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Retention strategies for clinical trials; exploring the costs, planning and communication processes.

Thesis presented by Ellen Murphy [https://orcid.org/0000-0001-7874-4331] for the degree of Doctor of Philosophy

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March 2025

Institutional requirements for PhD by publication

This PhD thesis follows the guidance provided by University College Cork for a Publication-based Doctor of Philosophy (PhD) Thesis. This guidance can be found in section 3 of the linked document below.

Link to guidance: PhDRegulationsApril2021.pdf (ucc.ie)

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List of Abbreviations

Each manuscript (Chapters Four to Seven) includes its own list of abbreviations. This section provides a list of key abbreviations used throughout the thesis in alphabetical order.

Clinical Trial Units (CTUs)

Clinical Trials of Investigational Medicinal Products (CTIMPs)

Grading of Recommendations, Assessment, Development and Evaluations (GRADE)

International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use – Good Clinical Practice (ICH GCP)

Joanna Briggs Institute (JBI)

National Institute for Health Research Health Technology Assessment (NIHR HTA)

Online Resource for Research in Clinical triAls (ORRCA)

Participant Information Leaflets (PILs)

Patient and Public Involvement (PPI)

Preferred Reporting Items for a Systematic Review and Meta-Analysis Protocols

Extension for Scoping Reviews (PRISMA-ScR)

Prioritising Retention in Randomised Trials study (PRioRiTy II)

Qualitative (QUAL)

Qualitative evidence synthesis (QES)

Quantitative (QUAN)

Randomised Controlled Trial(s) (RCTs)

Social Research Ethics Committee (SREC)

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

Studies Within a Trial (SWATs)

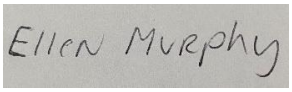
Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA)

U.S Food and Drug Administration (FDA)

United Kingdom (UK)

Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and intellectual property.

Signature: 

Date: 27/03/2025

Contributions to Research

This thesis consists of four papers, three of which have been published in peer-reviewed journals and one paper that is being prepared for journal submission.

The first published paper is presented in Chapter Four. Ellen Murphy (EM) led on this chapter which developed a costing approach for retention strategies in trials. Shaun Treweek (ST), Frances Shiely (FS) and EM devised the study. EM, ST, and FS discussed how to create the costing approach. EM gathered required data to create the costing approach to generate costs. The paper was drafted by EM, reviewed by FS and ST and revisions made by EM.

The second published paper is a scoping review presented in Chapter Five. EM led on this review. EM searched the literature, conducted title and abstract screening. FS conducted a 10% check of title and abstract screening. Full text screening conducted by EM with a 10% check by FS. EM conducted data extraction and result analysis. The paper was drafted by EM and reviewed by FS and Katie Gillies (KG). EM made edits and revisions.

The third published paper is a content analysis of participant information leaflets, which is presented in Chapter Six. EM led on all stages of this chapter. EM extracted data from the participant information leaflets and their corresponding protocols. EM generated the results and drafted the paper. FS and KG reviewed the paper and EM made the revisions.

The fourth paper is presented in Chapter Seven. This is a qualitative interview study with trialists. EM led this chapter. EM, FS and KG developed the topic guide with input from public partners. EM recruited interviewees and conducted the interviews. Framework analysis was conducted by EM, with input from KG and Sharon McCann (SM). The paper was drafted by EM and reviewed by KG, SM, and FS. EM made revisions.

List of Publications from this thesis

1. Murphy, E., Shiely, F. & Treweek, S. How much is the lack of retention evidence costing trial teams in Ireland and the UK? *Trials* 23, 396 (2022). **https://doi.org/10.1186/s13063-022-06223-x**

2. Murphy, E., Gillies, K. & Shiely, F. How do trial teams plan for retention during the design stage of the trial? A scoping review. *Trials* 24, 784 (2023). **https://doi.org/10.1186/s13063-023-07775-2**

   Linked protocol publication.
   Murphy, E., Gillies, K. & Shiely, F. How do trial teams plan for retention during the design stage of the trial? A scoping review protocol. *Trials* 23, 944 (2022). **https://doi.org/10.1186/s13063-022-06866-w**

3. Murphy, E., Gillies, K. & Shiely, F. Retention strategies are routinely communicated to potential trial participants but often differ from what was planned in the trial protocol: an analysis of adult participant information leaflets and their corresponding protocols. *Trials* 25, 372 (2024). https://doi.org/10.1186/s13063-024-08194-7

Intended on being submitted for review.

Murphy, E., McCann, S., Shiely, F., Gillies, K. Planning retention strategies in clinical trials; Qualitative interviews with members of trial teams. 2025. Unpublished manuscript, in preparation for submission to PLOS One.

Additional publications over the course of the PhD

1. Shiely, F., **Murphy, E.,** Gilles, K. *et al.* Trial participants' self-reported understanding of randomisation phrases in participation information leaflets can be high, but acceptability of some descriptions is low, especially those linked to gambling and luck. *Trials* **25**, 391 (2024). https://doi.org/10.1186/s13063-024-08217-3

2. Cuddihy, L., Howick, J., **Murphy, E**. *et al.* When describing harms and benefits to potential trial participants, participant information leaflets are inadequate. *Trials* **25**, 292 (2024). https://doi.org/10.1186/s13063-024-08087-9

3. **Murphy, E**., Gillies, K., Skea, Z., *et al.* Retention in trials: A Qualitative Evidence Synthesis of studies reporting participant reasons for trial non-completion. 2025. Unpublished manuscript, in preparation for submission to BMC Open.

Presentations conducted over the course of the PhD.

Oral Presentations

- Murphy, E. Retention strategies for clinical trials; exploring the costing, planning and communication. HRB TMRN Peer Pathways 2025. February 2025. Dublin, Ireland.

- Murphy, E. Do trial teams plan for and communicate retention strategies during the design and consent stage of a trial. 3rd September 2024. International Clinical Trial Methodology Conference. Edinburgh, UK.

- Murphy, E. Investigating the communication of retention strategies in clinical trials. 8th Trial Methodology Symposium. October 2023. Galway Ireland.

Poster Presentations

- Murphy, E., Shiely, F. & Gillies, K. How trial teams plan and communicate retention strategies in clinical trials, A qualitative interview study. 1st October 2024. International Clinical Trial Methodology Conference. Edinburgh, UK.

- Murphy, E., Shiely, F. & Treweek, S. How much is the lack of retention evidence costing trial teams in Ireland and the UK? 26th April 2023. School of Public Health “Bright Futures.” University College Cork.

- Murphy, E., Shiely, F. & Treweek, S. How much is the lack of retention evidence costing trial teams in Ireland and the UK? 3rd-6th October 2022. International Clinical Trial Methodology Conference. Harrogate, UK.

Personal and professional motivation for undertaking a PhD

Pursuing this PhD was driven by both personal and professional motivations. Prior to undertaking my PhD I was a research assistant working in the field of trial methodology. This developed a strong interest in research improving the conduct of trials, particularly in participant retention. The PhD offered me the opportunity to continue to enhance my research skills, learn more about participant retention in trials and allow me to contribute evidence to the area of participant retention in trials. On a personal level, completing a PhD offered the chance to expand career opportunities. I took it as an opportunity to invest in both my research skills and my future career prospects.

Acknowledgements

I will start by expressing my deepest gratitude to my supervisor Professor Frances Shiely, for her guidance, research expertise, and continuous support throughout the course of my PhD journey. I am extremely thankful for the ongoing encouragement, mentorship, and the research opportunities she has provided me with over the past several years. Thank you for always pushing me to achieve my best.

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Thank you to the HRB-TMRN team and wider network, particularly to Dr Sandra Galvin, for providing unwavering support and guidance over the course of my PhD. I am incredibly grateful to be part of such an enthusiastic and encouraging group of researchers. Being part of this amazing network has also provided me with one of the best outputs of this PhD which is the amazing network of friends I have made along the way. I want to shout out to all my fellow HRB TMRN PhD Scholars, especially to Éle Quinn for listening to me rant, and providing me with endless support and guidance. I would also like to thank my Aberdeen support crew with a

special mention to Dr Taylor Coffey and Sophie Greenwood for getting me through the last 18 months of my PhD - I really could not have survived Aberdeen without you both!

Lastly, I want to say a massive thank you to my family and friends for all the support they have given me over the past three and a half years; through all the highs and especially during the lows of my PhD journey. Thank you for tolerating my complaining. Love you all so much!

Dedication

“There is a world out there and it’s calling my name.”

Tame Impala, 2015

This thesis is dedicated to myself, in recognition of my hard work, commitment and perseverance that have led to this achievement.

Funding

Ellen Murphy's PhD studentship is funded by the Health Research Board– Trials Methodology Research Network in Ireland (grant ref: HRB-TMRN-2021-001) and the College of Medicine and Health, University College Cork, Ireland

Abstract

Background

Participant retention in randomised controlled trials is an ongoing challenge for trial teams. If trials lose large numbers of participants, the trials' ability to answer the research question is jeopardised. Trial teams often use retention strategies, activities aimed at facilitating ongoing trial participation, to reduce missing data and improve data completeness. There are several gaps in the literature on the costing, planning, and communication of retention strategies. Thus, the aim of this doctoral thesis is to investigate the costing, planning, and communication of retention strategies, specifically focusing on the trial design, planning, and consent stages.

Methods

This is a multi-phase sequentially mixed-methods thesis, which contains discrete (mixed) chapters, concluding with the overall findings synthesised. A pragmatic, mixed-methods research approach was taken. Chapter Four applies a costing approach to generate estimated costs of implementing retention strategies in trials. Chapter Five presents a scoping review investigating whether trial teams are planning retention strategies during the trial design stage. A content analysis of participant information leaflets (PILs) is presented in Chapter Six, to establish if potential trial participants are being informed about retention strategies during informed consent. Chapter Seven reports one-to-one interviews with trialists to get a more in-depth understanding of the planning and communication of retention strategies. Chapter Eight discusses the integrated findings in the context of the wider literature.

Findings

The planning and implementation of retention strategies in practice are better than their reporting in trial documents. Trialists typically plan retention strategies during the trial design and planning stages. However, if participant retention rates become a concern, retention strategies are also planned and implemented in real-time as the trial progresses. A wide range of both formal and informal strategies are used by trial teams to promote continued participation in trials. Formal strategies include: prompts, reminders, newsletters, monetary incentives, and offering different options for data collection according to participant preference. Informal strategies include building rapport with participants and having motivated trial staff. Unfortunately, the reporting of retention strategies in trial protocols is frequently inadequate, with protocols rarely outlining these methods despite best practice recommendations to do so. Trialists cite various reasons for this poor reporting. Even though the planning and implementation of retention strategies is common, research is needed to improve evidence-based decision making for trialists. Currently, trial teams often rely on personal experience when choosing strategies due to a lack of high-quality evidence demonstrating that retention strategies are effective at improving retention rates. Formal evaluations of strategy effectiveness are needed to reduce this evidence gap. Furthermore, retention strategies can be extremely costly and resource intensive, which underscores the need for evidence to determine which retention strategies justify the investment. Documentation practices around retention strategies, and the importance of retention, in PILs is variable. More research is necessary to understand participants' perspectives on

how, and when, they would prefer to receive communications about retention strategies and the importance of staying involved in trials.

Conclusion

Planning and implementing retention strategies is common, while the reporting of these strategies in trial documents tends to be inconsistent. There is a need to enhance the reporting of retention strategies in trial protocols, and to better understand the most effective ways to communicate retention strategies, and the importance of trial participation, to participants. Trial teams must consider numerous factors when planning and communicating retention strategies. However, more research is needed to support evidence-based decision-making in this area.

Keywords

Retention, retention strategies, activities to promote participant retention, trials, clinical trials, randomised controlled trials, costing, planning, communication, implementation, trial methodology research, trial design, protocol development, informed consent.

Chapter One. Introduction

1.1 Introduction

This chapter provides an overview of the thesis. It outlines the rationale for the research, its aim, the research objectives, and presents a summary of the chapters that address these objectives. It concludes with a brief overview of the methodology and methods used and outlines the structure of the thesis.

1.2 Rationale for the thesis

Randomised controlled trials (RCTs), herein referred to as trials in this thesis, are the most reliable and rigorous method for evaluating the effectiveness of interventions, if they are conducted properly, as they minimise the risk of confounding and other forms of biases (1, 2). Conducting trials is, however, not without its challenges. Participant retention, i.e., the process of keeping participants in a trial for the trials' full duration (3), has been acknowledged as an ongoing issue facing trial teams, and thus it is a top research priority in trial methods research (4). Up to 50% of trials have loss-to-follow-up rates, i.e., the proportion of participants failing to provide valid primary outcome data, exceeding 11% (3, 5). Additionally, between 60-89% of all trials have some level of missing data (6).

The problem with poor participant retention is that it contributes to concerns about the validity and generalisability of the results, leading to doubts in the confidence of the trial findings (6-10). Additionally, ethical issues arise as trials recruit more participants to counterbalance poor retention. This exposes more people to the risks of trial participation, such as the potential adverse effects associated with the intervention being tested, which could be avoided if retention was improved (3, 11,

12). Furthermore, poor retention delays effective treatments from being implemented into practice (13). For these reasons, inefficiencies in participant retention in trials contribute to research waste (13-15). The optimal solution is to retain all trial participants (16), and while we acknowledge that for credible reasons such as participants' health status, experiences of the trial medication, participants' lifestyle and other commitments, this is not possible (17), optimising participant retention to the maximum is prudent.

To help direct research on trial methods to improve retention in trials, a prioritisation study, PRioRiTy II (Prioritising Retention in Randomised Trials Study), was conducted. This was a Priority Setting Partnership which included members of the public and/or patients with experience in trials, frontline research staff, investigators, and trial methodologists with experience in trials across both Ireland and the UK. A list of unanswered questions in the literature about the topic of trial retention were generated, these questions were then ranked, and the priority list was agreed by all stakeholders. These questions are orientated around topics such as barriers/enablers to continued trial participation, trial burden/design, communication, and patient/public involvement to improve retention. This doctoral thesis aims to contribute evidence to help answer PRioRiTy II question 10; "How should people who run trials plan for retention during their funding application and creation of the trial (protocol development)?" (4).

1.3 Aim and objectives

1.3.1 Aim

The aim of this doctoral thesis was to gain a better understanding of the costing, planning, and communication of retention strategies in trials during the design, planning, and consent stages.

1.3.2 Research objectives

The research objectives to achieve the aim were as follows:

Research objective one; To estimate how much routinely used retention strategies might be costing trial teams in Ireland and the UK.

Research objective two; To identify if, and how, trial teams document plans for participant retention in trial protocols, reflecting the extent of retention planning during the protocol development stage of the trial.

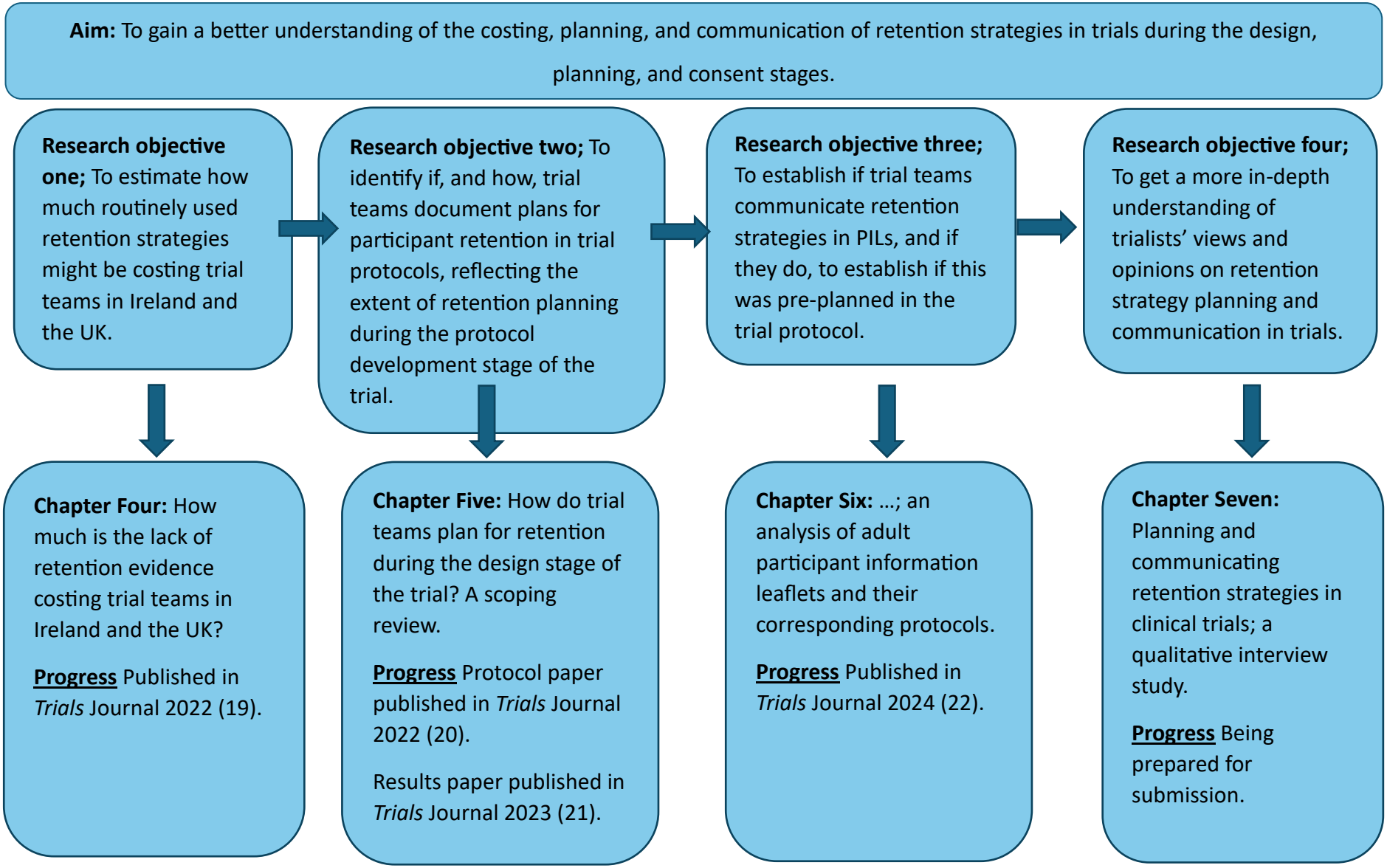
Research objective three; To establish if trial teams communicate retention strategies in participant information leaflets (PILs), and if they do, to establish if this was pre-planned in the trial protocol.

Research objective four; To get a more in-depth understanding of trialists' views and opinions on retention strategy planning and communication in trials.

1.4 A summary of chapters addressing the research objectives

Each of the research objectives are answered in a chapter of the thesis and these are summarised here and displayed in Figure 1.1

Figure 1.1 Overview of the thesis objectives and chapters.



Chapter Four. How much is the lack of retention evidence costing trial teams in Ireland and the UK? (18).

- The top ten most routinely used retention strategies by Clinical Trial Units (CTUs) in the UK were selected. We made assumptions as to how each of these strategies was most likely to be implemented and the costs involved in doing this.
- We created and applied a costing approach to various trials to generate cost estimates of the retention strategies.
- *Result:* Retention strategies can be very expensive and high-quality evidence to support their effectiveness is lacking. Without the evidence to show if retention strategies are effective, trial teams are potentially wasting resources on activities to retain participants that may, or may not, work.

Chapter Five. How do trial teams plan for retention during the design stage of the trial? A scoping review (19).

- A scoping review of 824 trial protocols was conducted to determine if, and how, trial teams develop retention strategies during the design stage of the trial.
- *Result:* Trial protocols do not routinely report plans to promote participant retention, suggesting that proactive consideration and planning of retention strategies may not occur during trial design and protocol development or that such strategies are not documented in the protocols. Prospectively planning, however, may allow trial teams more time to consider the choice

of strategy, and budget needed for them. Communicating plans to promote retention in trial protocols improves transparency in trial conduct.

Chapter Six. Retention strategies are routinely communicated to potential trial participants but often differ from what was planned in the trial protocol; an analysis of adult participant information leaflets and their corresponding protocols (20).

- A content analysis of 92 PILs was conducted to determine whether trial teams outline retention strategies to potential participants during informed consent through PILs.
- We also compared retention strategy information outlined in the PILs with the corresponding trial protocols, to assess whether these strategies were pre-planned and consistently communicated across trial documents.
- *Result:* PILs often outline retention strategies, however, the information about plans to promote retention often differ between the PIL and corresponding protocol. While it appears that trial teams consider participant retention during the trial design and planning stages, they do not always consistently communicate plans to promote retention across trial documents, nor explain the importance of retention to potential trial participants in PILs.

Chapter Seven. Planning and communicating retention strategies in clinical trials; a qualitative interview study.

- One-to-one interviews were conducted with 24 trialists, in the UK and Ireland – individuals involved in the design, delivery, analysis of trials such as, trial managers, principal investigators, statisticians, study co-ordinators, and research nurses – to gather insights on the planning and communication of retention strategies.
- *Finding:* Trialists mostly report proactively planning retention strategies during trial design and planning, and implement strategies from the outset of the trial. Trialist are also, however, reactive to problematic retention rates as the trial is ongoing. A range of different retention strategies are implemented, and the choice is made by the core trial management team. Retention strategies are mostly chosen based on personal experience, but other factors such as budget, scientific literature, mode of data collection, input from patient and public partners, as well as ethics committees, can also influence strategy choice. The reporting of retention strategies in trial documents varies. Some trialists report strategies in protocols, and strategies that participants must consent to are outlined in PILs. Reasons for lack of documentation in protocols and PILs include lack of reporting requirements or template guidance, belief that strategies do not need to be included in protocols or PILs, strategies are reported in other documents such as standard operating procedures, and due to efforts to shorten PILs. More research and work with trial stakeholders is needed to encourage formal documentation of strategies.

1.5 Scope of the thesis

The research presented in this thesis focuses on the retention of participants in trials. Retention refers to the process of keeping participants in a trial for the trials' full duration (3). In this thesis we defined retention strategies as an activity/action that is conducted, for the purpose of retaining participants in a trial, to reduce missing data or improve data completeness. Activities relating to improving compliance/adherence to the intervention being evaluated were not included in the scope (3, 21). In this thesis we are focused on the trial design, planning, and consent stages. Throughout the thesis we refer to the trial design and planning stages, as the initial stages of the trial when the trial is being designed and planned, both before, and after, funding is received, and when the protocol is being developed. The consent stage is when potential trial participants are provided with information about the trial, to ensure they are adequately informed about the research, to assist informed decision making about trial participation (22). The clinical context we examined was broad, as we were interested in retention strategies used across a wide variety of different clinical contexts. The types of trials were limited to randomised controlled trials (RCTs), Phase II and onwards, including randomised pilot and feasibility trials and mixed-methods studies that included an RCT element. We excluded first in human and Phase I studies because they are not prone to retention issues compared to other trial phases. The participant population in the scoping review in Chapter Five, included all adults and children. For the PIL analysis (Chapter Six) we restricted the participant population to trials for adults with capacity to consent. For Chapter Seven interviews were also limited to adults with capacity to consent. The geographical setting of the thesis is primarily Ireland and

the UK. The scoping review, (Chapter Five), was not limited geographically, as our aim was to provide a broad overview of how retention strategies are reported in protocols globally. Due to the methods taken to conduct Chapter Four the context was limited to Ireland and the UK. For the PIL analysis in Chapter Six, our inclusion and exclusion criteria resulted in a sample limited to the UK. In Chapter Seven, interview participants were recruited from both Ireland and the UK.

1.6 Methodology and methods overview

Pragmatism is the research paradigm that underpins this thesis. The research paradigm of pragmatism allows the researcher to be flexible in their research approach and choose the most appropriate and suitable methods that best answer the research question (23, 24). Researchers who subscribe to a pragmatic approach to conducting research can use a combination of qualitative and quantitative methods to answer the research question (23). This is a multi-phase sequentially mixed-methods thesis, which contains discrete (mixed) chapters. The mixed-methods approach allows researchers to use both qualitative and quantitative data collection and analysis techniques to address the research question (25). Chapter Three details the paradigm of pragmatism and the research method chosen for each chapter. Table 1.1 provides a summary of the methods used to conduct the research presented in Chapters Four to Seven and how the chapters are linked. The results and findings from Chapters Four to Seven are integrated in Chapter Eight.

Table 1.1 A brief overview of the methods used in each chapter.

Chapter	Method	Chapter linkage
Chapter Four. Costing approach	Triangulation design; Data Transformation model. Qualitative (qual*) and quantitative (QUAN) data were collected. The qualitative data was transformed into quantitative data to create the costs of retention strategies (QUAN). This is a QUAN chapter.	The results informed the topic guide for interviews in Chapter Seven.
Chapter Five. Scoping review	A quantitative chapter. The excerpts extracted from the trial protocols were written text. We did not conceptualise this as qualitative data (Conceptualisation statement - Chapter Three, section 3.7). We classified this as quantitative data and thus a quantitative (QUAN) chapter.	The results and data extraction method informed the data extraction and analysis of results of the PIL analysis in Chapter Six. The results informed the topic guide for interviews in Chapter Seven.
Chapter Six. PIL analysis	A quantitative chapter. The excerpts extracted from the PILs, and corresponding protocols were written text. We classified this as quantitative data thus a quantitative (QUAN) chapter.	The results informed the topic guide for interviews in Chapter Seven. The sample of PILs created the sampling frame and sampling matrix to recruit potential interviewees in Chapter Seven.
Chapter Seven. Interviews	A qualitative (QUAL) chapter. One-to-one interviews with trialists. Data analysed using the Framework approach (Framework analysis - Chapter Seven, section 7.3.2).	The topic guide was informed by the results from Chapters Four to Six. The sampling frame and matrix for

		recruiting potential interviewees comprised of the PILs in Chapter Six.

