention strategies. Although no evidence of a boost to retention was found, embedding a SWAT in multiple host trials simultaneously has been shown to be possible.

Figure 3: Visual abstract

7.7 Trial Forge Guidance 2: how to decide if a further SWAT is needed

Trial Forge, comprised of experienced trial methodologists, produced a methodological piece on when it's important to consider not conducting any further SWATs on the same topic.

Reading
This was published open access in the journal Trials, and can be accessed here.[17]


Treweek et al. Trials (2020) 21:33
https://doi.org/10.1186/s13063-019-3980-5

Trials

METHODOLOGY Open Access

Trial Forge Guidance 2: how to decide if a further Study Within A Trial (SWAT) is needed

Shaun Treweek[1*], Simon Bevan[2], Peter Bower[3], Matthias Briel[4], Marion Campbell[1], Jacquie Christie[5], Clive Collett[6], Seonaidh Cotton[1], Declan Devane[7], Adel El Feky[1], Sandra Galvin[7], Heidi Gardner[1], Katie Gillies[1], Kerenza Hood[8], Jan Jansen[9], Roberta Littleford[10], Adwoa Parker[11], Craig Ramsay[1], Lynne Restrup[12], Frank Sullivan[13], David Torgerson[11], Liz Tremain[2], Erik von Elm[14], Matthew Westmore[2], Hywel Williams[15], Paula R. Williamson[16] and Mike Clarke[17]

7.8 Practical Things to Consider When Conducting a SWAT

Table 3: Practical Things to Consider When Planning a SWAT

1. Cost • Relatively inexpensive, SWATs tend to cost between £5,000/€5,500 and £10,000/€11,000. Ideally, SWATs should be included in the host trial from the beginning.
2. Randomisation • Depends largely on whether the SWAT question is focusing on measuring effect sizes. If it is looking at the effect of alternative methods of conducting a trial process, randomisation should be considered. If the SWAT is not aiming to measure an effect size, it is highly likely there will be no need for randomisation. • SWAT randomisation can be carried out separately to the host trial randomisation.
3. Ethics • Ethical approval guidelines for conducting research in humans can differ between countries so it is advised that researchers check national guidance. • Likely that some SWATs will require ethical approval. • In the Republic of Ireland, there is a system of national approval for trials of medicinal products but not for non-medicinal products and, therefore, for the latter ethical approval is usually sought from sites conducting the host trial and/or from the SWAT principal investigator's host institution. • SWATs are generally low-risk and rarely add extra risk for participants so it is not normally necessary to get participant consent. • SWATs focusing on staff but which directly impacts patients / participants (e.g. how information is delivered to participants), may require ethical approval.
4. Analysis • Generally simple so can be carried out by any member of trial team rather than a senior member or Principal Investigator. • SWAT sample size calculations can be done in the normal manner using estimates of minimum important differences that the investigator believe are appropriate. • For qualitative SWATs, a suitable qualitative methodological framework and methods should be applied.
5. Implementing the SWAT • SWATs generally do not need to run for the full duration of the host trial so any extra work should be modest and short-term.

[17] https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3980-5

6. Publication • SWAT findings should be put into the public domain and be accessible to others whether this is through being included in the host trial report, a separate publication or being included in a relevant systematic review.

7.9 Writing a SWAT protocol

Just as in a trial, a SWAT protocol is important so that study sites involved in the SWAT will conduct the SWAT in the same way. Equally important is reporting a SWAT. In order to have the information to report, it must be collected and thus has to be considered at the design stage of the SWAT. The University of York in the UK are leaders in SWAT conduct, and established the PROMETHEUS (PROMoting the USE of SWATs) group. We have adapted their reporting guidelines to guide the SWAT protocol here.

Table 4: Items in the SWAT Protocol

1. Title to include the term SWAT
2. Introduction: Background and Objectives
3. Methods a. Trial Design – Description of the SWAT (such as parallel, factorial, cluster) including allocation ratio. b. Participants – State eligibility criteria in SWAT, including differences to those from the host trial. Include setting(s) and location(s). c. Interventions – Describe SWAT intervention to enable replication, include how and when interventions were administered and recruitment dates. d. Controls – If a randomised SWAT, include control details. e. Outcomes – State primary and secondary outcome measure for SWAT. Include how and when they are assessed. f. Sample size – How sample size was determined for the SWAT. g. Randomisation – If a randomised SWAT. Method used to generate the random allocation for the SWAT. The type of randomisation and details of any restriction. Who generated the random allocation sequence. h. Allocation concealment – Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned for the SWAT. i. Enrolment – Who enrolled participants and who assigned them to the interventions for the SWAT. j. Blinding – If done, who was blinded to the SWAT after assignment to interventions. k. Statistical methods – Statistical methods used to compare groups for primary and secondary outcomes for the SWAT. Methods for additional analyses, such as subgroup analyses.
4. Host Trial: a. Host trial details, including phase of trial, study design and disease area. b. Host trial registration including registration number and name of trial registry. c. Commercial or academic host trial. d. Host trial protocol.
5. Funding – funding details for SWAT
6. Data sharing
7. Registration details of SWAT on NI SWAT repository

Co-funded by the Erasmus+ Programme of the European Union

8 Conclusion

This concludes the chapter on trials methodology research. Remember, trials methodology is about making trials more efficient so that we do not waste money, resources, researchers time, participants time etc. We have covered many new concepts in detail. Take the opportunity to read further on these topics by exploring the literature in reputable journals.