*Lowercase indicates the secondary method used in the chapter, e.g., qual. Uppercase indicates the primary method used in the chapter, e.g., QUAN.

1.7 Thesis structure

This thesis consists of eight chapters, three of which are published peer-reviewed journal articles and one manuscript in preparation. Given the papers were published prior to the submission of this thesis, there is some repetition within the chapters. Within the manuscripts included in Chapters Four to Seven the additional/supplementary files are included in the thesis as appendices. The tables within the thesis are labelled in the following manner: Chapter One, Table One is Table 1.1, Chapter Four, Table Four is Table 4.4 etc. Within the Appendices the tables are labelled in the same manner with the letter 'A' included to clearly highlight the table is within the appendix, e.g., Appendix 6, Chapter 5, Table 1 is Table A5.1. Figures will follow the same labelling format. Tables and figures will be outlined in separate tables of contents.

Chapter One. An introduction to the thesis and structure of the thesis.

Chapter Two. An overview of the existing literature on retention of participants in trials which includes: the importance of retention in trials, the extent of the issue of poor retention, influences on participant retention, and how poor participant retention is currently managed in trials.

Chapter Three. The methodology employed to answer the research aim and objectives is outlined. It also provides a brief description of each method used in Chapters Four to Seven and how the chapters are linked.

Chapter Four. Published peer-reviewed article one: "How much is the lack of retention evidence costing trial teams in Ireland and the UK?" (18) which addressed research objective one.

Chapter Five. Published peer-reviewed article two: "How do trial teams plan for retention during the design stage of the trial? A scoping review" (19). This chapter addressed the second research objective.

Chapter Six. Published peer-reviewed article three: "Retention strategies are routinely communicated to potential trial participants but often differ from what was planned in the trial protocol; an analysis of participant information leaflets and their corresponding protocols" (20). This chapter addressed research objective three.

Chapter Seven. This manuscript is being prepared for submission. "Planning retention strategies in clinical trials; a qualitative interview study". This chapter addressed the fourth research objective.

Chapter Eight. The final chapter discusses the integrated findings from Chapters Four to Seven within the context of the existing literature. The chapter also outlines recommendations for practice and future research and highlights the strength and limitations of the research conducted in this thesis. The chapter concludes with my reflections on my PhD journey.

Chapter Two. Background

2.1 Introduction

This chapter provides an overview of the existing literature on the topic of participant retention in trials. The chapter begins with an introduction to trials and participant retention, then progresses to explore the magnitude of the retention problem, its implications for trials, and the causes of poor retention. It also outlines the current literature on retention strategies, their use, and how trial teams manage retention. The chapter concludes by highlighting the gaps in the literature, outlining the rationale for this thesis.

2.2 What are randomised controlled trials and why are they important

Randomised controlled trials (RCTs), herein referred to as trials, are near the top of the hierarchy of evidence, and are considered the 'gold standard' research design when evaluating the efficacy and effectiveness of healthcare interventions (1, 26-31). A trial is defined as a "prospective study comparing the effects, and value of intervention(s) against a control in human beings" (2:2). The history of the modern-day trial dates to the eighteenth century, when James Lind, a Scottish Naval Surgeon, evaluated different treatments for scurvy among 12 sailors using a control group. He provided them with varying treatments: oranges and lemons, vinegar, seawater, cyder, and elixir vitriol, to try to cure scurvy. He established with certainty, that oranges and lemons were effective when compared to the other treatments (2, 31, 32). Since the eighteenth century, trials have advanced significantly in their

design and conduct, with the introduction of randomisation, blinding, risk-based monitoring, and ever more complex and adaptive trial designs (2, 33-38). Most recently, since COVID-19, the idea of a decentralised trial has emerged, where trials have no physical 'home base' (39-41). What has not changed, however, is the fact that, in the past two centuries, trials have been the centrepiece of major advancements in medicine and healthcare (31, 35, 42). Trials that are effectively designed and conducted are the most rigorous method for identifying whether an intervention is effective and safe. This study design type, when compared to other epidemiological study designs, e.g., cross sectional design, case-control design, minimises the risk of confounding and other biases, which can negatively influence study results (1, 2, 35, 43). The results, therefore, generated through conducting trials, are likely to be closer to the true effect of the intervention, compared to the results generated from other types of study designs (1, 35, 44, 45). Trials that are conducted to the accepted standards are very important, as trial results contribute to changes in healthcare practice (2, 46-48).

Despite the evolution of trial design and conduct, there are, however, many ongoing issues that trialists continually face. One of these challenges, and the focus of this thesis, is retaining participants in trials.

2.3 Retention in trials: definitions

Retention refers to the process of keeping participants in a trial for the trials' full duration (3). Non-retention is defined as instances where participants are prematurely 'off-study', i.e., participants withdraw their consent or they are lost-to-follow-up, and as a result participant outcome data cannot be obtained (3, 21).

'Non-retainers' describe participants who are not retained. Trial non-retention is different to non-adherence to the trial intervention, which refers to the degree of compliance among participants to the intervention they have been assigned (3). Loss-to-follow-up, is when participants are unable to return a follow-up assessment (6), e.g., to a clinic visit, return a questionnaire, or do not continue to provide follow-up data. As a result, participants' outcome data may not be obtained by the trial team, unless routine data is being used. Consequently, the trial team does not know whether the outcome of interest has occurred among participants who are lost-to-follow-up (16). Attrition is another term used to describe the reduction in the number of participants in a trial as it progresses (10, 49). High rates of attrition mean low rates of participant retention and vice-versa.

Withdrawal means that participants can revoke their consent, stopping their participation in a trial at any stage, without providing a reason and without any negative consequences for the participants (50). The term 'withdrawal' is used to describe when a participant actively decides to no longer take part in all or some aspect of the trial and formally leaves. For example, participants may actively decide to stop taking the intervention treatment, but to continue to provide follow-up data, while others may want to discontinue with trial activities outright (50). There is ambiguity and interchangeable use of terms to describe when a participant decides to stop trial participation, such as 'withdrawal', 'loss-to-follow-up', 'off-trial', or 'drop-out'. There are now efforts to streamline and clarify the terminology used by trial teams (50).

This thesis describes retention strategies as activities/actions that are conducted for the purpose of retaining participants in a trial, to reduce missing data or improve data completeness. Activities to improve adherence or compliance to a trial intervention are not in scope (3, 21)(Scope of the thesis – Chapter One, section 1.5).

2.4 The importance of retention; the scale and impact of poor retention in trials

Participant retention in trials is extremely important to help ensure the success of the trial. Research on retention in trials has been identified as a priority, among professionals working in the field of trial methodology in the UK and Ireland (4). It has been estimated, that up to 50% of trials have loss-to-follow-up rates, i.e., the proportion of participants failing to provide valid primary outcome data, exceeding 11% (3, 5). Additionally, between 60-89% of all trials have some level of missing data (6). There is no universal agreement on acceptable rates of loss-to-follow-up. A general rule of thumb, however, assumes that rates less than or equal to 5% are deemed to have little consequence on the results of the study, however, rates higher than this, especially exceeding 20%, are considered to have implications on the validity of trial results (7, 43, 51). The statistical significance of trial results can hinge on very few events (8, 52). The overall result of the trial can change if the outcomes for participants who are not retained, are assumed in the opposite direction – a phenomenon called the Fragility index (8, 16, 52). In high impact journals, it was found that 25% of trials had a Fragility Index of three or less. This means that in 25% of trials, the results were no longer statistically significant if the

outcomes for three non-retained participants were changed, from not experiencing the primary outcome to experiencing the primary outcome (8).

Even low rates of loss-to-follow-up can cause issues for trial validity. If there is a higher rate of loss-to-follow-up in one trial arm, then the balance of baseline characteristics created via randomisation is altered and disturbed (6, 7). Bias is introduced when the characteristics of those lost-to-follow-up differ between randomised groups (49, 51). Without sufficient rates of participant retention, the trials' ability to answer the research question is jeopardised, loss-to-follow-up can impact: the power of the trial, the generalisability, the reliability, the confidence, and the integrity of the trial findings (6-10). Poor retention can contribute to the occurrence of both Type I and Type II error. Type I error occurs when there is a false positive result, wrongly concluding that one treatment is more effective than another, when it is not. Type II error occurs when there is a false negative result, wrongly concluding that a treatment is not effective when, in fact, it is effective (2, 45, 53, 54).

Poor participant retention rates can also have cost implications for the trial. The average cost per participant in a trial run by the UK's National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme, has been estimated to be £2,987 GBP (55). Other estimates for the UK are £7,890/€9,758 (56). These costs are higher in other countries such as Spain (€7,310) and Germany (€7,232) (56). Costs associated with loss-to-follow-up include costs linked to the administration and delivery of trial materials to participants lost-to-follow-up, as well as the data management of these participants. Funders can also incur costs,

such as costs spent on recruiting and retaining participants who end up being lost-to-follow-up, thus leading to lower return on investment. A case study of a trial, with a loss-to-follow-up rate of less than 10% showed, that despite the low rate of participant loss, the aggregate cost of participant loss-to-follow-up was £9,712 from the economic perspective of the trial team (57). Failing to retain participants has both direct and indirect cost implications for the trial. Not only is it costly to directly lose participants, it is costly to compensate for these losses by recruiting additional participants to the trial to account for non-retention (58).

Ethical concerns also arise when discussing poor participant retention rates in trials. The main concern is that sample sizes are inflated to compensate for expected rates of participant attrition, which are usually expected to be between 10-20% (5, 59). Increasing the number of participants recruited to the trial, exposes greater numbers to the risks associated with trial participation (11). These risks include: medication side-effects, discomfort caused by any medical tests/procedures, and risks associated with stopping existing treatments/medications. If recruited participants are not retained, the trial may become underpowered. Underpowered trials are problematic, and results may be less reliable and have limited generalisability to the wider population, as certain endpoints may have an insufficient sample size to detect important results (1, 60, 61). Participants in underpowered trials are exposed to the same risks, as participants in adequately powered trials, however, they have been exposed to the risks of participation without the opportunity for their trial contributions to lead to improved care or any benefit (1, 61-63). Additionally, poor retention contributes to increases in trial

duration (13). This increases the amount of time that participants are exposed to the risks associated with the trial.

In summary, poor participant retention rates can have serious implications for the results of the trial. Poor retention delays the delivery of research in practice and can inflate the costs of conducting the trial if it needs to be prolonged (13). This all contributes to research waste (13-15).

2.5 What influences participant retention in trials?

Identifying why participants leave trials, and proactively addressing the barriers to continued trial participation, may prevent participants leaving trials in the first instance, thus minimising the consequences of poor retention (17). Two qualitative evidence syntheses (QES) have explored participant reported reasons for trial non-retention, and have identified several factors that influence whether participants remain in the trial for its full duration (17, 64). Factors are broadly linked to either issues relating to the intervention that is being tested or due to wider trial processes, i.e., data collection and overall trial experience (17, 64).

Participants leave trials due to side-effects caused by, or concerns about, the trial medication being tested (17). Participants' changing health status can hinder ongoing trial participation. For example, when participants feel, and perceive themselves to be too ill to continue participation, they leave the trial. Contrastingly, when participants experience improvements in their health status, they feel there is no longer a need to participate as they have gained what they needed from the trial (17, 64). Struggling to come to terms with an illness diagnosis, and the associated emotional impact of the diagnosis, can also be the reason as to why participants no

longer remain in a trial (17, 64). The timing of data collection in conjunction with participants' health status at the collection time point influences completion of data collection. Additionally, dislikes towards aspects of the mode of data collection are factors as to why some participants no longer continue with clinic visits or return questionnaires (64).

The burden of trial participation is also a commonly cited reason for ceasing trial participation, e.g., financial issues related to trial participation such as, the need for childcare, the travel requirements, and time off work to attend clinic visits. Participants' personal life and existing life priorities often get in the way of continued participation, e.g., pregnancy, college, moving house, and carer responsibilities (64). Cultural influences need to be considered when conducting trials in low and middle income countries or among certain populations. Often cultural reasons, such as bereavement traditions and the role participants' hold within their family unit, impact participants' ability to attend follow-up visits. Barriers to continued participation such as work commitments may also be exacerbated in these contexts (64).

Additionally, when participants' expectations around care, support, and relations with the trial team are not met, this contributes to participants leaving trials (64). A key finding from the most recent QES, is often participants who leave trials are not aware that the trial team considers them to be 'lost-to-follow-up' (64). Participants may not have made an active decision to leave the trial, however, through missing data collection activities, participants have ended up being deemed 'lost-to-follow-up' by the trial team. These findings indicate that participants' consent may not be

fully informed, as participants are not completely aware of what is expected of them to remain in the trial. Poorly setting trial participants' expectations of what trial participation involves has been suggested to be a factor that influences retention, particularly when the trial information the participant receives and their trial experience does not match (65).

Making efforts to overcome and address these identified barriers to participant retention in trials, may help to facilitate improving retention rates.

2.6 Management of poor participant retention rates

2.6.1 Statistical considerations and assumptions about missing data

Trial teams take different approaches to tackling poor participant retention. Participant retention is commonly, indirectly, yet proactively, accounted for by the trial team at trial inception, when making statistical considerations and calculations regarding attrition rates. It is often standard practice for trials to inflate their sample size to account for anticipated participant attrition rates, which are usually between 10-20% (5, 59). Additionally, while calculating sample size the risk of both Type I and Type II error are adjusted for, and enough participants are recruited to the trial to prevent these errors (53). If, however, insufficient numbers of participants remain at the end of the trial, there is a risk of the trial becoming underpowered. The risk, therefore, of these errors occurring increases, as the sample size is no longer big enough to minimise these errors (53).

Poor retention is statistically dealt with reactively by making assumptions to adjust for missing data, i.e., making assumptions about the outcomes for the participants who have not provided outcome data. One could assume the following outcome

scenarios have occurred: the outcome did or did not occur for all those lost-to-follow-up, the outcome did not occur for all those lost in the treatment group but did occur for all those lost in the control group (and vice versa), or that based on existing information a proportion of those lost-to-follow-up in both the treatment and control group either experienced or did not experience the outcome (16, 66). Various other types of analyses can also be carried out to adjust for missing data, such as sensitivity analysis, survival analysis, and complete case analysis (9, 59, 66, 67). These methods are not without disadvantages. In five top medical journals, up to one-third of papers that reported significant results could lose their significance, if plausible assumptions are made for the outcomes of participants who are not retained in the trial. Large rates of loss-to-follow-up can lead to both overestimations, and underestimations of the treatment effect (6). The ideal solution is to retain trial participants (16), but for various reasons outlined previously, participants leave trials (17, 64). Mitigating this loss, however, needs to be prioritised.

2.6.2 Implementing retention strategies

To help optimise retention rates, trial teams need to be aware of, and pre-empt, any reasons that may deter ongoing participation. To address some of the barriers to retention, trials teams can implement strategies, ideally in a proactive manner, to attempt to enhance the retention of participants, thus, reducing missing outcome data. There is a plethora of retention strategies that trial teams implement. Clinical Trial Units (CTUs) in the UK have reported their most routinely used retention strategies and these have been ranked. The three most routinely used retention

strategies are: newsletters, a timeline of participant visits to sites, and inclusion of pre-paid envelopes for questionnaire return (68). Additionally, monetary incentives, organising and covering transport costs to clinics, sending out prompts and reminders for clinic visits, or questionnaire completion, offering different modes of data collection, and collecting data during routine care visits, are examples of strategies used to retain participants (3, 68). Building and maintaining good rapport with participants has also been reported as an important aspect of participant retention (69, 70). The most recent Cochrane review on strategies to improve retention in trials highlights, that variations and combinations of these different retention strategies have been used by trial teams to help encourage ongoing participation and reduce missing data (3).

2.7 Existing literature on retention strategies; Effectiveness and Perspectives

2.7.1 Retention strategies; evidence of effectiveness

The existing evidence base to support the use of retention strategies is limited. There is little evidence to show the top 10 most routinely used retention strategies in the UK, identified by Kearney et al., are effective (3, 68). For example, among these strategies, the use of newsletters, including pre-paid envelopes for questionnaire return, and the use of telephone prompts, have been evaluated (3). According to the Cochrane review of strategies to improve retention in trials, the certainty of evidence of the effectiveness of these three routinely used retention strategies, is rated ‘low’ or ‘very low’ when using GRADE, (Grading of Recommendations, Assessment, Development and Evaluations), to make the judgement. Evidence from the Cochrane review is largely based on studies that have

methodological limitations, causing the certainty of evidence to be rated ‘low’ or ‘very low’ when using GRADE (3). This limits the confidence in findings from the retention strategy evaluations.

There are currently no retention strategies with ‘high’-certainty evidence that can be used by trial teams to improve retention in trials. Three retention strategies: giving a pen at the recruitment stage of the trial, monetary rewards combined with a prompt/reminder, and the use of self-sampling kits, all have ‘moderate’ certainty evidence, assessed by GRADE, to show these retention strategies improve retention rates. Providing a participant diary in addition to usual follow-up, compared to usual follow-up alone, has ‘moderate’ certainty evidence to show it likely reduces participant retention rates. The remaining retention strategies in the review, (of which there are a total of 52 comparisons), are all supported by evidence that is deemed of ‘low’ or ‘very low’ certainty by GRADE (3).

The evidence is limited and uncertain as to whether retention strategies have any effects on participant retention rates (3). Additionally, there is uncertainty as to whether retention strategies are cost-effective. Evidence suggests, that providing participants with vouchers of up to £10 during follow-up could be cost-effective, likewise, providing trial-branded pens could be cost-effective, but this cannot be stated with confidence (71). Results are inconclusive as to whether activities such as pre-notification cards, electronic prompts, or unconditional monetary incentives (versus conditional), are cost effective (71). Therefore, not only is there a lack of evidence to show that retention strategies are effective at retaining participants, but

they also lack evidence of cost-effectiveness (3, 71). The implication is that trial resources are being wasted on implementing retention strategies, which may be both ineffective and an inefficient use of resources.

A key recommendation from the Cochrane Review is that, if trials are implementing retention strategies, these strategies are evaluated for effectiveness in Studies Within A Trial (SWATs)(3). A SWAT is a standalone, often randomised, study, embedded in a host trial to evaluate different methods of delivering or organising certain trial processes (72). SWAT evaluations are recommended because evidence is needed to know whether retention strategies work (3). As seen in the Cochrane review, single SWAT evaluations often do not have the ability alone to provide high-certainty evidence (3). Multiple evaluations of the same retention strategy are needed to reach a certain conclusion about the effectiveness of a retention strategy, this however, can take time. To overcome this obstacle, a group of researchers simultaneously conducted the same SWAT across eight host trials. The SWAT evaluated the impact of sending participants Christmas cards on the trial retention rate. Results show that, sending out Christmas cards to trial participants does not improve retention rates. This popular activity to encourage retention should now be avoided, as it does not improve retention rates and, is a waste of resources (73). While activities to enhance retention are being routinely used by trial teams, many more evaluations are needed to ensure we have confidence in the evidence to support (or not support) the use of retention strategies.

2.7.2 Retention strategies; trial participants' perspectives

While there are many retention strategies that can be used to promote ongoing trial participation, it is important to understand and consider participants' views on the use of these strategies. Research in this area has produced mixed results.

Trial participants find it helpful when the trial team provides pre-paid return envelopes, clear instructions, and questionnaires that are not too long. Supporting completion of data collection activities, for example receiving prompts or reminders from the trial team to complete questionnaires, is also deemed helpful by participants (65, 74). The tone of the reminder is important to make sure the reminder does not appear to be forceful (65). Participants have varied views on the use of monetary incentives/rewards to promote retention in trials. Some participants viewed incentives/rewards, such as vouchers, as acceptable and a nice gesture from the trial team. Others, however, believed incentives are not needed, deemed them as coercive, and felt they did not want to be bribed (65, 74). The use of non-monetary incentives were deemed suitable, such as offering additional health checks. Social incentives such as sending out a 'thank you' note were also deemed suitable (74). Offering a summary of findings once the trial is complete, was also suggested to be a motivating factor to complete the trial to the end (74). Building personal relationships with the trial staff appears to be important to participants, as not feeling supported by trial staff was cited as a reason for trial non-retention (74).

Clearly, trial participants have opinions on the use of retention strategies, and sometimes these opinions differ. Trial teams may be too reliant on generic

approaches to retention strategies in trials, whereby all participants receive the same strategy. Specific groups of participants within the trial may need to be targeted with different strategies to help encourage retention (75). There may be generational, or cultural differences, in terms of retention strategy preferences. Research synthesising individual participant data from multiple trials, has been used to identify groups of participants who are at higher risk of dropping out of trials. Results found that participants with increasing levels of co-morbidity, regardless of participant age or sex, are at higher risk of leaving a trial (76). For trials in these specific clinical contexts, more targeted work may be needed to ensure these high-risk groups remain in the trial.

2.7.3 Retention strategies; trial staff perspectives

Understanding trial staff perspectives on retention and retention strategies, is important to gain insights into how retention is prioritised, and perhaps how, and why, certain retention strategies are chosen.

Trial staff often believe that there is a stronger emphasis on participant recruitment, rather than their retention (70, 77). Trial performance, which influences funding, is based on recruitment rates and targets, resulting in a greater focus on recruitment compared to retention of participants during the initial stages of the trial (70). This emphasis on recruitment means that, recruitment responsibilities are often incorporated into staff roles. This, however, is less common for participant retention, therefore, trial staff may not be adequately informed about strategies that can be used to promote participant retention (77). As a result, retention may

end up being an afterthought for trial teams, despite the awareness among staff of the importance of retaining trial participants (70).

Trial staff members' views on trial retention strategies have been investigated previously (69, 70, 77). It is reported that staff are unsure how effective strategies are at improving participant retention rates (69, 77). Trial staff support the use of monetary incentives to promote retention. There are, however, concerns about the potential for coercion and bribery (69, 70). Trial staff report that non-monetary incentives could come across as patronising, not useful, and a waste of public resources, as these incentives are usually not the reason for participation in a trial. Staff feel the finances for non-monetary incentives could be better used to help subsidise the cost of participants attending follow-up visits (69). Staff understand the importance of being flexible to accommodate continued participation in trials, such as offering participants different methods, timings, or location of data collection, to facilitate retention. Staff highlight, however, that aspects of trial design, such as the design of questionnaires, and aspects of the consent process, often make them feel restricted in what can be done to facilitate continued trial participation (77).

The importance of building rapport and maintaining a relationship with trial participants to facilitate retention has also been reported (70, 77). Building relationships with participants takes time, and some trial staff feel these efforts to help retain participants may not always be valued by the wider trial team, and not acknowledged at a system level from funding bodies (70). Staff responsible for collecting follow-up data have stated, that sometimes their own morals combined

with the participants' health status, influence how comfortable they are to pursue participants for follow-up data (70). Clearly, there are barriers within individual trial teams as well as the wider research system that can hinder the retention efforts of staff. Furthermore, the Cochrane review of strategies to improve retention in trials found that, out of 69 evaluations of interventions to improve retention, only two evaluated interventions aimed at the trial staff involved in retention (3). Not targeting trial staff involved in efforts to improve participant retention rates, could be a missed opportunity to enhance retention.

2.8 Retention strategies; the evidence gap

There is a large amount of existing evidence regarding, the effectiveness of and perspectives on, retention strategies. There are, however, gaps in the literature when it comes to aspects around how much retention strategies cost, their planning, and the communication of these strategies.

2.8.1 Retention strategies; cost and resource evidence gap

Retention strategies are not without their costs and resource requirements. Depending on the size of the trial, number of sites and participants, and what retention strategy is implemented, the costs and resources required are likely to significantly vary. Costs and resources for strategies naturally include, the direct cost of the strategy, e.g., the value of the monetary incentive, but also any indirect costs required to implement the strategy, e.g., staff time. It is unclear if most retention strategies actually improve participant retention rates (3), thus, any associated costs and resources are potentially being wasted on retention strategies. Exactly just how

costly and resource intensive retention strategies are to trial teams is currently unclear in the literature.

2.8.2 Retention strategies; planning and communication evidence gap

There is limited evidence on whether retention strategies are prospectively planned, during the design and planning stage of the trial, i.e., during the trial design and protocol development stage, or whether trial teams reactively respond to poor retention, and plan and implement retention strategies once the trial is underway.

Some trial teams prospectively incorporate retention strategies into protocols and standard operating procedures. Often these strategies are related to trial processes, such as setting expectations and being clear about follow-up data collection (70). For other teams retention strategies are designed, and implemented only when needed, i.e., when retention rates become problematic (70). Informal activities, such as building rapport and maintaining relationships with trial participants, can be difficult to report. This is often the reason why these activities are not formally planned, outlined in trial documents, or evaluated (69, 70). The issue and implications of poor participant retention are well-known; therefore, it should not be a surprise to trial teams that they may struggle to retain participants. As a result, it should be expected that ways to mitigate barriers to continued participation and retention strategies are proactively considered and designed during trial design, planning, and protocol development, to ensure that trial resources are correctly allocated to these activities.

Neither the U.S. Food and Drug Administration (FDA) (78) or ICH-GCP, (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP)), guidelines (79) state requirements for retention strategies to be included in trial protocols. The FDA, however, acknowledges the importance of retention of participants and states that poor retention needs to be tackled by improving aspects of trial design and trial conduct (78). The Declaration of Helsinki recommends that protocols should include information on incentives for participants (22). The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidelines outline in item 18b that the following information should be included in trial protocols; "Plans to promote participant retention and complete follow-up including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols" (21:3). The Health Research Authority also recommend the inclusion of retention strategies in their example protocol template for Clinical Trials of Investigational Medicinal Products (CTIMPs), and recommends the use of the SPIRIT 2013 guidelines when writing trial protocols (80). It is not mandatory to abide by and endorse these recommendations or follow the SPIRIT 2013 guidelines. Whether this guideline is followed, and strategies to promote participant retention are proactively developed, at the planning stage of the trial and communicated in protocols is unclear within the literature.

Minimal existing evidence shows that general information on the topic of trial retention is often poorly and infrequently communicated, both in participant information leaflets (81) and in trial recruitment consultations (12). During the informed consent stage there is limited information on whether retention strategies

specifically are communicated to potential trial participants. According to the Declaration of Helsinki, during informed consent participants "must be adequately informed in plain language of the…incentives for participants" (22:4). In terms of participant information leaflets (PILs), there are ethical obligations to include information on monetary compensation and any other forms of compensation that the trial is planning to provide. There are also strong recommendations to outline retention strategies, such as providing participants with supports such as, covering costs of travel, meals, child-care, and compensation for loss of earnings, to facilitate ongoing trial participation. These plans should be included in PILs if the trial team are intending on using such strategies (79, 82). Apart from these forms of compensation there are a plethora of strategies that can be used to promote participant retention, e.g., prompts, reminders, newsletter, different methods of follow-up completion, non-monetary incentives etc. (3). Whether retention strategies are routinely outlined in participant information leaflets is currently unknown.

2.9 Rationale for this thesis

This chapter defines what we understand by retention in trials, outlines the issues associated with poor participant retention, how retention is typically managed by trial teams, and provides an in-depth review of the existing literature on retention strategies. There are several gaps in the literature in terms of the costing, the planning, and the communication of retention strategies in trials. The research presented in this doctoral thesis aims to generate evidence to address these gaps, and develop a better understanding of the costing, planning, and communication

processes associated with developing and implementing retention strategies, during the design, planning, and consent stage of a trial. This thesis will contribute evidence to help answer PRioRiTy II question 10; “How should people who run trials plan for retention during their funding application and creation of the trial (protocol development)?” (4).

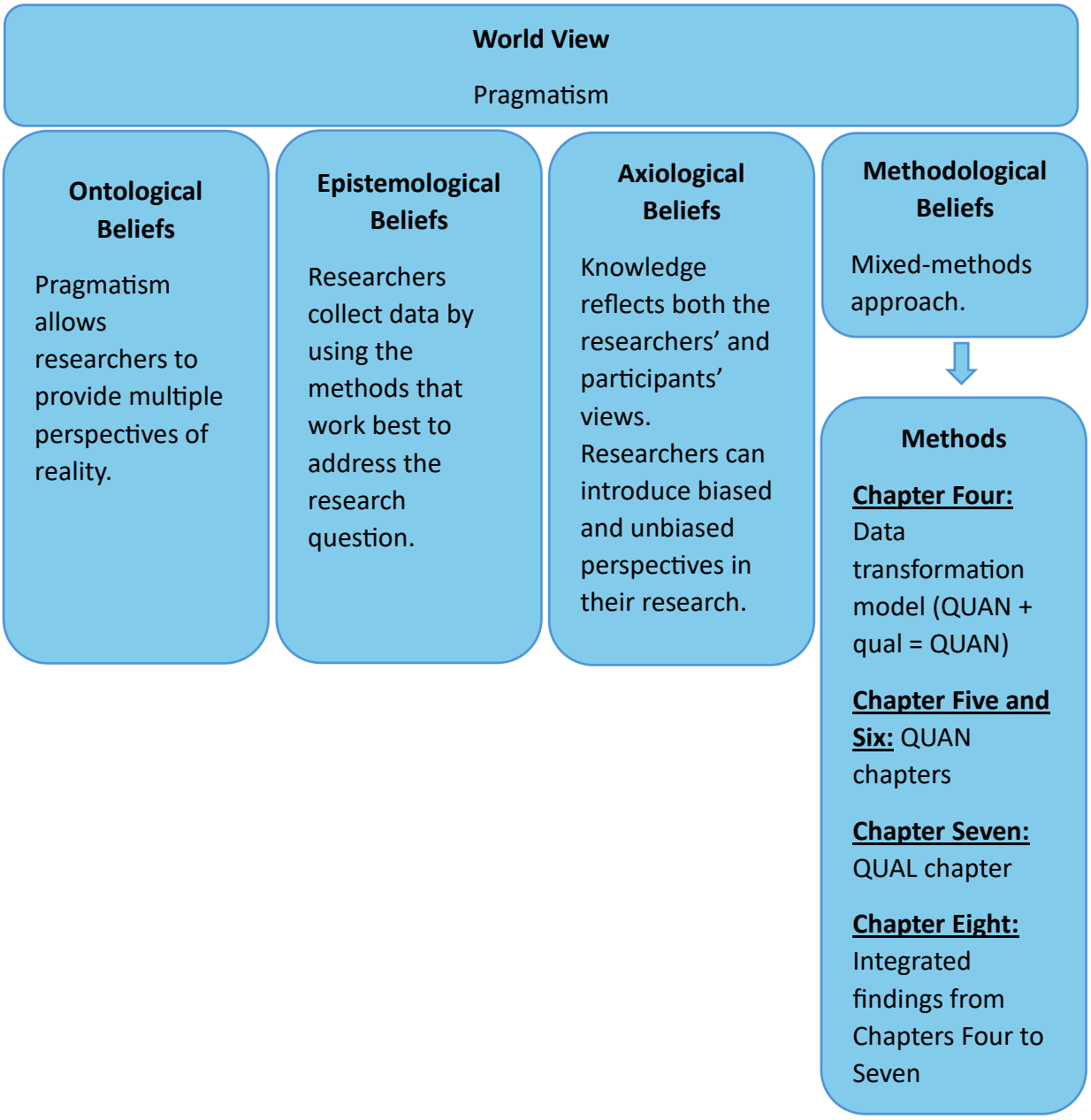
Chapter Three. Methodology

3.1 Introduction

This chapter outlines the research paradigm that underpins the thesis, and the methods selected for Chapters Four to Seven. In short, the paradigm of pragmatism and a mixed-methods approach was taken. The chapter firstly outlines the paradigm of pragmatism and its philosophical components. The chapter then provides an overview of mixed-methods research, and details the methods chosen for Chapters Four to Seven.

A brief overview of the research paradigm and methods chosen for Chapters Four to Seven are shown in Figure 3.1.

Figure 3.1. An overview of the research paradigm of pragmatism and the mixed-methods research approach.[1] [2]



[1] *Adapted from; 83. Creswell JW, Plano Clark VL. Designing and conducting mixed methods research. Thousand Oaks, Calif;London;: SAGE Publications; 2007. and 23. Creswell JW, Poth CN. Qualitative inquiry and research design: Choosing among five approaches: Sage publications; 2016.*

[2] *Uppercase letters (QUAN/QUAL) indicate the primary method used in the chapter; the lower-case letters (quan/qual) indicate the secondary method used in the chapter. (+) indicates the methods used occur at the same time. The arrow indicates the methods occur in sequence. 84. Morse JM. Approaches to qualitative-quantitative methodological triangulation. Nursing research. 1991;40(2):120-3..*

3.2 Philosophical underpinning of the research

Researchers are encouraged to situate their research within a selected research paradigm (23). In simple terms, a paradigm is a way of viewing the world (85). Paradigms shape how problems are viewed, how research questions are formulated, and the approaches that are used to answer research questions. A paradigm consists of the following philosophical assumptions about reality and knowledge: ontology (the nature of reality), epistemology (the relationship between the researcher and what is being researched), axiology (the nature of values), and methodology (the process of conducting the research) (23-25, 83, 85, 86). Each research paradigm has different assumptions about reality and knowledge, and this is reflected in the methodological approaches and methods taken to conduct research (87).

3.3 The paradigm of pragmatism

The paradigm of pragmatism arose to try and end what has been called the 'paradigm war' between the positivist paradigm (quantitative research methods) and the interpretivist paradigm (qualitative research methods)(88-90). Philosophers who advocate for pragmatism argue that a traditional singular research paradigm view, (either being a positivist or an interpretivist), is insufficient and restrictive when it comes to conducting research. Instead these philosophers believe a research paradigm that allows for a combination of paradigm views, and research methods, should be used to gain a better understanding of the research problem (89).

The paradigm of pragmatism is not tied to a specific philosophy. It is aimed at research practicality, on the problem being studied, and the questions being asked about this problem, instead of focussing on the philosophical positioning and the nature of the research methods (23, 83, 85, 89). Researchers, therefore, in practice are focused on the practical implications of the research. Researchers can select research methods that best meet the needs and purposes of the research they are conducting, rather than having to select a singular approach to conducting their research (23, 24).

3.3.1 Philosophical components of pragmatism

3.3.1.1 Ontology

The paradigm of pragmatism is not tied to one system of reality (23). The two traditional stances on reality are that; there is one singular reality which is endorsed by positivist researchers, or, that there are multiple versions of reality which is the view endorsed by interpretivists (83, 91). Researchers that endorse pragmatism believe that reality is not fixed, and cannot be determined outright (92). There can be both singular and multiple realities, but pragmatists strongly believe that reality is what approach works to address the research question (91, 92). Pragmatism allows the researcher to reject the two traditional views of reality (92). Pragmatism allows researchers to provide multiple perspectives of reality, as the researcher can use both qualitative and quantitative data within a singular or across a group of linked studies (83). Due to this ontological stance, researchers who adopt a pragmatic approach to conducting their research choose the methods that best address the research question (23).

3.3.1.2 Epistemology

According to Lincoln and Guba, epistemology, encapsulates questions such as; how do we know what we know, what is the truth, and what is the nature of the relationship between the knower and what can be known (93, 94). More simply, "what is the relationship between the researcher and what is being researched?" (83:24). Researchers who are positivists will collect data objectively using measurement tools, whereas interpretivists will try to become close to the participants being studied to understand the context of what participants are describing (23, 83). Pragmatists believe knowledge is both constructed, and based on the reality of the world we live in and our experiences, i.e., knowledge is based on interactions between people and their environments (24, 90). Researchers who take a pragmatic approach to research do not value one type of knowledge over another, this means the researcher must carefully consider which type of knowledge best answers the research question (24). In order to gain that knowledge, again a practical stance is taken, e.g., researchers collect data by using the methods that work to address the research question (83).

3.3.1.3 Axiology

Axiology refers to the role that values play in research. It encourages researchers to consider the role their own values and beliefs have in the design, conduct, and interpretation of findings. Positivists aim for objectivity in their research, to remove subjectivity and the chance of bias. Interpretivists are aware that their research is more open to subjectivity and bias (95). Due to the nature of pragmatism, which

can allow researchers to use both quantitative and qualitative research methods, researchers can introduce both biased and unbiased perspectives in their research (83). When conducting research, inevitably there will be some sort of unavoidable bias that is introduced by the researcher, however, this is not necessarily a weakness, as a researchers' values, experiences, and beliefs may help to achieve the research objectives, but importantly not all forms of bias are acceptable (91). Being reflexive about values and beliefs, allows for transparency and, allows the readers of the research to understand the lens in which the research has been conducted (96).

3.3.1.4 Methodology

Methodology refers to the principles, procedures, and practices that govern the research being conducted. It refers to the overall process of carrying out the research from the planning stages through to the dissemination of the findings (97). Pragmatic researchers are able to select research designs and methods that are most appropriate to answer the research question (92). For this thesis, we have chosen a mixed-methods approach.

Thashakkori and Teddlie are two of the main researchers that linked pragmatism to mixed-methods research. They advocate that mixed-methods research approaches can be used, and that a practical and applied research philosophy should guide methodological choices (83, 98). The research paradigm of pragmatism, therefore, supports the use of mixed-methods research (83).

3.4 Mixed-methods research

Mixed-methods research positions itself between the quantitative purists (positivists) and the qualitative purists (interpretivists), offering an alternative approach to research that values both objective and subjective knowledge. It is recognised as the third research paradigm (25, 90, 99, 100). Using a mixed-methods approach allows researchers to use both qualitative and quantitative data collection and data analysis techniques in combination to address the research question (100). The mixed-methods approach draws on the strengths, and minimises the weaknesses, of quantitative and qualitative methods by using both within individual and/or across a group of research studies (90). When taking a mixed-methods approach, it is important that the data is mixed during the research so that both the quantitative and qualitative aspects of the data form a more complete and comprehensive picture of the research topic/problem than they do individually (25, 83).

Within the field of mixed-methods research there are many different definitions as to what taking a mixed-methods approach means and how mixed-methods research should be conducted (90, 100, 101). The definition that has been selected for this thesis is the definition put forward by Creswell and Clarke (83);

> *"Mixed methods research is a research design with philosophical assumptions as well as methods of inquiry. As a methodology, it involves philosophical assumptions that guide the direction of the collection and analysis of data and the mixture of qualitative and quantitative approaches in many phases in the research process. As a method, it focuses on collecting, analysing, and mixing both quantitative and qualitative data in a single study or series of studies. Its central premise is that the use of quantitative and qualitative approaches in combination provide a better understanding of research problems than either approach alone" (83:5).*

There are many ways of mixing the data throughout the research process depending on the approach taken (83). Due to the complex nature of mixed-methods research, a notation system was developed by Morse (84) to visually aid the understanding of the mixed-methods nature of the research. Quantitative and qualitative research are shortened to 'quan' and 'qaul'. The primary method being used in the research is notated using all uppercase letters, e.g., QUAN/QUAL. The lowercase (quan/qual) indicates this is the secondary method used within the research. The plus (+) symbol notates that the methods are used at the same time and the arrow symbol means the methods are used sequentially (83, 84). This notation system is used throughout the thesis. Due to the complexity of research problems and the research world becoming more interdisciplinary, the need to collect multiple forms of data and conduct mixed-methods research has become increasingly popular and important (83, 90, 102).

3.5 Methods

We chose a mixed-methods approach for this thesis, to gain an in-depth, comprehensive, and nuanced understanding of the costing, planning, and the subsequent communication, to both trial teams and potential trial participants, of retention strategies during the trial design, planning, and informed consent stages. Taking only a qualitative or quantitative approach would not provide adequate information to address the research aim in a well-rounded manner. This thesis is a multi-phase sequentially mixed-methods PhD, which contains discrete (mixed) chapters, with the overall findings being synthesised together.

Different methods were used for the individual studies, Chapters Four to Seven, and were chosen to best answer the research question. An overview of the different research methods used in each chapter and how the chapters are linked is presented in Figure 3.2. A detailed description of the methods used are reported in full in Chapters Four to Seven.

3.6 Integration of findings

Integration is an important aspect of mixed-methods research, as it allows for a more holistic and comprehensive understanding of the research findings (102). While the methodology for integration varies (83, 102-105), the most suitable for our research is the Triangulation protocol method. The Triangulation protocol method is used during the interpretation stage of the research, after different datasets have been analysed separately, their findings are then compared to see if the findings converge (are the same/similar), offer complementary information, or appear to be contradictory (102, 105). We have followed the guidance outlined by Farmer et al. (105) to provide an integrated interpretation of findings, in this multi-phase sequentially mixed-methods thesis, that contains discrete (mixed) chapters, to gain a more complete picture of the research topic (102, 105, 106). Chapter Eight discussed the integrated findings from Chapters Four to Seven.

3.7 Conceptualisation of qualitative data

In this thesis, we have conceptualised qualitative data (QUAL) in the traditional sense, i.e., participant reported information from one-to-one interviews, focus groups, or open-ended research questions from surveys/questionnaires. Written information in trial documentation was not conceptualised as qualitative data, we conceptualised this as quantitative data, as it was not participant reported.

3.8 Chapter Four. Costing approach

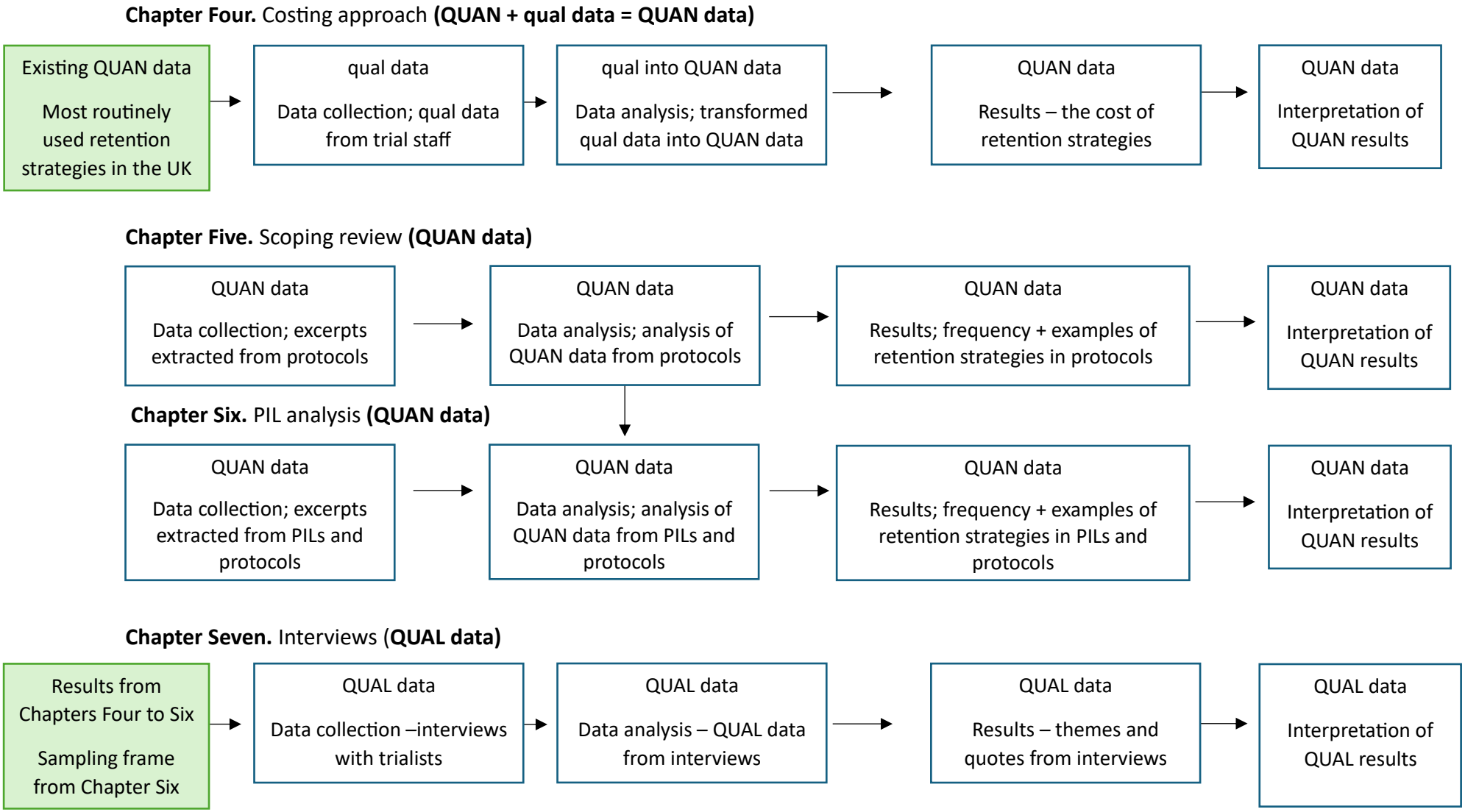
Chapter Four follows the Triangulation Design: Data Transformation model, transforming qualitative data into quantitative data (83). This work involved the simultaneous, yet separate, collection of experiential data from trial personnel (qual data) and the collection of pre-existing quantitative data (ranking of the most routinely used retention strategies in Clinical Trial Units in the UK (68)) (QUAN data). During the analysis, the qualitative data (qual) was transformed into quantitative data (QUAN data) to create the quantitative results (QUAN), the cost of routinely used retention strategies. The results of this chapter informed the topic guide for the interviews with trialists conducted in Chapter Seven.

3.9 Chapters Five, Six and Seven. Scoping review, PIL analysis, and interviews

Chapters Five to Seven are combined in accordance with the Triangulation Design: Convergence model (83, 107). These chapters are mixed at various levels. The data extraction used in the scoping review, (Chapter Five), informed the data extraction and analysis of the PILs in Chapter Six. The results of Chapters Five and Six informed the topic guide for the interviews conducted in Chapter Seven. The sample of PILs

analysed, in Chapter Six, created the sampling frame and matrix to recruit potential interviewees in Chapter Seven. Data in each chapter was collected and analysed separately on the topic of planning and communicating retention strategies in trials. Chapters Five and Six were QUAN chapters. Chapter Seven was a QUAL chapter. The results across Chapters Four to Seven were then integrated, helping to provide a more well-rounded understanding of the separate results (Chapter Eight).

Figure 3.2. Research methods used for Chapters Four to Seven.



3.10 Reflections and reflexivity

At the end of Chapters Four to Seven I have included my reflections and what I have learned from conducting each chapter. In Chapter Seven I have outlined my position within the research, and how this may have influenced the data collection, analysis, and interpretation of the interview data.

3.11 Ethical considerations

Ethical approval was required for the one-to-one interviews (Chapter Seven). Accordingly, ethical approval was obtained from the Social Research Ethics Committee at University College Cork (SREC) (Record number: 2023:149).

Chapter Four. How much is the lack of retention evidence costing trial teams in Ireland and the UK?

4.1 Introduction

This chapter presents a costing approach to generate the costs of the most routinely used retention strategies in the UK. The chapter starts with the rationale for the chapter. The published paper is then presented. Following this, my reflections and a summary of key points are outlined.

4.2 Rationale for the costing chapter

Participant retention is a major issue for trials. These issues not only include implications for the results of the trial but also include implications for the cost of the trial (6, 8, 9, 55). It is estimated that the cost per participant in trials run by the UK's National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme is £2,987 GBP (55). Other estimates indicate the average cost per participant in the UK is £7,890 (56). Even trials with loss-to-follow-up rates less than 10% can still incur significant opportunity costs (57). Usually, to compensate for poor retention rates, trials will inflate their sample size to counterbalance an expected 10-20% attrition rate (5, 59). This means trial funders are spending more money on recruiting extra participants to account for poor retention rates (58). Additionally, poor retention can mean trials need to be extended which further increases the costs associated with running the trial (13).

One way of trying to improve participant retention is to use retention strategies. These are activities that are conducted for the purpose of retaining participants in a

trial, to reduce missing data or improve data completeness. Retention strategies, however, have little high-quality evidence to support their use (3). Trial teams are forced to choose retention strategies that have a large amount of uncertainty regarding their effectiveness on improving participant retention rates (3). Additionally, retention strategies require development costs and/or initial capital cost and need further trial resources to be implemented, as the trial is ongoing, in the form of staff time and ongoing implementation costs. The lack of high-quality evidence to support the use of retention strategies, is likely to be costly to trial teams and trial funders (55, 56, 58). Exactly how costly, in terms of trial resources, retention strategies are, is currently unclear.

The aim of this costing approach was to estimate how much retention strategy implementation is costing trial teams in Ireland and the UK. In the context of the thesis, this chapter addressed the first research objective, *'to estimate how much routinely used retention strategies might be costing trial teams in Ireland and the UK'.* This chapter is a gateway to the thesis, identifying the resource wastage on retention strategies, and the need to establish how these strategies are planned and communicated in trials.

4.3 Thesis Paper One

Start of Publication

Title: How much is the lack of retention evidence costing trial teams in Ireland and the United Kingdom?

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Abstract

Background

Evidence to support the use of many retention strategies in clinical trials is lacking. Despite this, trial teams still need to have some form of retention strategy in their trials to try and avoid high attrition rates. This study aimed to estimate how much this lack of retention evidence might be costing trials in Ireland and the UK.

Methods

We selected the top ten most routinely used retention strategies by Clinical Trial Units (CTUs) in the UK and made assumptions as to how each of these strategies was most likely to be implemented and the costs involved in doing this. We applied our costing model to a hypothetical trial scenario in both Ireland and the UK as well as to three published trial protocols. We developed the costing model and calculated the costs in Microsoft Excel.

Results

Retention strategies were often poorly specified, meaning we had to make assumptions about implementation and in some cases about the strategy itself. Based on our assumptions, some retention strategies can be extremely expensive; some of the costliest strategies included “data collection scheduled with routine care” (€900 - €32,503.25), “a timeline of participant visits for sites” – with integrated participant reminder (€304.74 –€14,803.70), and “routine site visits by CTU staff” and “investigator meetings face to face”, both costing (€777.67 - €14,753.48). Others such as “telephone reminders for questionnaire response” (€34.58 - €568.62), “a timeline of participant visits for sites” – site reminder alone

(€79.18 - €112.23), and “targeted recruitment of sites/GPs” (€30 - €1,620) were less costly compared to the other strategies.

Discussion

The resources invested in the use of some retention strategies may outweigh known or imagined benefits on retention. Where benefits are currently unknown, evaluation should be a priority.

Conclusion

More evaluation of the effectiveness and cost of trial retention strategies is needed to avoid widespread use of strategies that are both expensive and ineffective.

Keywords: randomised trials, trial retention, retention strategies, cost

Background

Randomised trials can be no better than the data they collect. If retention has been poor, in other words, data are missing for many participants, then the usefulness of the trial starts to come into question. Patchy datasets can lead to a trial becoming underpowered for its primary outcome and very underpowered for its secondaries, which were anyway probably not part of power calculations. Participants who do not provide data may differ to those who remain (10, 108, 109), making interpretation harder. It might be possible to overturn trial conclusions by simply imagining that the results from missing participants had gone against those conclusions (8). In short, potential users of the trial results now have doubts and doubt undermines trials.

Poor retention is a major cause of research waste as it can delay the implementation (or removal) of healthcare interventions (13), as missing primary outcome data can reduce the power of the study to detect significant findings (68). Poor retention may also increase trials costs (13, 110). A recent prioritisation exercise (PRioRiTy II) identified 20 priority unanswered research questions for research in trial retention, including questions around what motivates participants to stay involved, how to provide information and how what is done at recruitment might influence retention (4).

Although there are plenty of unanswered research questions in trial retention, trial teams nevertheless have to use some form of retention strategy in their trials. In the UK, Clinical Trials Units (CTUs) registered with the UK Clinical Research Network use many approaches and Kearney et al. asked them what these strategies were. Thirty-three (70%) CTUs responded outlining commonly used strategies (68). While

evidence is available for some strategies, none have compelling evidence of benefit (3).

The current study aimed to estimate how much this lack of retention evidence might be costing trials in the UK and Ireland. When referring to retention strategy we mean an activity that is done with the explicit aim of improving trial data completeness and/or quality. Trialists have many options for how to do this but we focus on estimating the costs of the ten retention strategies used most often by UK CTUs as identified in the study by Kearney and colleagues (68).

Methods

The top ten most routinely used retention strategies used by UK CTUs are shown in Table 4.1, along with the percentage of CTUs that use this strategy routinely (68) and the evidence of benefit provided by the most recent Cochrane Systematic Review (3). The top ten strategies were identified in a survey of UK CTUs (68), where respondents outlined the strategies they use to improve retention. However, the responses provided to Kearney and colleagues did not contain detail as to how trial teams implement these strategies. We extracted as much information as possible from the paper and Dr Kearney provided additional information where available, but we were nevertheless left to make many assumptions as to how retention strategies were implemented, particularly for the strategy “a timeline of participant visits”, where the very nature of the strategy itself remained unclear.

Table 4.1. Top 10 most used missing data strategies by CTUs in the United Kingdom (68).

	Missing data strategies	**Number (N) and percentage of CTUs that routinely use strategies**	**Evidence of reported evaluations into their effectiveness according to the most recent Cochrane Systematic Review (3).**
1	Newsletters	N=23, 70%	"The evidence is very uncertain about the effect on retention of including a newsletter compared to no newsletter; RD = -0% (95%CI, -4% to 3%); GRADE; very low", evidence is based on four studies from various disciplines, (n=5622)
2	A timeline of participant visits for sites	N=19, 58%	No evidence
3	Inclusion of prepaid envelopes (questionnaires)	N=19, 58%	"Various strategies compared to usual practice for return postage, such as free post versus second class stamp, high priority mail stamp versus usual postage and personal form may increase retention slightly: RD= 4% (95% CI -0% to 9%), GRADE; low". Evidence is based on three studies, (n=1543)
4	Telephone reminders	N=18, 55%	"Telephone reminders compared to postal reminders may result in a large increase in retention, evidence is from one study (111) (RD= -19% (95%CI -33% to -5%) GRADE low, (-1 level: study limitations unclear risk of bias; -1 level: imprecision single study, n=148)" "Telephone reminders compared to usual follow-up[1] may result in little or no difference in retention, (smoking cessation(112) (RD =-1% (95% -18% to 15%) GRADE low, (-2

			levels: imprecision-single study, n = 127; wide CI crossing RD = 0))" [2]
5	Data collection scheduled with routine care	N=18, 55%	No evidence
6	Site initiation training on missing data	N=18, 55%	No evidence
7	Investigator meetings face to face	N=17, 52%	No evidence
8	Routine site visits by CTU staff	N=15, 45%	No evidence
9	Targeted recruitment of sites/GPs	N=15, 45%	No evidence
10	Flexibility in appointment times	N=15, 45%	No evidence

Notes: GRADE, grades of evidence; Low certainty: the confidence in the effect estimate is limited; the true effect may be substantially different from the estimated effect. **Very low certainty:** very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of the effect (3).[1]From this single study "usual follow-up" is as follows; "We followed-up participants by any of the means they agreed to at the start of the trial, including post, e-mail, and telephone calls to mobile, home, or work numbers (113). We used all the effective evidence-based methods that were feasible to introduce into the procedures of the trial (113), as identified in the systematic reviews by Edwards *et al*. and Hoile *et al*. (114). These included monetary incentives, posting correspondence by recorded delivery, pre-notification, follow-up contact, unconditional advance cash incentives, short, concise questionnaires, duplicate questionnaires sent at repeat follow-up attempts, mentioning that commitment to the trial implied an obligation to respond, mention of university sponsorship, prepaid return envelopes with stamps, an assurance of confidentiality, and first-class outward mailing" (112) . [2]We present all evidence regarding telephone reminders however we chose to select telephone reminders compared to usual follow up in Table 4.4 to calculate cost per participant retained as we believe it is the most relevant comparison for trial teams.

To estimate the cost of the retention strategies, we made assumptions as to how each of these strategies would be implemented and the costs involved. We called this our costing model for each strategy. We contacted experienced clinical trial professionals such as trial managers, clinical research nurses, and professionals working in clinical

research facilities in the UK and Ireland for information to inform our costing models. We identified these individuals through workplace inquiries and personal knowledge of suitable personnel to answer specific costing queries.

We applied our costing models to each of the ten strategies in two ways. First, we created a hypothetical trial scenario (Table 4.2). We made assumptions about how the retention strategies would most likely be conducted and then calculated and applied the costs of running each of the ten retention strategies in both Ireland and the UK. The costing models for some strategies differed slightly between Ireland and the UK due to differences in the responsibilities held by staff members involved in running clinical trials and differences in how some retention strategies are conducted in each country (See Additional File 1 for full details).

Table 4.2. Hypothetical trial characteristics.

Trial Characteristics	
Number of participants	500
Number of sites	10 sites
Duration of participant follow-up	1 year
Number of trial visits	3
Data collection	1 questionnaire is sent out: three trial visits
Location of the trial	Ireland / United Kingdom

Secondly, we chose three trial protocols published in the journal *Trials* between 2016 and 2020. We chose these three for convenience reasons: they fit well into our costing model well, represented trials of various sizes and the trials had different characteristics. We used these to estimate the cost associated with each retention strategy in a “real-life” randomised controlled trial. Our costing assumptions for the

ten retention strategies were applied to each of the three trials, regardless of whether the trial protocols explicitly stated that these strategies were used.

An example costing model for both a hypothetical trial and published trial protocol (115), with costs and assumptions, is shown in Table 4.3. A full description of the costing models and the assumptions we made to create them, together with details of the three trials selected from the *Trials* journal are outlined in Additional File 1.

Table 4.3. Assumptions and costings for "Newsletters" – Hypothetical trial Ireland and the MAMI trial (115).

Hypothetical trial (Ireland)	
Strategy 1	**Assumptions made**
Newsletter	→ 2 newsletters sent out over the 1-year trial period. → 5 hours to develop the newsletter. → 2 hours work to electronically send out 500 newsletters. → 8 hours to manually post out 500 newsletters. → Stamp costs in Ireland = €1.10. → Mailchimp subscription is €151.78 for 1 year. → Developing the newsletter carried out by a Research Nurse (€54 hourly rate) → Emailing/posting out the newsletter carried out by a Research Assistant (€25 hourly rate)
Costings	**Costings** **Staff costs for developing and manually posting out the newsletter:** → Developing newsletter: 5 hours x €54 = €270.

	→ Manually posting newsletter: 8 hours x €25 = €200 → Total staff costs = €470 **Postage (stamp) costs:** → 500 x €1.10 = €550 **Total costs: Staff hours plus postage costs x frequency of activity:** → €1020 x 2 = **€2040** **Staff costs for developing and electronically posting out the newsletter twice a year:** → Developing newsletter: 5 hours x €54 = €270. → Electronically posting newsletter: 2 hours x €25 = €50. → Total staff costs = €320. **Electronic postage costs:** Mailchimp = €151.78 **Total costs: Staff costs x frequency of activity plus flat rate of Mailchimp:** → €320 x 2 = €640 plus €151.78= **€791.78**
MAMI trial (Trials Journal)	
Strategy 1	**Assumptions made**
Newsletter	→ 4 newsletters sent out over the 2-year trial period → 5 hours to develop the newsletter. → 0.24 hours to electronically send out 60 newsletters (2 hours work to electronically send out 500 newsletters, therefore 60 newsletters is 0.24 hours) → 0.96 hours of work to manually stuff and post 60 newsletters (8 hours to manually post out 500 newsletters, therefore 60 newsletters take 0.96 hours) → Stamp costs in the Netherlands = €0.96 → Mailchimp subscription for two years is €303.56 (€151.78 for 1 year) → Developing the newsletter carried out by a Research Nurse (€30 hourly) → Emailing/posting out the newsletter carried out by a Research Assistant (€17 hourly)

Costings	**Costings** **Staff costs for developing and manually posting out the newsletter twice a year:** → Developing newsletter: 5 hours x €30 = €150 → Manually posting newsletter: 0.96 hours x €17 = €16.32 → Total staff costs = €166.32 **Postage (stamp) costs:** → 60 x €0.96 = €57.60 **Total costs: Staff hours plus postage costs x frequency of activity:** → €223.92 x 4 = **€895.68** **Staff costs for developing and electronically posting out the newsletter twice a year:** → Developing newsletter: 5 hours x €30 = €150 → Electronically posting newsletter: 0.24 hours x €17 = €4.08 → Total staff costs = €154.08 **Electronic postage costs:** Mailchimp = €151.78 x 2 = €303.56 **Total costs: Staff costs x frequency of activity plus flat rate of Mailchimp:** €154.08 x 4 = €616.32 plus €303.56= **€919.88**

In addition to the ten most routinely used retention strategies, we further elaborated and included additional actions that are likely to be carried out by trial units when trying to retain participants that were not specifically outlined by Kearney et al. (68).

These assumptions reflect actions that are likely to be conducted by trial teams during the implementation of the listed strategies. For example, under the strategy "inclusion of pre-paid envelopes (questionnaires)" along with sending out pre-paid envelopes to enhance questionnaire response we also assumed a reminder schedule would be sent out to 30% of participants who initially did not return the questionnaire. A full list of the additional assumptions can be found in Additional File 1.

Where there was evidence of effectiveness of the retention strategy, we calculated the cost per participant retained. For example for the ease of calculation, we calculated the cost per participant retained by using pre-paid return envelopes based on a 4% benefit (3). In the Irish hypothetical trial scenario 4% of 500 participants is 20. The total cost of "inclusion of pre-paid envelopes (questionnaires)" was €1,690. Therefore, the cost per participant retained was €84.50.

All our calculations were done within Microsoft Excel. Additional File 2 contains our Excel spreadsheet with our cost calculations. For ease of comparison all our costs are presented in Table 4.4 in both EUR and GBP based on exchange rates of 1 GBP = 1.16279 EUR,

1 EUR = 0.860001 GBP, 1 USD = 0.843802 EUR and 1 USD = 0.725647 GBP,

taken from Xe Currency Converter - LIVE Foreign Exchange Rates on the 7th of September 2021.

Results

We discussed the top ten most routinely used trial retention strategies in the UK and made assumptions as to how each of these strategies would be implemented and the costs involved. We applied this costing model to our hypothetical trial scenario, (1-year participant follow-up, 10 sites, 500 participants, 3 trial visits, 1 questionnaire sent out) in Ireland and the UK, and found that the strategies ranged from very cheap to very expensive to implement. The cheapest strategy to implement in both countries would be "a timeline of participant visits for sites" – site reminder alone costing €79.18 (£68.09) and €111.95 (£96.28) respectively and the most expensive strategy would be "data collection scheduled with routine care" costing €20,250 (£17,415.02) in Ireland, and €15,697.67 (£13,500) in the UK.

For the "real life" trials, "a timeline of participant visits for sites" – site reminder alone would be the cheapest strategy in the CINNAMON trial (€112.23 (£96.52)). For the MAMI and MOON trial "targeted recruitment of sites/GPs" would be the cheapest strategy in these two single centre trials costing €30 (£25.80) and €35.35 (£30.40) respectively. The most expensive strategy in the MAMI trial would be either "investigator meetings face to face" or "routine site visits by CTU staff" both costing €1,600 (£1,376). For the MOON and CINNAMON trials, the costliest strategy for the trial teams to use would be "data collection scheduled with routine care" costing €4,834.88 (£4,158) and €32,503.25 (£27,951.92) respectively.

The cost of retention strategies differed across the trials due to differences in the trial size (number of sites and participants), staff roles and responsibilities in different countries and the number of follow-up visits. For the smaller single site

trials, such as the MAMI trial (60 participants, 1 site, 1 trial visit) it naturally costs less to implement retention strategies compared to the larger trials such as the CINNAMON trial (428 participants, 5 sites and 9 trial visits).

Newsletters were identified as the most routinely used retention strategy by CTUs in the UK (68). The cost of sending newsletters would be one of the cheaper retention strategy options ranging from €755.17 (£649.45) to €2,040 (£1,754.40) for manually posting the newsletters, and €546.59 (£470.07) to €1,094.17 (£940.96) to electronically send newsletters. However, the most up-to-date evidence suggests there is no retention benefit when using this strategy “RD = -0% (95% CI -4% to 3%); GRADE: very low” (3). This costing model has shown that “data collection scheduled with routine care” is one of the most expensive strategies across all trials (€900 (£774) - €32,503.25 (£27,951.92)).

The retention strategy with the best available evidence is “inclusion of pre-paid envelopes" for questionnaire return. The cost of this retention strategy ranges from €170.98 (£147.04) to €1,690 (£1453.40), one of the cheapest retention strategies trial teams can use. The Cochrane review found that return postage which included “preaddressed second class stamped envelope”, “high priority stamp to the mailing” and “personalised postal follow-up” may lead to a 4% retention benefit “RD= 4% (95% CI -0% to 9%)”. However, the evidence was based on three low quality studies (n=1543), and the single study of pre-paid return envelopes itself, did not find a beneficial effect on retention (3).

Table 4.4 Total cost and cost per participant for each retention strategy for all trials.

Strategy	**Cost**				
	Ireland (Hypothetical trial)	**United Kingdom (Hypothetical trial)**	**MAMI trial (115)**	**MOON trial (116)**	**CINNAMON trial (117)**
Strategy 1: Newsletters (posted)	€2040 (£1754.40)	€1657.67 (£1425.60)	€895.68 (£770.29)	€755.17 (£649.45)	€1931.83 (£1661.33) ($2289.44)
Assumptions	2 newsletters per year; 500 participants; 1-year trial period.	2 newsletters per year; 500 participants; 1-year trial period.	2 newsletters per year; *60 participants; 2-year trial period*[1].	2 newsletters per year; *154 participants; 1-year trial period.*	2 newsletters per year; *428 participants; 2-year trial period.*
Effect estimate[2]	"The evidence is very uncertain about the effect on retention of including a newsletter compared to no newsletter: RD = -0% (95% CI -4% to 3%); GRADE: very low"				
Cost per participant retained	Current evidence suggestions no retention benefit, unable to calculate cost per participant retained due to lack of evidence				
	Ireland (Hypothetical trial)	**United Kingdom (Hypothetical trial)**	**MAMI trial**	**MOON trial**	**CINNAMON trial**
Strategy 1: Newsletters (emailed)	€791.78 (£680.93)	€639.45 (£549.93)	€919.88 (£791.10)	€546.59 (£470.07)	€1094.17 (£940.96) ($1296.72)
Assumptions	2 newsletters electronically sent per year; 500 participants; 1 year trial period	2 newsletters electronically sent per year; 500 participants; 1 year trial period	2 newsletters electronically sent per year; *60 participants; 2-year trial period*	2 newsletters electronically sent per year; *154 participants; 1 year trial period*	2 newsletters electronically sent per year; *428 participants; 2-year trial period*

Effect estimate	"The evidence is very uncertain about the effect on retention of including a newsletter compared to no newsletter: RD = -0% (95% CI -4% to 3%); GRADE: very low"				
Cost per participant retained	Current evidence suggestions no retention benefit, unable to calculate cost per participant retained due to lack of evidence				
	Ireland (Hypothetical trial)	**United Kingdom (Hypothetical trial)**	**MAMI trial**	**MOON trial**	**CINNAMON trial**
Strategy 2: A timeline of participant visits for sites (site reminder)[3]	€79.18 (£68.09)	€111.95 (£96.28)	€101.34 (£87.15)	€111.95 (£96.28)	€112.23 (£96.52) ($133.01)
Assumptions	Data Manager develops reminder schedule software, electronically emails the software to the sites (10 sites). Carried out once. This software is used to notify staff of upcoming participant trial visits	Data Manager develops reminder schedule software, electronically emails the software to the sites (10 sites). Carried out once. This software is used to notify staff of upcoming participant trial visits	Data Manager develops reminder schedule software, electronically emails the software to the sites *(1 site).* Carried out once. This software is used to notify staff of upcoming participant trial visits	Data Manager develops reminder schedule software, electronically emails the software to the sites *(1 site).* Carried out once. This software is used to notify staff of upcoming participant trial visits	Data Manager develops reminder schedule software, electronically emails the software to the sites *(5 sites).* Carried out once. This software is used to notify staff of upcoming participant trial visits

Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
A timeline of participant visits for sites (participant reminder)[3]	€9232.18 (£7939.68)	€6103.57 (£5249.08)	€304.74 (£262.08)	€1957.37 (£1683.34)	€14803.70 (£12730.79) ($17544.05)
Assumptions	Research nurse contacts 500 participants– 5 minutes per call- carried out once for each visit (3-visits) Failed contact attempts – research nurse contacts 500 participants - 2 failed contact attempts (1 minute each) – carried out for each visit (3 visits)	Trial Manager contacts 500 participants– 5 minutes per call- carried out once for each visit (3-visits) Failed contact attempts – trial manager contacts 500 participants - 2 failed contact attempts (1 minute each) – carried out	Research nurse contacts *60 participants*– 5 minutes per call- carried out once (1 trial visit) Failed contact attempts – research nurse contacts *60 participants* - 2 failed contact attempts (1 minute each) – carried out once (1 trial visit)	Trial Manager contacts *154 participants*– 5 minutes per call- carried out once for each visit (*3-visits*) Failed contact attempts – trial manager contacts *154 participants* - 2 failed contact attempts (1 minute each) – carried out for each visit *(3 visits)*	Research nurse contacts *428 participants*– 5 minutes per call- carried out once for each visit (*9 trial visits*) Failed contact attempts – research nurse contacts *428 participants* - 2 failed contact attempts (1 minute each) –

		for each visit (3 visits)			carried out once for each visit *(9 trial visit)*
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
	Ireland (Hypothetical trial)	**United Kingdom (Hypothetical trial)**	**MAMI trial**	**MOON trial**	**CINNAMON trial**
Strategy 3: Inclusion of pre-paid envelopes (questionnaire)	€1690.00 (£1453.40)	€1346.56 (£1158.04)	€170.98 (£147.04)	€832.79 (£716.20)	€667.40 (£573.94) ($790.94)
Assumptions	1 questionnaire to all 500 participants; cost of stamp to send out and to return; 1 reminder to 30% of participants (150); cost of stamp to send out and to return;	1 questionnaire to all 500 participants; cost of stamp to send out and to return; 1 reminder to 30% of participants (150); cost of stamp to send out and to return	*1 questionnaire to all 60 participants*; cost of stamp to send out and to return; 1 reminder to 30% of participants (18); cost of stamp to send out and to return	*2 questionnaires to all 154 participants*; cost of stamp to send out and to return; 1 reminder for each questionnaire to 30% of participants (47); cost of stamp to send out and to return	1 questionnaire to all *428 participants*; cost of stamp to send out and to return; 1 reminder to 30% of participants (129); cost of stamp to send out and to return

Effect estimate	"Various strategies compared to usual practice for return postage, such as free post versus second class stamp; high priority mail stamp versus usual postage; and personal form may increase retention slightly: RD = 4% (95% CI -0% to 9%); GRADE: low" [4]				
Additional participants retained	20	20	3	7	18
Cost per participant retained	€84.50 (£72.67)	€67.33 (£57.90)	€57 (£49.02)	€118.97 (£102.31)	€37.08 (£31.45) ($43.94)
Strategy 4: Telephone reminders	**Ireland (Hypothetical trial)**	**United Kingdom (Hypothetical trial)**	**MAMI trial**	**MOON trial**	**CINNAMON trial**
Telephone reminders for trial visits	€9153 (£7871.59)	€5991.62 (£5152.80)	€203.40 (£174.92)	€1845.42 (£1587.06)	€14691.47 (£12634.27) ($17411.04)
Assumptions	Research nurse contacts 500 participants– 5 minutes per call- carried out once for each visit (3-visits) Failed contact attempts – research nurse contacts 500 participants - 2 failed contact attempts (1 minute each) –	Trial Manager contacts 500 participants– 5 minutes per call- carried out once for each visit (3-visits) Failed contact attempts – trial manager contacts 500 participants - 2	Research nurse contacts *60 participants*– 5 minutes per call- carried out once (1 trial visit) Failed contact attempts – research nurse contacts *60 participants* - 2 failed contact	Trial Manager contacts *154 participants*– 5 minutes per call- carried out once for each visit (*3-visits*) Failed contact attempts – trial manager contacts *154 participants* - 2 failed contact attempts (1	Research nurse contacts *428 participants*– 5 minutes per call- carried out once for each visit (*9 trial visits*) Failed contact attempts – research nurse contacts *428 participants* - 2 failed

	carried out for each visit (3 visits)	failed contact attempts (1 minute each) – carried out for each visit (3 visits)	attempts (1 minute each) – carried out once (1 trial visit)	minute each) – carried out for each visit *(3 visits)*	contact attempts (1 minute each) – carried out once for each visit *(9 trial visit)*
Effect estimate	"Telephone reminders compared to usual follow-up may result in little or no difference to retention (smoking cessation (112)): RD = -1% (95% CI -18% to 15%); GRADE low (-2 levels: imprecision-single study, n = 127; wide CI crossing RD = 0)" [5]				
Cost per participant retained	With a risk difference of negative 1 there are no participants retained with this strategy so cost per participant retained cannot be calculated				
Telephone reminders for questionnaire response	€423.75 (£364.43)	€568.62 (£489.01)	€34.58 (£29.74)	€356.33 (£306.44)	€246.00 (£211.56) ($291.54)
Assumptions	Research assistant contacts 30% of participants (150) – 5 minutes per call – carried out once **Failed contact attempts** – research assistant contacts 150 participants– 2 failed attempts - 1 minute per attempt –carried out once	Research assistant contacts 30% of participants (150) – 5 minutes per call – carried out once **Failed contact attempts** – research assistant contacts 150 participants– 2 failed attempts - 1 minute per	Research assistant contacts 30% of participants (18) – 5 minutes per call – carried out once **Failed contact attempts** – research assistant contacts 18 participants– 2 failed attempts - 1 minute per attempt –carried out once	Research assistant contacts 30% of participants (47)– 5 minutes per call – carried out twice **Failed contact attempts** – research assistant contacts 47 participants– 2 failed attempts - 1 minute per attempt –carried out twice	Research assistant contacts 30% of participants (129) – 5 minutes per call – carried out once **Failed contact attempts** – research assistant contacts 129 participants– 2 failed attempts - 1 minute per attempt –carried out once

		attempt –carried out once			
Effect estimate	"Telephone reminders compared to usual follow-up may result in little or no difference to retention (smoking cessation(112)): RD = -1% (95% CI -18% to 15%); GRADE low (-2 levels: imprecision-single study, n = 127; wide CI crossing RD = 0)"[5]				
Cost per participant retained	With a risk difference of negative 1 there are no participants retained with this strategy so cost per participant retained cannot be calculated				
Telephone reminders for at home data collection			€244.08 (£209.91)		
Assumptions			Research nurse contacts 30% of participants (18) – 5 minutes per call - 1 reminder for each at *home data collection (4 in total)*		
Effect estimate	"Telephone reminders compared to usual follow-up may result in little or no difference to retention (smoking cessation (112)): RD = -1% (95% CI -18% to 15%); GRADE low (-2 levels: imprecision-single study, n = 127; wide CI crossing RD = 0)"[5]				
Cost per participant retained	With a risk difference of negative 1 there are no participants retained with this strategy so cost per participant retained cannot be calculated				
	Ireland	**United Kingdom**	**MAMI trial**	**MOON trial**	**CINNAMON trial**

	(Hypothetical trial)	**(Hypothetical trial)**			
Strategy 5: Data collection scheduled with routine care	€20250 (£17415.02)	€15697.67 (£13500)	€900 (£774.00)	€4834.88 (£4158)	€32503.25 (£27951.92) ($38520)
Assumptions	Carried out by a research nurse during a routine care visit – 15 minutes – carried out 3 times for each participant (once for each trial visit)	Carried out by a research nurse during a routine care visit – 15 minutes – carried out 3 times for each participant (once for each trial visit)	Carried out by a research nurse during a routine care visit – 15 minutes – carried out twice for each participant (*outpatient clinic data collection and data collection at birth*)	Carried out by a research nurse during a routine care visit – 15 minutes – carried out 3 times for each participant *(3 trial visits)*	Carried out by a research nurse during a routine care visit – 15 minutes – carried out 9 times for each participant *(9 trial visits)*
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
	Ireland (Hypothetical trial)	**United Kingdom (Hypothetical trial)**	**MAMI trial**	**MOON trial**	**CINNAMON trial**
Strategy 6: Site initiation	€7000 (£6020.00)	€7376.74 (£6344)	€400 (£344.00)	€388.83 (£334.40)	€2953.31 (£2539.76) ($3500)

training on missing data					
Assumptions	Prep, site training and report per site @€400 per day plus travel and overnight costs. Carried out once for each site (10 sites)	Prep, site training and report by Trial manager (11 hours of work) – plus travel and overnight costs. Carried out once per site (10 sites)	Prep, site training and report per site @€400 per day. Carried out once *(1 site)*	Prep, site training and report by Trial Manager (11 hours of work) Carried out once *(1 site)*	Prep, site training and report per site @€400 per day plus travel and overnight costs. Carried out once for each site *(5 sites)*
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
	Ireland (Hypothetical trial)	**United Kingdom (Hypothetical trial)**	**MAMI trial**	**MOON trial**	**CINNAMON trial**
Strategy 7: Investigator meetings face to face	€14000 (£12040.01)	€14753.48 (£12688)	€1600 (£1376)	€777.67 (£668.80)	€11813.22 (£10159.06) ($14000)
Assumptions	Prep, meeting, and report per site @€400 per day plus travel and overnight costs.	Prep, meeting, and report by Trial manager (11 hours of work) – plus travel and	Prep, meeting, and report per site @€400 per day Carried out 4 times for each site over 2-	Prep, meeting, and report by Trial manager (11 hours of work). Carried out twice per site over 1	Prep, meeting, and report per site @€400 per day plus travel and overnight costs.

	Carried out twice per site over 1 year trial period (10 sites)	overnight costs. Carried out twice per site over 1 year trial period (10 sites)	year trial period *(1 site)*	year trial period *(1 site)*	Carried out 4 times for each site over 2-year trial period *(5 sites)*
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
	Ireland (Hypothetical trial)	**United Kingdom (Hypothetical trial)**	**MAMI trial**	**MOON trial**	**CINNAMON trial**
Strategy 8: Routine site visits by CTU staff	€14000 (£12040.01)	€14753.48 (£12688)	€1600 (£1376)	€777.67 (£668.80)	€11813.22 (£10159.06) ($14000)
Assumptions	Prep, site visit and report per site @€400 per day plus travel and overnight costs. Carried out twice per site over 1 year trial period (10 sites)	Prep, site visit and report by Trial manager (11 hours of work) – plus travel and overnight costs. Carried out twice per site over 1 year trial period (10 sites)	Prep, site visit and report per site @€400 per day Carried out 4 times per site over 2-year trial period *(1 site)*	Prep, site visit and report by Trial manager (11 hours of work). Carried out twice per site over 1 year trial period *(1 site)*	Prep, site visit and report per site @€400 per day plus travel and overnight costs Carried out 4 times per site over 2-year trial period *(5 sites)*

Effect estimate*	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
	Ireland (Hypothetical trial)	**United Kingdom (Hypothetical trial)**	**MAMI trial**	**MOON trial**	**CINNAMON trial**
Strategy 9: Targeted recruitment of sites/GPs[6]	€1620 (£1393.20)	€1060.46 (£912)	€30 (£25.80)	€35.35 (£30.40)	€506.28 (£435.39) ($600)
Assumptions	Research nurse carries out site selection and investigation (1 hour work per site) – 30 sites are targeted	Trial manager carries out site selection and investigation (1 hour work per site) – 30 sites are targeted	Research nurse carries out site selection and investigation (1 hour work per site) – single centre so only 1 site targeted	Trial manager carries out site selection and investigation (1 hour work per site) – single centre so only 1 site targeted	Research nurse carries out site selection and investigation (1 hour work per site) – 15 sites are targeted
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				
	Ireland (Hypothetical trial)	**United Kingdom (Hypothetical trial)**	**MAMI trial**	**MOON trial**	**CINNAMON trial**

Strategy 10: Flexibility in appointments	€4050 (£3483.00)	€3139.53 (£2700)	€270 (£232.20)	€1004.65 (£864)	€2177.01 (£1872.17) ($2580)
Assumptions	Research nurse carries out out-of-hours visits for 10% of participants (50) – 1.5-hour visit	Research nurse carries out out-of-hours visits for 10% of participants (50) – – 1.5-hour visit	Research nurse carries out out-of-hours visits for 10% of participants (6) – 1.5-hour visit	Research nurse carries out out-of-hours visits for 10% of participants (16) – 1.5-hour visit	Research nurse carries out out-of-hours visits for 10% of participants (47) – 1.5-hour visit
Effect estimate	No evidence provided in the systematic review				
Cost per participant retained	Unable to calculate cost per participant retained due to lack of evidence				

[1]*Italic underlined font indicates the real trial information that we used e.g., number of trial participants, number of trial sites, number of trial visits and any retention methods used within the trials e.g., MOON trial sent out 2 questionnaires to participants.* The non-italic-underlined font which indicates the assumptions we applied. A full description of the trial characteristics and any retention activities conducted by the real-life trials are documented in Additional File 1. [2]Evidence from the most recent Cochrane Systematic Review (3). [3]There was no clear explanation as to what this strategy entails therefore, we made the following two assumptions. *Assumptions for "a timeline of participant visits for sites – site reminder"*: The data manager develops reminder schedule software, which is costed as 3 hours of work, the software is emailed to the trial sites for the sites to use, costed at 10 minutes of work. This reminder schedule software can be modified to suit the trial follow-up schedule and to notify staff of upcoming participant trial visits. *Assumption for "a timeline of participant visits for sites – participant reminder"*: this costing assumption includes the cost of the "site reminder" plus the cost of the trial manager/research nurse telephoning each participant for each visit (5 minutes of work) plus the cost of failed telephone contact attempts (2 attempts per participant). [4]We assumed benefit was applied across the whole response to all cycles. The Cochrane review found that return postage which included "preaddressed second class stamped envelope", "high priority stamp to the mailing" and "personalised postal follow-up" all combined likely lead to a 4% benefit, so it is likely that pre-paid envelopes on their own may not provide a 4% benefit on retention. For the ease of calculation, we calculated the cost per participant retained by using pre-paid envelopes based on a 4% benefit. [5]We chose to select telephone reminders compared to usual follow up compared to postal follow up in as we believe it is the most relevant comparison for trial teams. [6]Assumptions for "targeted recruitment of GPs/sites" again there was no clear information what this strategy entails therefore we interpreted this as trial teams targeting sites that would be most likely to participate/site that had the facilities and experience to participate/sites that have conducted similar trials previously, we costed the time taken to conduct background research into which sites these would be and associated investigation into recruitment.

Discussion

Our findings show that the evidence available to support the ten most-used trial retention strategies by CTUs in the UK is weak or lacking entirely but that the cost of using them can be very large.

The most routinely used strategy outlined by Kearney et al. (68) is "newsletters", this strategy was found to be one of the cheaper retention methods particularly emailing newsletters, (€546.59 (£470.07) to €1,094.17 (£940.96)). Another cheap strategy across all the trials would be "telephone reminders for questionnaire response" costing between €34.58 (£29.74) and €568.62 (£489.01). We are able to say that these retention strategies would be cheap, but more evidence is needed to show that they are also effective at retaining trial participants.

The second most routinely used retention strategy outlined by Kearney et al. (68) is "a timeline of participant visits for sites". The site reminder schedule alone would be cheap, costing between €79.18 (£68.09) and €112.23 (£96.52). Integrating a participant reminder schedule would significantly increase the cost (€304.74 (£262.08) - €14,803.70 (£12,730.79)). Similarly "data collection scheduled with routine care" (€900 (£774.00) - €32,503.25 (£27,951.92)), "routine site visits by CTU staff" (€777.67 (£668.80) - €14,753.48 (£12,688)) and "investigator meetings face-to-face" (€777.67 (£668.80) - €14,753.48 (£12,688)), would also be expensive to implement yet none of these have compelling evidence demonstrating that they are effective at retaining trial participants (3). They may be very effective. The point is that we cannot say with any certainty whether they work or not, and therefore substantial amounts of money and other resources are potentially being invested into

strategies that lead to no improvement in retention. We recognise that participant retention may not be the only reason for some of these strategies to be implemented in a trial. For example “routine visits by CTU staff” may also be used for monitoring purposes and the costs may be justified for purposes other than retaining participants. However, it is worth remembering that all these strategies were specifically identified by CTUs as strategies they use to support retention and if a strategy is to be used to improve retention and the jury is out as to whether the majority of the top ten strategies are effective.

Even some of the less costly strategies have limited evidence showing effectiveness and much of the existing evidence is from single studies often with low GRADE ratings (3). “Telephone reminders for questionnaire response” (€34.58 (£29.74) - €568.62 (£489.01)), “newsletters (emailed)” (€546.59 (£470.07) - €1,094.17 (£940.96)), “targeted recruitment of sites/GPs” (€30 (£25.80) - €1,620 (£1,393.20)) and “a timeline of participant visits for sites” – site reminder alone (€79.18 (£68.09) - €112.23 (£96.52)) would be less costly compared to the other strategies but not all have evidence in support of them. A cheap but ineffective strategy is still not something worth using, especially if it takes resources away from other potentially more useful strategies.

Lack of trial process evidence is a sadly enduring problem and despite the paucity of evidence, trial teams need to try and ensure retention is high. Based on our work, a reasonable approach might be to use strategies that are inexpensive when compared to the overall cost of conducting the trial. Building in an evaluation, perhaps a Study Within a Trial (SWAT) (72) would improve decision-certainty for the next trial. For

more expensive strategies, we'd suggest only using them in the context of an evaluation. An estimate of the clinical trial cost per participant in the UK's National Institute for Health Research Health Technology Assessment (NIHR HTA) Programme is £2,987 GBP (55). Some of that cost is due to retention problems, often because trial teams increase the recruitment target to compensate for later retention loss. Having a collection of evidence-informed retention strategies just might bring down the average cost per participant and perhaps reduce some recruitment problems too.

Strengths and limitations

We acknowledge that a limitation of this study is that we have had to make assumptions to calculate our cost estimates, and these may not be truly representative, or the assumptions made may not be accurate depending on how trials are run, especially those outside of Ireland and the UK. Making assumptions was unavoidable due to the lack of information regarding the strategies available from the study by Kearney et al. (68). We also acknowledge that others may make different assumptions, that there is not a standardised approach to implementing these strategies and that the assumptions affect the costs. However, to help to address this limitation, we have made the costing spreadsheet available as an additional file, which means readers can modify it to suit their own trial and input their own information on how the strategy will be implemented.

One of the strengths of this study is that regardless of the costs, it highlights the lack of evidence for routinely used trial retention strategies. Even if our estimates are very wrong, no strategy costs nothing and if there is weak or no evidence in support of it, we should pause and consider what we want to do. If trialists go ahead and use the

strategy, we think at least some of them should use SWATs or other research design to investigate the impact of the strategy on retention. The combination of routine use of a strategy to support retention and a lack of evidence that the strategy actually improves retention, is a recipe for research waste.

Recommendations for future research

This paper highlights the need for further research into the effects of trial retention strategies. The cost of some of the strategies that are currently routinely used are significant, and so is the lack evidence to support their use. We recommend the wider use of SWATs to evaluate the effects of retention strategies used in clinical trials to avoid persistent and widespread research waste. Replication of evaluations will add to the existing evidence to support/not support the use of these strategies.

We also think it would be useful for trial teams to include clear descriptions of their retention strategies and the associated costs in trial publications. The challenges of how to implement a retention strategy based on current descriptions became very clear in this work. Communicating the costs of retention strategies can be helpful to other trial teams to estimate budgets required for implementing similar strategies. A better idea of costs will allow for better 'cost-per-participant-retained' calculations, which in turn will give trial teams another way to compare retention strategies when making choices about which to use in their trial.

Conclusion

Without evidence regarding the effectiveness of trial retention strategies, trial teams will continue to put substantial amounts of money into strategies that potentially have no beneficial impact on participant retention. More evaluation of the

effectiveness and cost of trial retention strategies is needed to avoid widespread use of strategies that are both expensive and ineffective.

Abbreviations

Prioritising Retention in Randomised Trials study (PRioRiTy II)

United Kingdom (UK)

Clinical Trials Units (CTUs)

Studies Within a Trial (SWATs)

National Institute for Health Research Health Technology Assessment (NIHR HTA)

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable

Availability of data and materials: All datasets supporting the conclusions of this article are included within the articles' additional files.

Competing interests: ST is an Editor-in-Chief of Trials. The other authors declare that they have no competing interests.

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Authors' contributions: ST conceived the idea for the project. ST, FS and EM developed the assumptions regarding the conduct and likely costs of the retention

strategies. EM reviewed the academic literature, created the costing model, and drafted the manuscript with input from all authors. All authors read and approved the final version of the manuscript.

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End of Publication

4.4 Reflections and learnings

From my experience of conducting the costing work, I have several reflections. Firstly, there is a lack of high-quality evidence supporting the use of retention strategies. This was the first project I conducted that specifically looked at retention strategies in trials. Conducting this project highlighted the lack of high-quality evidence supporting their effectiveness in improving participant retention in trials. Methodological limitations in evaluating the effectiveness of retention strategies have led to limited confidence and certainty in the findings. These findings are assessed using the GRADE system (Grading of Recommendations, Assessment, Development, and Evaluations) (3, 118).

Secondly, trial resources are potentially being wasted on activities that may, or may not, work at promoting retention rates. Developing and refining the costing

assumptions emphasised how resource intensive retention strategies can be, e.g., how much staff time and costs can be involved in activities that may seem simple and straightforward such as sending postal reminders for questionnaires. Despite retention planning being one part of the trial design, resources need to be planned for and allocated to conduct these activities. This raises questions about if, and when, retention strategies are being planned and resourced. For example, is it during the design and planning stages of the trial (proactive planning) or when trial teams are faced with the issue during trial conduct (reactive planning).

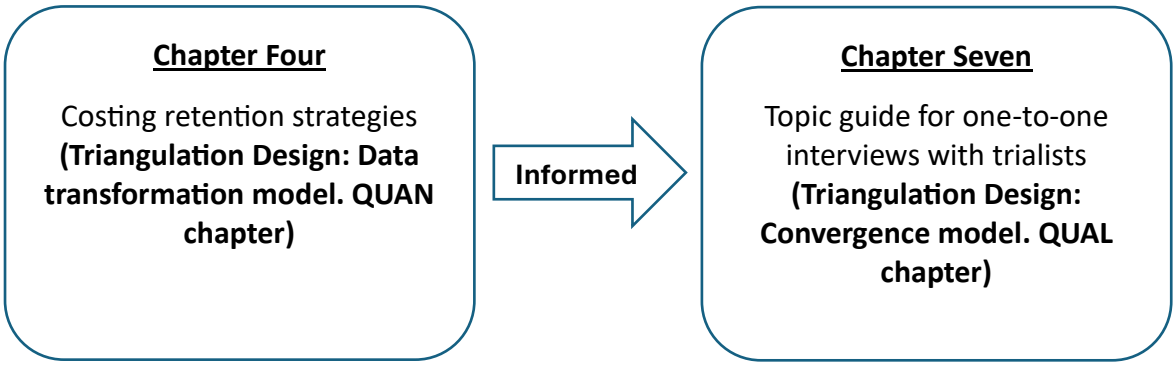
My final reflection is that there is a lack of published information on the topic. One of the challenges of this work was to gather information on how retention strategies are conducted, and specifically, how much they cost. This information was not readily available in the literature and was sourced from our professional contacts to gather the necessary insights into how trial activities were conducted and the likely costs and resources involved.

Ultimately this work showed me just how little evidence there is to support the use of retention strategies in trials. This chapter started wider discussions around the planning and resources that are involved in retention strategy implementation and the communication of retention strategies in trials. This narrowed the scope and the focus of my thesis to specifically investigate the planning and communication of retention strategies in trials.

4.5 How this chapter links in with other chapters

The results from this chapter have informed the topic guide for interviews with trialists conducted in Chapter Seven (Appendix 11 – Topic guide).

Figure 4.1. Diagram of how Chapter Four links with other chapters.



4.6 Summary of key points from the chapter

Summary of key points from the chapter

- Due to the limited high-quality evidence to show retention strategies are effective (3), trial teams are investing resources into retention strategies that may not lead to any improvements in retention rates in trials. How costly retention strategies are to trial teams is unknown.
- We made assumptions as to how the top 10 most routinely used retention strategies in the UK are most likely to be conducted, the resources required, and the costs involved. We applied these cost assumptions to a hypothetical trial and three published trial protocols to generate estimated costs of these strategies.

- Routinely used retention strategies can be quite costly but have little high-quality evidence to support their use.
- We need to formally evaluate retention strategies to gather evidence to ensure trial teams are investing in strategies that will retain trial participants.
- The work in this chapter led to more in-depth thinking and reflections that guided the focus of this thesis. The costing work was an introduction into the "behind-the-scenes" of retention strategies and emphasised the cost and resources that are required to be considered by trial teams when planning retention strategies.

Chapter Five. How do trial teams plan for retention during the design stage of the trial? A scoping review

5.1 Introduction

This chapter presents a scoping review, investigating whether, and how, trial teams plan for retention during the design stage of a trial. The chapter starts with the rationale for the review, and why we chose a scoping review as the review method. The published scoping review is then presented followed by reflections, and learnings from the review. The chapter concludes with a summary of key points.

5.2 Rationale for the scoping review

The widespread issue and consequences of poor participant retention are well documented (3, 5-10, 53). These well-reported issues suggest that trial teams should be aware that the participant retention rates in their trials are likely to be a challenge. Trial teams, therefore, should be considering actions to promote participant retention during the design and planning stages of the trial. Developing retention strategies during the trial design and planning stages allows trial teams to anticipate barriers to retention and be proactive in mitigating these barriers to help facilitate ongoing trial participation, rather than being reactive as participants are lost-to-follow-up.

How this planning should occur has been specifically identified as a key research question that needs to be addressed by PRioRiTy II (Prioritising Retention in Randomised Trials study) question 10; “how should people who run trials plan for retention during their funding application and creation of the trial (protocol development)”(4). The existing literature provides limited, and mixed evidence, on

whether retention strategies are developed proactively during trial design and detailed in trial protocols (70). Guidance, however, from the SPIRIT 2013 guidelines item 18b, indicates that trial protocols should include the following; "plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols" (21:3).

The primary aim of the scoping review, therefore, was to establish if, and how, trial teams report plans to promote retention during the design stage of trials. The secondary aim was to compare the reported retention strategies with the existing evidence of their effectiveness, outlined in the Cochrane Systematic Review of strategies to improve retention in randomised trials (3). In the context of the thesis, the scoping review addressed research objective two, *'To identify if, and how, trial teams document plans for participant retention in trial protocols, reflecting the extent of retention planning during the protocol development stage of the trial'.*

5.3 Why we undertook a scoping review

Many different types of review methods have been identified in the literature (119-121). Scoping reviews can be used to map the key concepts that underpin a field of research and clarify working definitions, and/or the conceptual boundaries of a topic (122). Common reasons for conducting a scoping review include to explore the breadth/extent of the literature, to map and summarise the evidence, and to inform future research (123, 124). We wanted to explore the breadth of the evidence to examine if, and how, retention strategies are planned during the design stage of the trial and communicated in trial protocols. Our research question was

broad. We wanted to look at trials in any clinical context rather than focusing on a specific clinical area or trial intervention type. We wanted to identify a certain concept (retention strategies) in sources of evidence (trial protocols), making our research question more suited to a scoping review rather than a traditional systematic review (120, 125). Scoping reviews are also useful to analyse gaps in a knowledge base (125). Based on existing literature it is unclear whether retention strategies are planned during the design stage of the trial and reported in trial protocols. Additionally, the PRioRiTy II study outlined the following gap in the literature, question 10; "how should people who run trials plan for retention during their funding application and creation of the trial (protocol development)"(4). This again makes the choice of a scoping review suitable to address our research question. Furthermore, we did not aim to produce critically appraised results to a specific question, another reason why a scoping review was the most suitable review method to address our research question (120, 125).

It is well established that scoping reviews are systematic in their conduct, and to ensure that this review was carried out systematically, we followed the guidance outlined by the Joanna Briggs Institute (JBI) (123). This guidance was chosen as it was the most up to date guidance at the time of conducting this scoping review. Prior to conducting the scoping review, we published a protocol for the review to increase transparency in the review process (126). This protocol was written following the guidance from the JBI (123) (Appendix 3 - Scoping review protocol (published)).

5.4 Thesis Paper Two

Start of Publication

Title: How do trial teams plan for retention during the design stage of the trial? A scoping review

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Abstract

Background

Retention to trials is important to ensure the results of the trial are valid and reliable. The SPIRIT guidelines (18b) require "plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols" be included in trial protocols. It is unknown how often protocols report this retention information. The purpose of our scoping review is to establish if, and how, trial teams report plans for retention during the design stage of the trial.

Methods

A scoping review with searches in key databases (PubMed, Scopus, EMBASE, CINAHL (EBSCO), and Web of Science from 2014-2019 inclusive) to identify randomised controlled trial protocols. We produced descriptive statistics on the characteristics of the trial protocols and also on those adhering to SPIRIT item 18b. A narrative synthesis, of the retention strategies was also conducted.

Results

Eight-hundred and twenty-four protocols met our inclusion criteria. RCTs (n=722) and pilot and feasibility trial protocols (n=102) reported using the SPIRIT guidelines during protocol development 35% and 34.3% of the time, respectively. Of these protocols, only 9.5% and 11.4% respectively reported all aspects of SPIRIT item 18b "plans to promote participant retention and to complete follow-up, including list of any outcome data for participants who discontinue or deviate from intervention protocols".

Of the RCT protocols, 36.8% included proactive “plans to promote participant retention”, regardless of whether they reported using SPIRIT guidelines or not. Most protocols planned ‘combined strategies’ (48.1%). Of these, the joint most commonly reported were “reminders and data collection location and method” and “reminders and monetary incentives”. The most popular individual retention strategy was “reminders” (14.7%) followed by “monetary incentives- conditional” (10.2%). Of the pilot and feasibility protocols, 40.2% included proactive “plans to promote participant retention” with the use of ‘combined strategies’ being most frequent (46.3%). The use of “monetary incentives – conditional” (22%) was the most popular individual reported retention strategy.

Conclusion

There is a lack of reporting of plans to promote participant retention in trial protocols. Proactive planning of retention strategies during the trial design stage is preferable to the reactive implementation of retention strategies. Prospective retention planning and clear communication in protocols may inform more suitable choice, costing and implementation of retention strategies and improve transparency in trial conduct.

Keywords: Scoping review, randomised controlled trial, protocol, reporting, retention, methodology

Background

Retention of participants to trials is an ongoing challenge with little evidence to support what works and what does not work (3). The most recent Cochrane systematic review of strategies to improve retention in trials found that there were no strategies that improved retention for which the quality of evidence was high. Despite this, many are used in trials frequently (3, 68) with some trials evaluating multiple retention strategies simultaneously (3). We recently conducted a study to investigate how much the most routinely used trial retention strategies cost trial teams in the UK and Ireland. Even when calculated conservatively, the financial cost is staggering (18). Even more staggering, it is estimated that roughly 50% of trials experience loss-to-follow-up of at least 11% with some experiencing loss-to-follow-up rates as high as 20% (3, 5). Higher rates of loss-to-follow-up are shown to be associated with longer length of follow-up (6). These statistics suggest that trial teams should consider retention strategies at the design stage, before the trial begins, particularly for trials at higher risk of loss-to-follow-up.

Poor retention causes bias to be introduced into the trial (6) and reduces the power of the trial which means the ability to detect significant findings and the confidence in the conclusions drawn from the trial are both affected (6, 8, 9). Poor retention also results in incomplete data, it can delay the delivery of interventions and increase the costs associated with running trials (13). This contributes to research waste (13-15). Missing data and poor retention can be dealt with by statistical techniques in the analysis of the trial (6, 9), but no missing data technique is as

good as retaining the participant and having complete data. Recruiting larger numbers of participants to counteract the expected dropout rate is also used to mitigate missing data, but this is more expensive and exposes more people to the risks associated with trial participation (12). Rather than dealing with the problem after it occurs, trial teams could/should be looking to factor in plans to mitigate poor retention at design stages – a question identified as a priority for research by the trials community (4).

Trial protocols are an essential document for planning and conducting the trial. Protocols are reviewed and approved by ethics committees before the trial begins to ensure the trial team has fully accounted for any potential issues that may arise during the course of the trial (127). Having a comprehensive clearly written protocol increases the transparency in trial conduct (21, 127) and allows for the replication of trial methods (21). Protocols need to be published and be freely assessable for the readers of the corresponding results paper to fully appraise and interpret the results of the trial (128, 129). Despite the importance of trial protocols research shows that the content of protocols varies greatly (21, 127). They often fail to report, in sufficient detail, some key trial design elements such as the primary outcome of the trial (130), statistical methods (131) and allocation concealment (132). Deficiencies in protocol content may result in trial teams seeking ethical amendments, and may lead to poor trial conduct (127).

According to ICH GCP guidance there is no requirement or recommendation that retention strategies be included in trial protocols but it does recommend that protocols should specify "the type and timing of the data to be collected for withdrawn subjects" (79:40). The new Clinical Trial Regulation (133) makes no comment on retention either. However, the U.S. Food and Drug Administration (FDA) recommend that preventing poor retention needs to be dealt with by improving trial design and trial conduct (78). One document, developed to improve the completeness and reporting of content of trial protocols, SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) was developed in 2013. The SPIRIT statement is a 33-item checklist for minimum protocol content that aims to promote and improve the transparency and description of trial activities by encouraging trial teams to consider potential and important issues during the design stage of the trial (127). One of these issues is retention, and as per the SPIRIT 2013 statement it is recommended that the following be included "plans to promote participant retention and complete follow-up including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols" (21:3). Existing evidence, from interviews with trial staff, as to whether trial teams actually prospectively plan retention strategies during the trial design stage is variable (70).

The purpose and primary aim of our scoping review is to establish if, and how, trial teams report plans for retention at the design stage of clinical trials by examining a body of trial protocols. Our secondary aim is to compare the reported retention strategies with their evidence of effect. This will contribute to the evidence base for the PRioRiTy (Prioritising Retention in Randomised Controlled Trials) unanswered

question “How should people who run trials plan for retention during their funding application and creation of the trial (protocol development)?” (4)

Methods

This scoping review has been conducted using the guidelines and framework outlined by the Joanna Briggs Institute (123), the most recent framework for scoping reviews (122, 134, 135). This scoping review was reported using the Preferred Reporting Items for a Systematic Review and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR)(136) (Supplementary File 1). The protocol for this review is published in *Trials* and is also available in Supplementary File 2.

Data sources and search strategy

The search strategy was developed in collaboration with a research librarian at University College Cork and is shown in Table 5.1. The following electronic databases were searched for relevant protocols, PubMed, Scopus, EMBASE, CINAHL (EBSCO), and Web of Science. The search was adapted as appropriate for each database using the software Polyglot (137) which translates search strategies across databases.

Table 5.1. PubMed Search Strategy
("randomised controlled trial"[Title/Abstract]) OR ("randomized controlled trial"[Title/Abstract])) OR ("randomised clinical trial"[Title/Abstract])) OR ("randomized clinical trial"[Title/Abstract])) OR ("randomized controlled trials as topic"[MeSH Terms])) AND ("protocol"[Title/Abstract])) OR ("clinical trial protocols as topic"[MeSH Terms])

Inclusion and Exclusion Criteria

We included the following: protocols for phase II, phase III and phase IV Randomised Controlled Trials (RCTs), pilot and feasibility trials, and mixed methods that included a RCT element; protocols published between 2014 and 2019 (inclusive) - we chose this timeline to allow for sufficient time for the uptake of the SPIRIT guidelines published in 2013 (21) and then included a 6 year time-horizon, as this would provide a sufficient sample size; protocols of RCTs from any setting, that involved adults and/or children of any age, investigating any treatment/intervention type for any disease area/clinical specialty, investigating any comparator including placebo and examining any outcome; protocols for trials randomised at the cluster or individual level; protocols published in the English language. Excluded were: non-protocol papers; protocols for non-randomised trials; protocols for quasi/partially randomised trials; protocols for single arm trials; protocols for studies within a trial (SWATs); protocols for statistical analysis plans; protocols for phase 1 trials; protocols for process evaluations; protocols for economic evaluations; protocols for N-of-1 trials.

Screening and selection process

EM imported titles and abstracts of all electronically sourced search results to EndNote, grouping results separately for each database. Duplicates were removed and the remaining results were exported to Rayyan QCRI software for screening. The screening process involved two reviewers (EM and FS). EM independently screened all titles and abstracts. FS screened a random selection of 10% of the

overall search output, this random 10% was selected using a random number generator. Where disagreement arose a third reviewer KG was consulted and when necessary, full protocol texts were obtained to determine eligibility. We set ourselves a target of 10% of the eligible protocols (n=8,224). We wanted a sample that was large enough to say something meaningful, but small enough to facilitate completion. 10% (n=824) seemed a reasonable compromise between size and feasibility. See Figure A5.1 for The PRISMA Flow Diagram.

Data management and data extraction process

The full list of extracted variables, discussed and agreed upon by all authors, are outlined in the protocol (Supplementary File 2). The data extraction form was piloted by EM using a sample of 10 protocols and was reviewed by FS and KG to ensure the variables extracted best met the objectives of the scoping review. Data extraction was performed by EM and a random sample (10%) of the protocols was selected by FS using a random number generator, and checked to ensure consistency and improve the reliability of the data extraction process. All extracted information was entered into a Microsoft Excel file.

For the purposes of this scoping review, we defined a retention strategy as an action/activity that is conducted, in addition to usual follow-up procedures, with the purpose of retaining participants in a trial, reducing missing data or improving data completeness. We were not concerned with extracting information regarding activities to improve adherence or compliance to an intervention.

The outcome of interest was adherence to SPIRIT item 18b, “Plans to promote participant retention and complete follow-up including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols” (21:3). We divided this statement into three categories; 18b(i) “plans to promote participant retention”, 18b(ii) “plans to complete follow-up including list of any outcome data to be collected for participants who discontinue from intervention protocols” and 18b(iii) “plans to complete follow-up including list of any outcome data to be collected for participants who deviate from intervention protocols”. For 18b(i) we defined this as proactive plans outlined in the protocol that aim to actively promote participant retention in the trial. For 18b(ii) and 18b(iii), we defined these as reactive plans outlined by the trial team to complete outcome data collection and to complete follow-up of participants who have withdrawn/discontinued or deviated from the intervention protocols.

Regardless of whether the protocol reported using the SPIRIT guidelines in the protocol, we analysed all protocols for information that we could map to SPIRIT item 18b “Plans to promote participant retention and complete follow-up including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols” (21:3). Which as described above we divided into three categories.

Data Synthesis

We produced descriptive statistics on the characteristics of the trial protocols and on those adhering to SPIRIT item 18b. A narrative synthesis, of the retention strategies was also conducted. The Guidance on the Conduct of Narrative Synthesis in Systematic Reviews were referred to during this process (138). The retention strategies were coded by EM based on the type of retention strategy, i.e., reminders, prompts, monetary incentives etc. We mapped each strategy to the ORRCA (Online Resource for Research in Clinical triAls) retention domains (139) (ORRCA_Retention_Domains.pdf) as has previously been done in the Cochrane systematic review of strategies to improve retention in randomised trials (3). The data items were mapped to 16 out of the 44 ORRCA domains, the most popular category being "B. Participants". A total breakdown of the number of protocols mapped to each ORRCA domain can be seen in Table 5.4 along with example quotes that were mapped to each domain.

When it was unclear which ORRCA domain a retention strategy mapped to FS and KG were consulted and a joint decision was made. Fifty of 307 data items were consulted upon. We made the following assumptions when mapping the retention strategies.

1) Following the approach taken by the Cochrane review (3), ORRCA domain "B1 Reminders" was divided into reminders (sent after a missed data collection time point) and prompts (sent before the data collection time point). In some cases, it was not clear if the strategy was intended as a reminder or prompt therefore

based on the wording of the surrounding text we made a judgement call as to whether it was a reminder or prompt. If it was still unclear from this and the strategy included the word reminder/prompt, we mapped it to ORRCA as such.

2) When a protocol outlined the use of more than one retention strategy, we created a new category called 'combined strategies'. We have detailed the most commonly combined strategies in Table 5.4.
3) Regarding monetary and non-monetary compensation for participants we made the assumption that all monetary compensation functioned as incentives rather than rewards. Our reasoning for this is that ethically, patient information leaflets must disclose to participants information about receiving monetary compensation (79). This prior knowledge of receiving monetary compensation means the compensation functions as an incentive rather than a reward.
4) We further classified monetary and non-monetary incentives as either conditional (based on the participant completing a task) or non-conditional (not based on participants completing a task).

Since we included pilot and feasibility trial protocols, we conducted a sub-group analysis of the retention strategies outlined in these protocols. The results from the pilot and feasibility protocols will be reported separately ("Analysis of pilot and feasibility trial protocols"). All other protocols that were not pilot and feasibility trials are included in what we will refer to as RCT protocols throughout the paper and Supplementary File 3.

Results

Protocol characteristics

Table 5.2 displays the characteristics of the protocols included in our analysis. In summary, of the 824 protocols included in the six-year period: 26.6% (n=219) were published in 2019; most trials were non-commercial, i.e. publicly funded trials that did not receive funding/donations from private for-profit companies (80.8%, n=666); tested non-drug interventions such as diet, exercise, therapy, and educational interventions (72%, n=593). Individually randomised designs dominated (84%, n=692). Thirty-point-three percent (n=250) of protocols were for trials conducted in vulnerable populations and 22% (n=181) were for trials conducted among populations consisting of both vulnerable and non-vulnerable individuals. Vulnerable populations were defined by this reviews' authors via local ethics committee (140) and ICH-GCP definitions (79) these included; infants and children aged 17 and under, pregnant women, institutionalised individuals, adults aged 60 and over, critically ill patients not able to consent for themselves, homeless individuals and refugees, see Table 5.2 for full definition of all included populations. The protocols covered a wide range of clinical specialties, 38 in total, including oncology, musculoskeletal diseases, cardiology, neurology, nephrology, and obstetrics and gynaecology. The topic of public health was the most common (15.9%, n=131). This category included trials evaluating interventions targeting for example physical activity, nutrition, smoking cessation, alcohol/drug misuse, gambling, obesity, sleep disorders, and family planning and contraception.

Table 5.2. Protocol characteristics (Total protocols = 824)	
Year of publication	**Number of protocols (n, %)**
2014	85 (10.3%)
2015	108 (13.1%)
2016	125 (15.2%)
2017	126 (15.3%)
2018	161 (19.5%)
2019	219 (26.6%)
Level of randomisation	
Cluster RCTs	132 (16%)
Individually randomised RCTs	692 (84%)
Funding type	
Commercial trial[1]	98 (11.9%)
Non-commercial trial	666 (80.8%)
No funding	27 (3.3%)
Unclear – no information provided	33 (4%)
Type of intervention	
Non-drug trial	593 (72%)
Drug trial	138 (16.7%)
Mix of intervention types	23 (2.8%)
Surgical trial	55 (6.7%)
Medical device trial	15 (1.8%)
Patient population[2]	**Number of protocols**
Vulnerable populations	250 (30.3%)
Mix of vulnerable and non-vulnerable populations	181 (22%)
Not vulnerable	73 (8.9%)
Unclear	320 (38.8%)
Planned sample size[3] Individual level randomisation (n=692)	**Number of protocols**
100 participants or less	222 (32.1%)
101 -200 participants	175 (25.3%)
201 – 300 participants	84 (12.1%)
301 -400 participants	58 (8.4%)
401 – 500 participants	19 (2.7%)

501 participants and greater	121 (17.5%)
Overlap of categories	2 (0.3%)
Unclear from protocol	11 (1.6%)
Planned sample size[4] **Cluster trials (n=132)**	**Number of protocols**
100 clusters or less	110 (83.3%)
101 -200 clusters	8 (6.1%)
201 – 300 clusters	4 (3%)
301 -400 clusters	
401 – 500 clusters	
501 clusters and greater	1 (0.8%)
Unclear from protocol	9 protocols (6.8%) – cluster size unclear but provided the participant size in 7 protocols • 1202 participants • 382 participants • 426 participants • 342 participants • 90 participants • 300 participants • 600 participants
Clinical Specialty[5]	**Number of protocols**
Public Health	131 (15.9%)
Musculoskeletal	80 (9.7%)
Oncology	77 (9.3%)
Mental Health	74 (9%)
Cardiology	74 (9%)
Obstetrics and Gynaecology	65 (7.9%)
Neurology	62 (7.5%)
Diabetes and Endocrinology	35 (4.2%)
Respiratory	33 (4%)
Sexual Health and STIs	30 (3.6%)
Nephrology	19 (2.3%)
Vascular diseases	19 (2.3%)
Gastroenterology	17 (2.1%)
Paediatrics	12 (1.5%)
Surgery and Anaesthesia	11 (1.3%)
Dental health	10 (1.2%)
Haematology	8 (1%)
Infectious Disease	8 (1%)
Intensive care	7 (0.8%)

Ophthalmology	7 (0.8%)
Hepatology	6 (0.7%)
Otology	6 (0.7%)
Autoimmune diseases	6 (0.7%)
Emergency care	4 (0.5%)
Palliative care	3 (0.4%)
Otolaryngology	3 (0.4%)
Dermatology	3 (0.4%)
Genetics	3 (0.4%)
Intellectual Disabilities	2 (0.2%)
Pathology	1 (0.1%)
Rehabilitation	1 (0.1%)
Trial Methods	1 (0.1%)
Secondary care	1 (0.1%)
Primary care	1 (0.1%)
Pharmacy care	1 (0.1%)
Geriatric medicine	1 (0.1%)
Orthopaedics	1 (0.1%)
Appendicitis	1 (0.1%)
Patient reported primary outcome	**Number of protocols**
Yes	298 (36.2%)
Partly[6]	78 (9.5%)
No	440 (53.4%)
Unclear from protocol	8 (1%)
Number of follow-up assessments	**Number of protocols**
1 follow-up assessment	124 (15%)
2 follow-up assessments	238 (28.9%)
3 follow-up assessments	156 (18.9%)
4 follow-up assessments	105 (12.7%)
5 follow-up assessments	34 (4.1%)
6 or more follow-up assessments	106 (12.9%)
Unclear from protocol	61 (7.4%)
Follow-up method for data collection	**Number of protocols**
In person clinic visit	290 (35.2%)
Postal questionnaire	13 (1.6%)
Electronic questionnaire /online assessment	49 (5.9%)
Telephone call	24 (2.9%)

Via patient records or databases[7]	25 (3%)
Home visits/visits to site outside the clinic by researcher	37 (4.5%)
A combination of follow-up methods	326 (39.6%)
All data collected while the participant is in the hospital	36 (4.4%)
Unclear from protocol	24 (2.9%)
Routine data sources for data collection[8]	
Yes	164 (19.9%)
No	660 (80.1%)
Trial Type	
Pilot or Feasibility Trial	102 (12.4%)
RCTs	722 (87.6%)
RCT protocols reported using SPIRIT guidelines	
Yes	253 (35%)
No	469 (65%)
Pilot and Feasibility protocols reported using SPIRIT guidelines	
Yes	35 (34.3%)
No	67 (65.7%)

[1]Commerial trials were defined as a trial that has any type of funding or donation from a private for-profit company/organisation for example partly funded by pharma or product provided by a commercial company was classified as a commercial trial. [2]Vulnerable populations were defined by this reviews' authors via local ethics committee definition (140) and ICH-GCP definition (79) these included; infants and children aged 17 years and under, pregnant women, institutionalised individuals (prisoners, in nursing homes, mental health institutions), critically ill/ICU patients/patients on ventilators unable to provide consent so deferred consent is gained, where stated in the protocol deferred consent is obtained, adults aged 60 and over, participants with learning disabilities, suffers of dementia, adults with terminal illness, homeless individuals and refugees, adults with mental illness, and members of the armed forces and medical/nursing/dental/pharmacy students where there is a hierarchy in the trial that would influence the decision to take part voluntarily.[3]The sample size groupings contain protocols that stated they would recruit "at least" or a "minimum (number) of" participants for example if a protocol stated they would recruit at least 80 participants this has been grouped into category 1. "100 participants or less". For dyad pairs, these have been grouped in terms of total number of participants for example 100 participants and their dyad i.e., 200 participants would be grouped in category 2. "101-200 participants". [4]The sample size groupings contain protocols that stated they would recruit "at least" or a "minimum (number) of" clusters for example if a protocol stated they would recruit at least 80 clusters this has been grouped into category 1. "100 clusters or less". [5]Categories were based on clinical specialty for example surgery for cancer was classed under "Oncology" rather than "Surgery and Anaesthesia", only surgeries or anaesthetic procedures for non-

specific clinical area/none of the clinical specialty categories listed above were grouped under "Surgery and Anaesthesia" for example "elective non-cardiac surgery". Similarly, "Paediatrics" only contains trials that did not involve a clinical specialty area listed above, for example "Chronic Fatigue Syndrome" was include in "Paediatrics" whereas "Children younger than 5 years of age with acute gastroenteritis" was grouped into "Gastroenterology". [6]Partly patient reported means aspects of the primary outcome were reported by the patient and other aspects were not. [7] In this category participants are not directly followed-up, all follow-up is via a database/registry/routine data source. [8] In this category routine data sources were used for outcome data/follow up data/demographic data on participants, these routine sources include patient records, registries, hospital databases and medical records etc.

Compliance with the SPIRIT 2013 Statement

Table 5.3 reports the key findings relevant to the use of the applicable retention items from the SPIRIT 2013 statement for RCT protocols (n=722). We report separately on the pilot and feasibility protocols (n=102). (A more detailed breakdown is provided in Supplementary File 3).

Of the 35% (n=253) of RCT protocols that reported using the SPIRIT guidelines when developing the protocol, 9.5% (n=24) fully complied and included all aspects of item 18b (18b(i) and 18b(ii) and/or 18b(iii)), and 41.5% (n=105) included item 18b(i) "plans to promote participant retention" (proactive rather than reactive plans).

Table 5.3. Key SPIRIT 2013 Statement Results*.

Table 5.3: Key SPIRIT 2013 Statement Results*	
Reported use of the SPIRIT guidelines	**Number of RCT protocols**
Yes	**253 (35%)**
No	469 (65%)
Reported using the SPIRIT guidelines and reported all aspects of item 18b (18b(i) and 18b(ii) and/or 18b(iii)) – "Plans to promote participant retention and complete follow-up, including list	

of any outcome data to be collected for participants who discontinue or deviate from intervention protocols" (21:3)	
Yes	**24 protocols out of the 253 that reported using SPIRIT (9.5%)**
No	229 (90.5%)
Reported using the SPIRIT guidelines (n=253) and reported item 18b(i) "Plans to promote participant retention"	**Number of RCT protocols**
Yes	**105 protocols out of the 253 that reported using SPIRIT (41.5%)**
No	148 protocols (58.5%)
RCT protocol SPIRIT item 18b figures, regardless of reporting SPIRIT guidelines in the protocol i.e., information mapped to SPIRIT item 18b	
	Number of protocols
Reported all aspects of item 18b (18b(i) and 18b(ii) and/or 18b(iii)) – "Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols" (21:3)	
Yes	**53 protocols out of the total (n=722) (7.3%)**
No	669 protocols (92.7%)
Reported item 18b(i) "Plans to promote participant retention" (out of the total 722 RCT protocols)	
Yes	**266 (36.8%)**
No	456 (63.2%)

*Excludes Pilot and Feasibility Protocol data (See Supplementary File 3, for a full breakdown of SPIRIT results)

Plans to promote participant retention

Of the RCT protocols (n=722) regardless of reporting using the SPIRIT guidelines, 7.3% (n=53) included all aspects of item 18b (18b(i) and 18b(ii) and/or 18b(iii)), "plans to promote participant retention and complete follow-up, including list of any outcome data to be collected from participants who discontinue or deviate from intervention protocols" (21:3).

SPIRIT ITEM 18b(i)

SPIRIT item 18b(i) "plans to promote participant retention" (proactive plans), was included in 36.8% (n=266) of the RCT protocols, regardless of whether they reported using SPIRIT guidelines or not. The most common retention strategy was the use of 'combined strategies' used in 48.1% of protocols (n=128). The joint most popular combined retention strategies were the use of "reminders and data collection location and method", (e.g. use of return postage such as pre-paid stamped return envelopes, options of home visits/telephone/postal data collection versus clinic visits), and "reminders and monetary incentives". The median number of retention strategies used in a singular protocol was 3. The highest number of strategies reported in any one protocol was 9.

In terms of individual retention strategies, the most common was "reminders" (14.7%, n=39) followed by "monetary incentives- conditional" (10.2%, n=27). Some of the least popular methods included "maintaining staff engagement" (0.4%, n=1), and "monetary incentives – unconditional" (0.4%, n=1).

Table 5.4 summarises the ORRCA domains mentioned in the protocols along with sample quotes from protocols. The most frequently used combined strategies are provided at the bottom of Table 5.4. A full list of all combinations of combined retention strategies can be found in Supplementary File 3.

SPIRIT Items 18b(ii) and 18b(iii)

A combined total of 13.7% (n=99) of the 722 RCT protocols considered a reactive plan to collecting outcome data (SPIRIT item 18(ii) and/or item 18b(iii)), "plans to complete follow-up including list of any outcome data to be collected for participants who discontinue and/or deviate from intervention protocols", regardless of reporting using SPIRIT guidelines or not. No strategy actively targeted those that might withdraw from the trial, i.e., strategies typically employed in 18b(ii) and 18b(iii) were seeking consent early in the trial for continued use of the data if they withdrew or deviated from the protocol. A full breakdown of results can be found in Supplementary File 3.

Table 5.4: Plans to proactively promote participant retention (n=266, 36.8%)*		
ORRCA Domains	**Number (%)**	**Examples of quotes from RCT protocols**
A. Data collection		
A2. Data collection frequency and timing	**1 (0.4%)**	Participants will be monitored monthly for signs or symptoms of adverse effects. One month later, the participants will be reviewed in the clinic and a possible side effect check list will be conducted. **To prevent attrition and to assess adherence to treatment, telephone interviews will be conducted again at 2 months from administration of the drug**
A3. Data collection location and method	**12 (4.5%)**	The survey will be available online via qualtrics (https://www.qualtrics.com/) with a direct link sent to participants. **For those who prefer a hard copy, it will be posted with a return envelope.** If participants in either group miss their scheduled visit, and it cannot be rescheduled within four weeks of their prior visit, the PC clinician may conduct the visit through telephone within seven days from the missed visit.
A5. Data collection during routine care	**4 (1.5%)**	To minimise loss to follow-up, assessments are timed to coincide with routine clinical follow-up.
		The primary outcome point will be collected at the final outpatient clinic appointment and, as such, it is anticipated that missing data for the primary outcome will be low.
B. Participants		

B1. Reminders (Including repeat contacting of participants via phone, post, email etc)	**39 (14.7%) – reminders**	**Reminders** Participants who do not complete and return the study questionnaires in the specified time period will be contacted by the research team via telephone or email, as a reminder about the study.
		Another potential limitation for this trial is the attrition rate. It is possible to have a high rate of participant dropout and subsequently a significant loss of data. Therefore, reminders via telephone contact, email, and SMS will be used.
Prompts	**17 (6.4%) – prompts**	**Prompts** The researcher will send reminder calls 3 days ***in advance*** to promote retention.
		To promote participant retention, we plan training sessions in consultation with the participants and inform participants timely about the entire training schedule and the assessments.
Unclear	**2 (0.8%)**	**Unclear** Phone or email reminders for completion of follow-up questionnaires were performed with phone or email prompts based on the tailored design method proposed by Dillman et al.
		To optimise follow-up, multiple attempts will be made to contact participants including contacting their referring doctor and at a minimum we will aim to record vital status for all participants.
B2. Monetary incentives – direct cash provided to participants/gift vouchers,		**Conditional monetary incentives** All families receive remuneration for their time: US $100 for completing the baseline assessment and US $100 for completing each of the 3 follow-up assessments, for a total of $400. Families can also earn a US $50 bonus if they complete all 4 assessments.

prizes that are monetary **Conditional Incentives** **Unconditional incentives**		
	27 (10.2%)	To maximize participation and follow-up rates, we offered patients $20 for completing each questionnaire.
	1 (0.4%)	**Unconditional monetary incentives** We recognise the importance of participant retention and will offer a voucher of £10 at recruitment.
B3. Non-monetary incentives – entry to raffles for prizes that are non-monetary, completion of trial certificates, offering the controls the intervention at the end of the trial		**Conditional non-monetary incentives** The success of the intervention is strongly dependent on enjoyment and active participation. In order to motivate children's active participation, the staff will use several strategies to celebrate success achieving the proposed objectives in both the healthy lifestyle education and the exercise programs: celebrate and recognize their efforts, reward with smiley emoticons, etc. Children who complete the program successfully will be rewarded with a certificate of completion.
		Moreover, patients who complete the intervention will have an 8-hour nutrition education programme for free.

Conditional incentives	**3 (1.1%)**	
Unconditional Incentives	**4 (1.5%)**	**Unconditional non-monetary incentives** The primary purpose of employing an attention control intervention is to limit principals' and teachers' disappointment at not receiving the iPLAY intervention, thereby increasing participation during data collection at the post-intervention and maintenance phases.
		To minimize loss to follow-up, all controls will be offered the intervention at study end.
B4. Maintaining participant engagement	**14 (5.3%)**	Once a participant is included, every reasonable effort is made to prevent attrition through the entire study period. In addition to the planned visits, all participants have, during the last 2 years, received two letters in connection with milestones and holidays. Distribution of letters will continue throughout the entire study period.
		Personal data will be used to contact the participant, to thank them for participating in the study, to facilitate the follow-ups at 6 months and 2 years of age, to co-ordinate the follow-ups and to disseminate the results of the study to participants.
B7. Supporting participation	**7 (2.6%)**	Participants will be advised at the initial trial enrolment meeting to carefully consider the required investment of time and effort involved in the current project. This will be undertaken to minimize any negative impact associated with loss to follow-up, and consequently likely withdrawal can be made prior to randomization.

		The CRA will explain the study to these patients using comprehensive ethics committee-approved documents and patients will be given opportunity to ask questions and receive further information. This process is to ensure participants are fully informed of the possible burden of appointments and data collection on their time and to enhance retention and reduce loss to follow up.
B8. Contact information	**3 (1.1%)**	Minimising attrition in follow-up assessments is vital to ensure the success of this trial. The at-risk and transient nature of the target population makes this task more difficult. To mitigate this, participants will provide a collateral person who can be contacted. Participants will not be precluded from taking part in the study if they are not comfortable giving the details of collateral persons.
		To increase follow-up data collection, clinicians will collect contact telephone numbers for the participant and at least two family members or caregivers.
B12. Motivations and experience	**1 (0.4%)**	According to Danish research ethics legislation, we will inform the participants about their rights as voluntary subjects in a scientific trial and interview them about their motivation for participation. We do this to make participants consider participation thoroughly to diminish the likelihood of their dropping out.
C. Sites and Site Staff		
C4. Maintaining staff engagement	**1 (0.4%)**	Newsletters from the project were regularly sent to all PHCC managers and RCs at both intervention and control centers.
E. Study Design		

E1. Choice of study outcomes	**1 (0.4%)**	PCOMS could also reduce the number of drop-outs and/or increased patient satisfaction, all leading to cost reduction.
E4. Randomisation method	**1 (0.4%)**	Subjects are randomised on arrival in the operating theatre to minimise the risk of dropouts after randomisation.
Combined strategies	**128 (48.1%)**	
Protocols with multiple retention strategies (n=128 (48.1%)) **Top most common combined strategies to pro-actively promote retention**		
Strategy		**Number of protocols (%)**
	• Reminder • Data collection location and method	**6 (4.7%)** **Example of quote** Participants can choose to complete the questionnaires online or by using a paper questionnaire. Non-respondents will be contacted by telephone within 2 weeks. If they do not respond to this reminder, they will be sent a reminder letter within 2 weeks.
	• Reminder • Monetary incentive	**6 (4.7%)** 4 of the these were conditional monetary incentives 2 were unclear if they were conditional or unconditional monetary incentives
		Example of quote Participants will receive up to three reminder emails if they do not complete the research questionnaires within the allocated time frame. If the questionnaires are

		still not completed participants will be offered $A20 to complete it. Participants who comply with all study procedures will receive $A50.
	• Prompt • Monetary incentive	**5 (3.9%)** All conditional incentives
	• Monetary incentives • Data collection location and method • Reminder	**5 (3.9%)** 4 of these were conditional monetary incentives 1 was an unconditional monetary incentive
	• Monetary incentives • Supporting participation	**4 (3.1%)** 3 of these were conditional monetary incentives For 1 it was unclear whether it was a condition or unconditional monetary incentive
	• Supporting participation • Maintaining participant engagement	**4 (3.1%)**
	• Prompt • Reminder • Monetary incentive	**4 (3.1%)** All conditional monetary incentives
	• Prompt • Reminder	**4 (3.1%)**
	• Reminders	**3 (2.3%)**

	• Maintaining participant engagement	
	• Non-monetary incentive • Monetary incentive	**3 (2.3%)** 2 were both conditional for both types of incentives 1 was a conditional monetary incentive combined with a non-monetary incentive, but it was unclear if it was conditional or unconditional
	• Monetary incentives • Data collection location and method	**3 (2.3%)** All conditional monetary incentives
	• Prompt • Maintaining participant engagement • Monetary incentive	**3 (2.3%)** 2 were conditional monetary incentives 1 included both a conditional and unconditional monetary incentive

*Excludes Pilot and Feasibility Protocol data.

Analysis of Pilot and Feasibility trial protocols

Of the 824 trial protocols, 12.4% (n=102) were for pilot and feasibility trials. Of these, 34.3% (n=35) used the SPIRIT statement during protocol development. Of those 35 protocols, 11.4% (n=4) included all three parts of SPIRIT item 18b (18b(i) and 18b(ii) and/or 18b(iii)) (21).

Overall, 40.2% (n=41/102) included item 18b(i) “plans to promote participant retention”, a pro-active plan to promote retention, regardless of whether they reported using SPIRIT guidelines or not. A combined total of 14.7% (n=15) of protocols included a reactive plan (SPIRIT items 18b(ii) and/or 18b(iii)) “plans to complete follow-up for those who discontinue and/or deviate from the intervention protocols”. A total of 6.9% (n=7) protocols reported all aspects of SPIRIT item 18b (18b(i) and 18b(ii) and/or 18b(iii)) (21).

A total breakdown of the number of pilot and feasibility protocols mapped to each ORRCA domain can be seen in Table 5.5 along with examples of quotes that were mapped to each domain. The top combined strategies are also shown in Table 5.5. See Supplementary File 3 for full details of all combinations of combined retention strategies.

Table 5.5: Analysis of Pilot and Feasibility trial protocols		
Pilot and feasibility trial protocols with a retention strategy (n=41, 40.2%)		
ORRCA Domain	**Number of protocols (%)**	**Examples of quotes from the protocols**
Data collection		
A3. Data collection location and method	2 (4.9%)	Patients who have consented to participate receive a questionnaire and pre-paid addressed envelope
B. Participants		
B1. Reminders (Including repeat contacting of participants via phone, post, email etc) Prompts	3 protocols (7.3%)	**Reminder** Patients who were allocated to Fatigue Information Sheet only, will be asked about their experience of reading the Fatigue Information Sheet. A postal reminder will be sent to non-responders two and four weeks after the seven-day response period has ended, utilising the Reminder Letter and/or a telephone call. Six and 12 months post randomisation, two more outcome booklets will be sent respectively, with two postal reminders and/or telephone calls for non-responders after two and four weeks.

	2 protocols (4.9%)	**Prompt** All clinical outcomes, except for limb circumference, will be collected via self-report questionnaires. Reminder emails and/or calls will be sent out by the Research Assistant **prior to each follow-up assessment** at Week 5 and Week 11.
B2. Monetary incentives – direct cash provided to participants/gift vouchers, prizes that are monetary Conditional incentives	9 protocols (22%)	Participants in both arms will receive a modest monetary compensation of $30CAD each time they meet with the research assistant for data collection every 3 months for an expected time of 1 hour (five times total). This amount is seen as a token of appreciation yet non-coercive
B3. Non-monetary incentives – entry to raffles for prizes that are non-monetary, completion of trial certificates, offering the controls the intervention at the end of the trial Unconditional incentives	1 protocol (2.4%)	To prevent attrition, condensed WheelSeeU training or iWheel information is offered to all participants at the end of the study.
B4. Maintaining participant engagement	1 protocol (2.4%)	All reasonable efforts, within the CRF local standard operating procedure, will be made to ensure optimum participant engagement and to reduce study attrition
B7. Supporting participation	1 protocol (2.4%)	The follow-up appointment will be arranged during the baseline meeting, at a time convenient to participants, and will take place in a clinic at the hospital.

B8. Contact information	2 protocol (4.9%)	Participants are asked to give their own details as well as those of a family member or friend in case it is difficult to contact them directly.
C. Sites and Site Staff		
C6. Trial site factors	1 protocol (2.4%)	The intention of conducting the study within the neighbourhood of the participant is to facilitate the transferability of training and to improve the ecological validity. In addition, training in the community aims to reduce participant burden of travelling to our research site, and to improve adherence
Combined strategies	19 protocols (46.3%)	
Top most common combined retention strategies;		
• Monetary incentives – conditional • Prompt	2 (10.5%)	Study participants will be contacted at three months by a study researcher to confirm contact details and as a reminder about the six-month assessment. A follow-up interview will then be scheduled for six months after randomization. All participants will be offered a £20 honorarium following completion of the six-month follow-up interview.
• Monetary incentives – conditional incentive • Supporting participation • Data collection location and method	2 (10.5%)	Women from both trial groups will be asked to attend an appointment with a research midwife to be weighed either at the study site or at their home at 6 and 12 months. Travel costs and £10 Love2Shop voucher to thank women for their time will be offered.....Follow-up appointments will be offered at weekends and week days, with the option to complete questionnaires at these appointments.

• Data collection location and method • Reminder	2 (10.5%)	The follow-up questionnaires are posted to participants with a reply paid envelope. The protocol for following up questionnaires begins with a 2-week waiting period (from postage date) and four phone calls over 7 days if it is not received within this time. Should phone contact be unsuccessful, research staff contact the recruiting site to check the situation of the patient (e.g. patient death). If the patient's situation has changed, research staff review carer's eligibility in collaboration with clinical staff at the site. If the patient's situation is unchanged, a replacement questionnaire is sent and the same waiting period and phone call schedule are followed. Participants are withdrawn if contact is not made after this second waiting period.

Evidence to support the use of retention strategies.

Table 5.6 displays the top 10 most popular retention strategies identified in this review mapped to the evidence of their effectiveness from the Cochrane review of strategies to improve retention in randomised controlled trials (3). The Cochrane review defines these strategies as "those designed to generate maximum data return or compliance and follow-up procedures that aim to collect data from participants" (3:22). The evidence to support the use of these strategies is either lacking entirely or in the majority of cases has a low-GRADE certainty rating. GRADE (Grading of Recommendations, Assessment, Development and Evaluations) is the most widely adopted tool for grading the quality of evidence and for making clinical practice recommendations and is endorsed by Cochrane.

Table 5.6: Most popular retention strategies compared against evidence for effectiveness.

Top 10 most popular retention strategies in the scoping review *	**Evidence from the Cochrane Review (3) to support the use of the strategies found in the scoping review**
Reminders (n=39, 14.7%)	**Reminders** Evidence to support the use of various types of reminders is very uncertain and may result in little or no difference to retention rates, the GRADE of evidence for such reminders is either low or very low. Only telephone reminders compared to postal reminders may result in a large increase in retention rates, however the GRADE of evidence is low.
Monetary incentives (conditional) (n=27, 10.2%)	**Monetary incentives.** Monetary incentives compared to no incentive may increase retention but the GRADE of evidence is low. The addition of monetary incentives in all trial arms may favour the higher value incentive to increase retention but the GRADE of evidence is low.

	Addition of a monetary reward to both trial arms delivered either with the prenotification or with the reminder letter, probably leads to an increase in retention rates, the GRADE of evidence is moderate.
	Evidence regarding the use of other types of monetary incentives are very uncertain and may lead to little or no difference in retention rates, with the GRADE of evidence being low or very low.
Prompts (n=17, 6.4%)	**Prompts** Evidence to support the use of prompts is very uncertain and may lead to little or no difference in terms of retention rates, GRADE of evidence is low or very low.
	Only prenotification cards vs no card and electronic prompts compared to electronic reminders looks to favour electronic reminders at increasing retention rates, however the GRADE of evidence for both of these methods is low.
	Personalised prompts versus usual follow-up may reduce retention rates slightly but again the GRADE of evidence is low.
Maintaining participant engagement (n=14, 5.3%)	The evidence to support the use of various strategies to maintain participant engagement with the hopes of improving retention is very uncertain and may lead to little or no improvement in retention rates, the GRADE of evidence is low or very low for these strategies.
	Including a newspaper article about the trial compared to no article may increase retention, similarly frequency of telephone contact comparing only at baseline to annual contact to contact only at baseline may increase retention but the GRADE of evidence for both strategies is low.
Data collection location and method (n=12, 4.5%)	Evidence is very uncertain and may lead to little or no difference in retention regarding postal vs clinic follow-up and regarding telephone follow-up vs postal follow-up, evidence GRADE is very low.
	The use of first-class postage for outward mail versus second class postage may increase retention slightly, but the GRADE of evidence is low.
	Using free post versus second class stamp; high priority mail stamp versus usual postage; and personal form all

	compared to usual postage practice for return postage may increase retention slightly but again the GRADE of evidence is low.
	The use of self-sampling kits (directly mailed or an invitation to order) probably increase retention, the GRADE of evidence is moderate.
Supporting participation (n=7, 2.6%)	No evidence from the Cochrane review
Data collection during routine care (n=4, 1.5%)	No evidence from the Cochrane review
Non-monetary incentives (unconditional) (n=4, 1.5%)	Including a pen compared to no pen may increase retention slightly but the GRADE of evidence is low.
	The inclusion of a societal benefit messaged compared to usual follow-up may lead to little or no difference in retention rates, however the GRADE of evidence is low.
	The evidence to support the use of providing a certificate of appreciation compared to no certificate is very uncertain, and the GRADE of evidence is very low.
Contact information (n=3, 1.1%)	No evidence from the Cochrane review
Non-monetary incentives – (conditional) (n=3, 1.1%)	See above for evidence for non-monetary incentives

*Note: Although the most common retention strategy in the review were the use of 'combined strategies' used we did not include this in the table as combined methods were not evaluated in the Cochrane Review (3).

Discussion

The protocols included in this review covered a wide variety of clinical specialties, intervention types, sample sizes, patient populations, numbers, and modes of participant follow-up. The overall reporting of the use of SPIRIT guidelines (21) during protocol development was low, with only 35% of RCT protocols and 34.3% of pilot and feasibility trial protocols reporting its use when developing the protocol.

The SPIRIT guidelines were published in 2013 and taking this into consideration our search started in 2014 allowing a year for guideline uptake. Despite this, our results show the reporting of the use of SPIRIT guidelines when developing protocols is still low. Given the endorsement of SPIRIT by many journals such as BMJ, The Lancet, and JAMA, and by Biomed Central Journals, we believe this is a reporting issues rather than an implementation issue. Though the level of endorsement varies, either though general support for SPIRIT, encouraging protocol authors to use SPIRIT when developing protocols or explicitly requiring protocols to adhere to SPIRIT (141), which is seen in journals such as *Trials* and PLOS ONE, trialists are inevitably aware of SPIRIT, thus confirming our view that reporting of SPIRIT is poor, while implementation of SPIRIT is undoubtedly better than we were able to provide evidence for in this scoping review. Our review searched for protocols published in 2019, in the same year the PRioRiTy II study results were published. This work highlighted the need for, and priority areas of, research required to help improve retention in trials. As a result, reporting practices may have changed in more recently published protocols, but our timeline did not capture it.

We were particularly interested in the reporting of item 18b which relates to trial retention. Adherence to this was quite low, suggesting that though trialists report using SPIRIT, reporting on retention is very poor. Of the 35% of RCT protocols that reported using SPIRIT, there was incomplete reporting of item 18b. Only 9.5% (n=24) of these protocols fully complied and included all aspects of this item, “plans to promote participant retention and to complete follow-up, including list of any outcome data for participants who discontinue or deviate from intervention protocols” (21:3). The poor reporting of plans to promote participant retention in

trial protocols could be because trial teams are initially worried about recruitment rates meaning retention is not a priority during planning but a reaction during conduct. It is also difficult to plan retention strategies when there is no evidence to support using most strategies (3), possibly lending itself into the issue of retention being considered after the fact. Additionally, strategies used to promote retention such as building relationships and maintaining rapport between trial staff and participants (69, 70) may not be reported in protocols as they may be considered more informal strategies (70) that may be difficult to plan, report and evaluate (69). Furthermore, the lack of reporting poses issues for replication, trial teams may have plans to actively promote participant retention however due to poor reporting, these plans cannot be replicated for evaluation in the future.

Regardless of reporting using SPIRIT guidelines, out of the total 722 protocols for RCTs, only 36.8% reported a proactive plan to actively promote participant retention, meaning 63.2% of protocols did not consider proactively tackling the issue of retention during protocol development. Of the 102 pilot and feasibility protocols only 40.2% outlined a proactive plan to promote participant retention. This lack of consideration for retention strategies during the design stage of the trial could be due to the emphasis on recruitment or other research priorities. Previous research shows there is still a stronger emphasis on recruitment more so than retention in trials (70, 77). Trial staff believe reasons for this include; funders and research networks place more emphasis on recruitment targets as trial performance is often based on recruitment rates (70). Additionally, there are statistical methods used in trials to predict outcomes for individuals who have not been retained based on the available data for these participants (9), a possible

factor as to why retention may not be considered as important as recruitment. This emphasis means that recruitment is incorporated into specific staff roles and trial teams may not be sufficiently informed about retention strategies (77). Retention is a widespread issue of concern within trials (3, 15) and poor retention rates should not be a surprise to trial teams, therefore, trial teams should be considering retention strategies when they are designing the trial and developing the protocol.

Not considering retention during trial design and protocol development may lead to protocol amendments, getting further ethical approval, implementing the amendments may require more time and more personnel time. Additionally, not considering retention strategies from the outset can have budget implications as some of the most routinely used retention strategies by CTUs (Clinical Trial Units) in the UK can be expensive to implement (18), the evidence to support their use is lacking (3) and few retention strategies show evidence of cost effectiveness (71). Therefore, careful consideration and foreplaning is needed to ensure resources are utilised in the best way possible to yield the highest chances of successfully retaining trial participants. We acknowledge that trial teams may have planned retention strategies but failed to report them in the protocol. This lack of communication can lead to implementation issues if there is no clear plan outlined in the protocol document as trial staff use protocols for trial conduct throughout all stages of the trial (21). A lack of information in the protocol also reduces transparency in trial conduct (21) and limits the replicability of retention strategies which has been recommended to investigate their effects on retention rates (3).

The use of 'combined strategies' was the most popular among trial teams (of those that reported a retention strategy) in protocols for both RCTs and pilot and feasibility trials. This concurs with the Cochrane review evaluating strategies to improve retention in randomised trials (3). Currently the evidence to demonstrate that retention strategies are effective at retaining participants is either weak or entirely lacking with low to moderate GRADE ratings and no retention strategy has a high certainty GRADE rating to support their use (3). Therefore, many trial teams are using strategies that may or may not improve retention rates, reinforcing the need for trial teams to plan, report in advance and evaluate the strategies used. This will help to generate evidence to determine which strategy to implement to maximise participant retention rates, while also weighing up the cost and resources required to implement the strategy. Implementing multiple strategies also needs further consideration in terms of evaluating their individual effectiveness, as this may be problematic if interaction effects between the different retention strategies are not considered.

Reducing the burden on participants to participate and to provide follow-up data is important in terms of retention (17) and identifying how best to retain participants will save time and trial costs (3). Patient and Public Involvement (PPI) in research is important and varying levels of involvement exist. Sometimes PPI members are involved in one specific aspect of the trial or they can be involved for the trial duration (142). PPI involvement (143) as well as involvement from healthcare professionals (144) during the initial stages of the trial development is important as

it can help optimise the relevance of the research to the participant (143, 144) and once the trial is developed and the research question is decided it becomes harder for PPI members to influence key trial aspects (143, 145, 146). Despite the importance of PPI involvement in the early stages of the trial such as trial development, there tends to be limited PPI input at this stage (146). This review found a lack of PPI involvement in trial protocols that reported "plans to promote participant retention". Therefore, we can only assume that PPI input was minimal at best. Thus, trial teams have lost an opportunity to ascertain if their chosen retention strategies are acceptable and suitable to their target population. This is another example of a chronic waste of participants' time, and undoubtedly adds unnecessarily to trial costs. Another important note is that the majority of retention strategies in our scoping review were generic trial population level strategies and did not make recommendations about target groups within the trial for whom retention may be poorer. There is often also an overreliance on blanket approaches to improve retention with little evidence to support their use (73, 75). Within trials there may be specific groups of individuals who are more likely to drop-out of trials than others and trial teams may need to consider this when planning retention strategies to ensure the strategies they choose target these individuals who are at a higher risk of changes to participation status. One such group would be those participants who actively withdraw from a trial.

Plans to collect outcome data for those who withdraw/discontinue or deviate from the trial protocol (SPIRIT items 18b(ii) and 18b(iii)) were also lacking. There were no

strategies that actively targeted withdrawers. Instead, the strategies were either passive - standard practice regarding continued use of collected data, or a more active plan asking participants for consent to continue data collection, despite discontinuation or deviation from the intervention protocol.

Recommendations for future research

Going forward trial teams need to consider plans to promote participant retention during protocol development, and these should be developed with PPI input. As part of this research programme, we will be conducting qualitative research to investigate why this currently does not seem to be the case, and to further delve into the nuances of these review findings. Retention strategies should be evidence-based strategies that are financially viable, operationalizable, implementable, and importantly, relevant for patients. It is also important for trial teams to consider the environmental sustainability of the retention strategies they choose to implement.

If existing evidence-based retention strategies are not suitable, or trial teams wish to use an alternative strategy, these should be evaluated alongside the trial or within the trial as a SWAT (study within a trial) to contribute to the evidence to support or not support their use. Most of the existing evidence is weak, or entirely lacking, regarding the effectiveness of retention strategies (3). The Northern Ireland SWAT Repository (https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWATStore/) contains protocols for SWATs that have a retention focus and would provide the much needed evidence

needed to decide if the most commonly used retention strategies are effective (72). We would encourage all trial teams to look at this repository and utilise it. Additionally, the Cochrane review outlines specific priorities for the evaluation of retention strategies which we urge trial teams to take guidance from (3). To ensure that resources are optimised to retain participants we need evidence to guide the decision-making process when choosing retention strategies, without this evidence resources are potentially being wasted on strategies that may or may not improve retention rates in trials.

We recommend improved communication of plans to promote participant retention. It was difficult in some cases to distinguish between the use of reminders and prompts due to the language used in some descriptions. We direct trial teams to the ORRCA retention domains (139) and to the most recent Cochrane review of strategies to improve retention in trials, with no high certainty evidence of improvements on trial retention, (3) to better communicate their retention strategies. This will assist the conduct of meta-analyses in the future.

Meaningful involvement of members from PPI groups and healthcare professionals (144) is important and valuable at the planning and design phase of a trial (142-144). Currently, not only is there a lack of planning and/or communication of plans to promote participant retention in protocols, but of those that do report a retention strategy, there appears to be little input from PPI colleagues to indicate if these methods are suitable and acceptable to use among the target audience. We

need the perspectives and opinions of these individuals to ensure that the strategies being planned are well received by the participants to have the best chance of success. In the UK the National Institute of Health Research now expects active PPI involvement in the research it funds (142, 147), but is it important this is not tokenistic (148). The Health Research Board in Ireland also recommends working with PPI colleagues in the research it funds. We also direct trial teams to read Trial Forge Guidance 3 which is available as an open access document, to ensure they are taking steps to help recruit and retain individuals from under-served groups and that members of these groups are included in PPI groups (149).

Strengths and limitations

The main strength of this review is the large sample size (n=824) which includes a wide variety of trial protocols covering different clinical specialties, intervention types etc. This means that the results are generalizable, representative of RCT protocols and are relevant to a wide variety of trial teams and researchers.

There are some limitations in this review. As mentioned in the methods section we had to make assumptions regarding some of the reported retention strategies due to a lack of detailed reporting in protocols. We assumed, based on standard ethics committees applications, that all monetary compensation would be disclosed to participants via patient information leaflets (79). This prior knowledge means that all monetary compensation acted as a monetary incentive rather than a monetary reward. Due to the use of the words reminder and prompt interchangeably we made assumptions based on the wording of the surrounding text indicating timing of delivery whether it was a reminder or prompt. Therefore, based on these

assumptions we may have misclassified certain retention strategies. We do not believe this has interfered with the overall findings and conclusions however we cannot state this for certain.

We are also aware that the published protocols in the review may not be the first iteration of the protocol, but it was not practical within the scope of our review to track down all versions of the trial protocols. A further limitation of the review is the results are restricted to protocols published in the five journals we searched (PubMed, Scopus, EMBASE, CINAHL (EBSCO), and Web of Science). We did not include grey literature or trial registries (e.g., ClinicalTrials.gov or ICTRP), protocol repositories/registries (e.g., PROSPERO and OSF) or the Cochrane library in our research. As a result, the review findings may not be generalisable to protocols published in these databases. Additionally, due to excluding clinical specific journals, such as PsycINFO from our search which specifically specialises in behavioural and mental health trials, these trial protocols may be underrepresented in this review.

Whilst EM screened and data extracted all included protocols, 10% were double screened and double data extracted by FS, and a third reviewer (KG) was consulted where disagreements arose between EM and FS during these processes. This is a limitation as there is a higher possibility of error in the screening (missed protocols/incorrect inclusion of protocols) and the data extraction (relevant data

not extracted) processes than if we had double screened and double data extracted all 824 included protocols. This may have impacted the results as relevant protocols and data, may have been excluded, therefore our results may be an underestimation of the reporting of retention strategies in trial protocols.

We also acknowledge that by the time this review is complete and published the timeline may seem out of date as it includes trials from 2014-2019 (inclusive), but we sought to establish if planning and reporting of retention plans occurs since the relevant SPIRIT 2013 guidelines were introduced and our inclusion criterion for a six-year period post 2013 was suitable for that. We still recognise however, that the findings may not as accurately reflect protocols written today, especially due to the publication of the PRioRiTy II study results in 2019. The PRioRiTy II publication emphasised the need for greater research on trial retention and may have influenced changes in retention strategy reporting practices in trial protocols in recent years which were not captured in this review.

Conclusion

The purpose of our review was to establish if and how trial teams plan for retention at the design stage of clinical trials. Results show that trial teams often do not report plans to prospectively promote participant retention at the design stage of the trial, indicating that the SPIRIT 2013 guidelines item 18b is not being fully considered by trial teams. A greater focus on prospectively planning proactive of retention strategies may inform more suitable choice of strategies and may help lay the groundwork for improving retention rates throughout the course of the trial.

Reporting these strategies in protocols also will increase replicability and transparency in trial conduct. Due to the widespread issue of poor retention in clinical trials, trial teams need to pay attention to retention.

Abbreviations

International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use – Good Clinical Practice (ICH GCP)

U.S Food and Drug Administration (FDA)

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

Prioritising Retention in Randomised Controlled Trials (PRioRiTy)

Preferred Reporting Items for a Systematic Review and Meta-Analysis Protocols Extension for Scoping Reviews (PRISMA-ScR)

Randomised Controlled Trial(s) (RCTs)

Studies within a Trial (SWATs)

Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA)

Online Resource for Research in Clinical triAls (ORRCA)

Grading of Recommendations, Assessment, Development and Evaluations (GRADE)

Clinical Trial Units (CTUs)

Patient and Public Involvement (PPI)

Declarations

Ethics approval and consent to participate

Not applicable to this scoping review of previously published protocols for randomised controlled trials

Consent for publication

Not application as this scoping review does not contain any individual person's data in any form.

Availability of data and materials

The dataset created, used and analysed during this review is available from the authors on reasonable request

Competing interests

All authors confirm that they have no competing interests

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Authors' contributions

All authors contributed to developing the review question and the review design. EM wrote the protocol and performed the searches. EM performed title and abstract screening, FS performed validation checks of this process. EM performed full text screening. EM performed data extraction and FS performed validation checks of this process. EM coded and analysed the data. EM wrote the manuscript with FS and KG providing critical manuscript feedback. All authors read and approved the final version of this manuscript.

End of Publication

5.5 Reflections and learnings

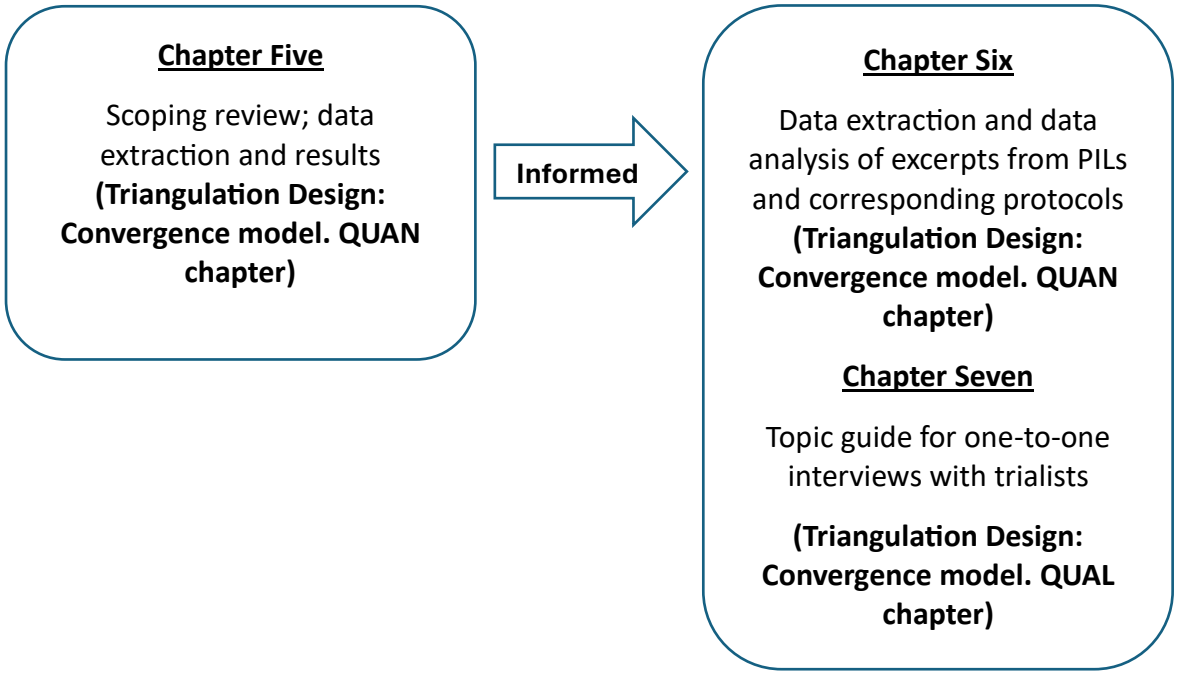
From this chapter I have one key reflection. Reporting of retention strategies in trial protocols is sparce, and inconsistent. Locating the information in the trial protocol was not easy and required a lot of time. For example, while extracting data, information on retention strategies (if reported) were not always clearly outlined in a specific section of the protocol. Retention strategies were included in various sections of the protocol, for example, in the data collection section, the follow-up of participants section, or included in different sections elsewhere in the protocol. This required reading the entire protocol carefully to ensure all relevant activities to promote retention, (whether they were clearly conceptualised to promote retention or not), were extracted. Not only do we conclude that outlining retention strategies in trial protocols is important but having them in a specific stand-alone section would be beneficial for researchers who may want to use a similar strategy in their

trial, or for those conducting research on this topic in the future. Including retention strategy information in trial protocols may be a challenge for, or neglected by trial teams, due to the already strict and extensive template guidance for protocol content (79, 80). Given the significant challenges posed by poor retention in trials, it may be beneficial to mandate certain requirements rather than merely provide guidelines outlining best practice, such as, the SPIRIT 2013 guidelines. These requirements could be enforced when trials are submitting for protocol publication, ethical, funder, or sponsor approval, or integrated into standardised templates used by trial units. This will help ensure that trial teams are thinking about potential barriers to retention, how to mitigate these issues, and retain participants from trial inception.

5.6 How this chapter links in with other chapters

The scoping review informed the data extraction and analysis of the PILs in Chapter Six. The results have also informed the topic guide for interviews conducted with trialists presented in Chapter Seven (Appendix 11 – Topic guide).

Figure 5.2. Diagram of how Chapter Five links with other chapters.



5.7 Summary of key points from the chapter

Summary of key points from the chapter

- A scoping review of trial protocols examining if, and how, trial teams plan to promote retention during the design stage of a trial found that, among main RCT protocols overall, 36.8% (n=266/722) included proactive plans to promote participant retention.
- Results indicate that trial teams are not planning retention strategies during the design stage of the trial and/or are not communicating these plans in trial protocols.
- We recommend trial teams proactively consider plans to promote retention during the design stage of the trial to mitigate barriers to retention, and to allow for these strategies to be sufficiently researched, and resourced, during the planning stages of the trial.
- Outlining these plans in trial protocols improves transparency and facilitates replication.

Chapter Six. Retention strategies are routinely communicated to potential trial participants but often differ from what was planned in the trial protocol; an analysis of adult participant information leaflets and their corresponding protocols

6.1 Introduction

This chapter presents a content analysis of participant information leaflets (PILs), to determine whether potential trial participants are being informed about retention strategies during informed consent. The chapter begins with a brief introduction and outlines why content analysis was chosen. The published paper is then presented, followed by reflections on the chapter and a summary of key points.

6.2 Rationale for the PIL analysis

The scoping review (Chapter Five) focused on whether trial teams plan and communicate retention strategies in trial protocols during the design and planning stage of a trial. This chapter focuses on the informed consent stage. In accordance with the Declaration of Helsinki, during informed consent participants "must be adequately informed in plain language of the…incentives for participants" (22:4). It does not, however, specify if this information should be provided verbally or in written format (22). Incentives can be conditional (provided on completion of follow-up activities) and unconditional (not dependent on completion of follow-up activities). Both monetary incentives, e.g., gift vouchers, and non-monetary incentives, e.g., pens, are commonly used in trials as retention strategies to encourage participants to remain in trials. There are recommendations that monetary incentives, should be outlined in PILs (79, 82). It would be, therefore,

expected that these retention strategies are routinely outlined these documents. However, apart from monetary incentives, a wide range of other strategies are used to support participant retention such as, prompts, reminders, and newsletters etc. (3, 68). Whether retention strategies, incentives or otherwise, are routinely outlined during informed consent via PILs is unclear.

Setting participants' expectations about trial participation is important to make sure they are fully informed about all aspects of the trial (17, 65, 77), as poorly setting participants' expectations may hinder retention (65). Expectation setting should encompass information about retention strategies, if planned by the point of informed consent, so participants are fully aware of all activities that are planned to occur during the trial, to aid informed decision-making.

The aim of the PIL analysis was two-fold; firstly, to establish whether retention strategies are outlined in PILs and secondly, to establish if the retention strategies outlined in the PILs were pre-planned and outlined in the corresponding trial protocol. This chapter addressed research objective three; *'to establish if trial teams communicate retention strategies in PILs, and if they do, to establish if this was pre-planned in the trial protocol'.*

6.3 Why we undertook content analysis

"Content analysis is a research technique for making replicable and valid inferences from texts (or other meaningful matter) to the context of their use" (150:2). This method of analysis provides new insights and increases understanding of a

particular phenomenon (150), in this case the communication of retention strategies in PILs and their corresponding trial protocols.

Content analysis is a method of examining qualitative or quantitative data, in either an inductive or deductive way. Since we conceptualised the data in the PILs and protocols as quantitative (Conceptualisation statement – Chapter Three, section 3.7), this approach was suitable to answer our research question. The aim of content analysis is to create a condensed and broad description of the phenomenon, by creating categories describing the phenomenon of interest (151). There are no hard and set rules for conducting content analysis. Each inquiry is different and depends on the skills, insights, and analytic capabilities of the researcher. Researchers are left to judge the most appropriate method (inductive/deductive) of content analysis to answer the research question (151). We conducted a "deductive" content analysis by using predetermined codes, to aid in the coding of identified retention strategies, informed by existing literature. To inform the predetermined codes, we used the ORRCA (Online Resource for Research in Clinical triAls) retention domains (139), retention strategies identified in the scoping review (Chapter Five), the Cochrane systematic review of strategies to improve retention in randomised trials (3), and current retention practices in the UK (68). Using the existing literature to create a categorisation matrix made our approach deductive (151, 152). Details of how this was conducted is outlined in the publication.

6.4 Thesis Paper Three

Start of Publication

Title: Retention strategies are routinely communicated to potential trial participants but often differ from what was planned in the trial protocol; an analysis of adult participant information leaflets and their corresponding protocols.

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Abstract

Background

Retaining participants in randomised controlled trials (RCTs) is challenging and trial teams are often required to use strategies to ensure retention or improve it. Other than monetary incentives, there is no requirement to disclose the use of retention strategies to the participant. Additionally, not all retention strategies are developed at the planning stage, i.e. post-funding during protocol development, but some protocols include strategies for participant retention as retention is considered and planned for early in the trial planning stage. It is yet unknown if these plans are communicated in the corresponding participant information leaflets (PILs). The purpose of our study was to determine if PILs communicate plans to promote participant retention and, if so, are these outlined in the corresponding trial protocol.

Methods

Ninety-two adult PILs and their 90 corresponding protocols from Clinical Trial Units (CTUs) in the UK were analysed. Directed (deductive) content analysis was used to analyse the participant retention text from the PILs. Data were presented using a narrative summary and frequencies where appropriate.

Results

Plans to promote participant retention were communicated in 81.5% (n = 75/92) of PILs. Fifty-seven percent (n = 43/75) of PILs communicated plans to use “combined

strategies" to promote participant retention. The most common individual retention strategy was telling the participants that data collection for the trial would be scheduled during routine care visits (16%; n = 12/75 PILs). The importance of retention and the impact that missing or deleted data (deleting data collected prior to withdrawal) has on the ability to answer the research question were explained in 6.5% (n = 6/92) and 5.4% (n = 5/92) of PILs, respectively. Out of the 59 PILs and 58 matching protocols that both communicated plans to use strategies to promote participant retention, 18.6% (n = 11/59) communicated the same information, the remaining 81.4% (*n* = 48/59) of PILs either only partially communicated (45.8%; n = 27/59) the same information or did not communicate the same information (35.6%; n = 21/59) as the protocol with regard to the retention strategy(ies).

Conclusion

Retention strategies are frequently communicated to potential trial participants in PILs; however, the information provided often differs from the content in the corresponding protocol. Participant retention considerations are best done at the planning stage of the trial, and we encourage trial teams to be consistent in the communication of these strategies in both the protocol and PIL.

Keywords: Retention, retention strategy, reporting, communication, participant information leaflet, patient information leaflet, informed consent

Background

Retention in trials has been identified as a research priority in the UK (4). It is estimated that up to 50% of trials have loss-to-follow-up rates, i.e., the proportion of participants failing to provide valid primary outcome data, exceeding 11% (3, 5). The overall result of the trial can be different if the outcomes for those not retained are assumed in the opposite direction (6, 8, 16). In high impact journals it was found that 25% of randomised controlled trials (RCTs) had a Fragility Index of 3 or less, meaning that the statistical significance of the results are lost if the outcomes for three participants are changed from not experiencing the primary outcome to experiencing the primary outcome (8, 52). Even low rates of loss-to-follow-up can cause issues for trial validity as the generalisability, the reliability and the confidence in the trial findings are affected (6-9). This contributes to research waste (13-15). To avoid these issues, the optimum solution is to retain the trial participants (16).

Retaining participants in RCTs however is challenging (3, 16) and trial teams are often required to use strategies to ensure retention or improve it (3, 68). Some of these strategies are implemented at the trial recruitment stage, e.g., video enhanced patient information versus standard information or providing a pen at recruitment versus no pen; however there is little evidence to support the use of these strategies or retention strategies in general (3). Research shows that at the recruitment stage, retention information is poorly communicated, if it is communicated at all, both in participant information leaflets (81) and in trial recruitment consultations (12). There is also an imbalance between retention

information and information on the right to withdraw, with a greater focus on participant withdrawal (12, 81). Providing a greater balance between the positives and negatives of trial participation may help aid participant retention as participants are more informed about trial expectations (153). It has been highlighted that some participants do not complete follow-up data collection due to the belief that their individual contribution did not make a difference to the trial (74). Additionally, in trial recruitment consultations it was found that potential trial participants were not provided with the opportunity to talk about aspects of trial retention that may be important regarding their initial decision to participate in the trial (12). Fixing this information imbalance may help to improve retention in trials (81).

Outlining information during informed consent helps to set participants' trial expectations (17, 65, 77) as poor expectation setting may hinder retention (65). Participant information leaflets (PILs) are required by regulation to outline information about the trial such as; the purpose of the trial, treatment information, the procedures involved, the anticipated risks and benefits, and information about data safety and handling (79, 154). There is also an ethical and moral obligation to do so (155). This information should include activities related to promoting retention if such activities are planned by trial teams. Disclosing information on monetary compensation and other supports, e.g. travel, meals, child-care, compensation for loss of earnings, etc. is recommended (79, 82). Apart from these forms of compensation there are a plethora of strategies that can be used to promote participant retention (3). However, there is no recommendation or

regulation on the need to disclose them to the participant and evidence on whether trial teams should, or not, is lacking. Additionally, some but not all strategies to promote participant retention are developed at the planning stage, i.e., post funding during protocol development (19, 70), therefore we would expect these plans to be outlined in PILs.

It is also recommended to include plans for promoting participant retention in protocols as per the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 guidelines item 18b "plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols"(21:3). Previous research shows that 36.8% of RCT protocols include proactive plans to use strategies to promote participant retention (19), but it is yet unknown if the retention strategy(ies) outlined in the protocol are communicated in the corresponding PILs.

The purpose of this study is two-fold; to establish if trial teams communicate retention strategies in PILs, and if they do, to establish if the retention strategy(ies) were outlined in the corresponding trial protocol.

Methods

Participant information leaflet and protocol selection

Our starting point was the PILs. As part of a previous research project, we collected PILs (n=214) from Clinical Trial Units in the UK and Ireland (See the "Acknowledgements" section). Given our intention was to compare the PIL to the trial protocol, the time period of interest was from 2014 to 2022, because guidelines on protocol development for trials, SPIRIT guidelines were published in 2013, and they contain an item on retention (item 18b) (21, 127). We permitted a one-year grace period to allow for uptake by trialists. There were 185 PILs corresponding to 144 protocols available in this time period. We sought the corresponding trial protocols and located 112 which were publicly available. We emailed Trial Managers and Chief Investigators to seek the remaining 32 protocols. Where a response was not received and/or the protocol could not be obtained we excluded the PIL from the analysis. Thus, 157 PILs and their 121 corresponding protocols were available for analysis. These numbers are different because some PILs corresponded to the same trial protocol, for example if a trial had a separate child and parent PIL. Our PIL repository contained PILs for both adult and paediatric RCTs. We divided the PILs into two groups: group 1 - adult PILs, for adults with capacity to make a decision for themselves, i.e., those who can provide their own consent (n=92); group 2 - child PILs, the corresponding parent PILs, legal/personal representative PILs and PILs for adults in research without prior consent. This study reports on the analysis of the 92 adult PILs and their 90 corresponding protocols.

Data extraction

The data to be extracted from both the PILs and the protocols was informed by a scoping review on the communication of retention strategies in trial protocols (19), and a prior study on reducing attrition in trials (81). These were agreed by all authors and are shown in Table 6.1. In this project we are specifically interested in SPIRIT item 18b "plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols" (21:3) . This was broken down into three parts. SPIRIT item 18b(i), plans to promote participant retention, item 18b(ii), plans to complete follow-up including list of any outcome data to be collected for participants who *discontinue* from intervention protocols and item 18b(iii), plans to complete follow-up including list of any outcome data to be collected for participants who *deviate* from intervention protocols (21, 127).

The data extraction form was piloted by EM using a sample of 5 PILs and was reviewed by FS to ensure the data extracted best met the objectives of the project. EM carried out the data extraction. Double extraction of 10% (n=9/92) of the total number of PILs was carried out by FS to ensure consistency and improve the reliability of the data extraction process. There were no disagreements. All extracted information was entered into a Microsoft Excel file.

Table 6.1: Data extracted from the participant information leaflets	
Study Characteristics	Trial name
	Year of the PIL
	Study design – cluster or individually randomised
	Phase of the trial
	Funding status

	Clinical Speciality
	Planned sample size
	Study population
	Intervention type
	Mode of follow-up
	Primary outcome
SPIRIT item 18b information	**Item 18b –** "plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols" (21:3)
	Does the PIL report item 18b(i) – plans to promote participant retention (yes or no)
	Does the PIL report item 18b(ii) - plans to complete follow-up including list of any outcome data to be collected for participants who ***discontinue*** from intervention protocols (yes or no)
	Does the PIL report item 18b(iii) - plans to complete follow-up including list of any outcome data to be collected for participants who ***deviate*** from intervention protocols (yes or no)
Retention information	Does the PIL explain the importance of retention in the trial / the importance of continued follow-up in the trial (yes or no)
	Does the PIL explain the impact of missing or deleted trial data* on the ability to answer the clinical/research question (yes or no)
Mention of Patient and Public involvement (PPI) involvement in the trial in the PIL	Does the PIL mention PPI involvement in the trial? (yes or no)
Corresponding protocol content regarding SPIRIT item 18b	
Protocol characteristics	Publication location (peer reviewed journal or trial website)
SPIRIT information	Does the protocol report using the SPIRIT 2013 guidelines when developing the protocol? (yes or no)
SPIRIT item 18b information	**Does the protocol report item 18b(i) –** plans to promote participant retention (yes or no)
	Does the protocol report item 18b(ii) – plans to complete follow-up including list of any outcome data to be collected for participants who ***discontinue*** from intervention protocols (yes or no)

	Does the protocol report item 18b(iii) - plans to complete follow-up including list of any outcome data to be collected for participants who *deviate* from intervention protocols (yes or no)
Mention of PPI in the trial in the protocol	Does the protocol mention PPI in the trial? (yes or no)

*****Deleting participant data collected prior to withdrawal (81)

Data Analysis

We analysed 92 PILs. PIL characteristics such as year, clinical speciality, mode of follow-up, sample size, population and intervention type were summarised using frequencies. Directed (deductive) content analysis was used to analyse the text from the PILs as per the process outlined by Elo and Kyngas (151, 152, 156, 157). This process has three main phases; the preparation phase, the organisation phase and the reporting phase (151, 152). Data were presented using a narrative summary and frequencies where appropriate.

The preparation phase

Prior to starting the extraction process, for the purposes of this study we defined a retention strategy as an activity/action that is conducted with the purpose of reducing missing data or improving data completeness. We did not extract information on improving adherence or compliance to an intervention. We also read relevant literature on retention strategies in clinical trials (3, 68, 139). This helped identify the types of retention strategies to look for during data extraction. The unit of analysis was the PIL. The meaning unit was defined as the textual unit within the PIL, i.e., the passage of text that represents a retention strategy.

The organisation phase

In each PIL we extracted any text that represented a retention strategy. All the meaning units were re-read and each of the passages was coded using predetermined codes which were derived from the Cochrane Review on strategies to improve retention in randomised trials (3), and retention strategies that were identified and routinely used by UK Clinical Trial Units (68). These codes were then mapped to the ORRCA (Online Recourse for Research in Clinical triAls) retention domains (139). The ORRCA project brings together work in the field of recruitment and retention into searchable databases, the ORRCA retention domains are the key retention themes seen throughout the database (158). Where multiple codes were identified within a single PIL a new code was developed; 'combined strategies'. Examples of the coding process are shown in Table 6.2. The full list of ORRCA domains and examples of codes within each domain can be seen in Supplementary File 1.

Table 6.2: Example of the coding process

Example from the PIL	**Pre-determined code**	**ORRCA Domain**
"As a thank you for taking part in the study and for completing the questionnaires, we will reimburse you for your time on this study after you have completed the 6 month questionnaire".	**Monetary incentive – conditional** - direct cash provided to participants/gift vouchers, prizes that are monetary – conditional based on the participant doing/completing an activity.	B2. Monetary incentives
"Although you won't be paid to take part in the study, we are able to cover all your expenses to attend the study visits. In most cases, we are happy to book a taxi for you to attend and go home	**Supporting participation** - If participants travel fees are remunerated, parking, day-care for their children is covered by the trial.	B7. Supporting participation

afterwards, as well as support any costs for food and drink".		
"We would be very grateful if you would complete them and post them back in the provided prepaid envelope".	**Data collection location and method** - If participants are provided with pre-paid return envelopes. If participants are offered multiple/alternative options of data collection.	A3. Data collection location and method

The reporting phase

We report the results regarding the communication of retention strategies in terms of SPIRIT items 18b(i) plans to promote participant retention, 18b(ii) plans to complete follow-up including list of any outcome data to be collected for participants who ***discontinue*** from intervention protocols, and item 18b(iii) plans to complete follow-up including list of any outcome data to be collected for participants who ***deviate*** from intervention protocols (21, 127). We present this information from the PILs, and we then compare the PIL and protocol content.

Results

Ninety-two PILs corresponding to 90 RCT protocols were included in the analysis. Figure A6.1 displays the flow diagram, showing the number of PILs at each stage of the screening process.

Participant information leaflet characteristics (results in Table 6.3)

Though we collected PILs from the UK and Ireland, only PILs from the UK remained after the exclusions. In summary, the majority, 95.7% (n=88/92) were for individually randomised trials. PILs for non-drug trials made up 42.4%(n=39/92) and 91.3% (n=84/92) were for non-commercial trials. A full breakdown of the PIL and associated trial characteristics are presented in Table 6.3.

Table 6.3: PIL characteristics	
PIL characteristics	**Number of PILs (%) Total N = 92 PILs from 90 trials thus 90 protocols**
Year	**Number of PILs (% out of total of 92 PILs)**
2014	9 (9.8%)
2015	12 (13%)
2016	19 (20.7%)
2017	15 (16.3%)
2018	22 (23.9%)
2019	3 (3.3%)
2020	7 (7.6%)
2021	4 (4.3%)
Not clear	1 (1.1%)
Funding status	
Non-commercial	84 (91.3%)
Commercial[1]	7 (7.6%)
Not clear	1 (1.1%)
Level of randomisation	
Individually randomised trials	88 (95.7%)
Cluster randomised trials	3 (3.3%)

Not clear	1 (1.1%)
Sample size	
200 and less	12 (13%)
201-400	14 (15.2%)
401-600	14 (15.2%)
601-800	5 (5.4%)
801-1000	6 (6.5%)
1001 and more	12 (13%)
Not clear	29 (31.5%)
Median sample size	500 participants
Study population	
Vulnerable[2]	15 (16.3%)
Mix of vulnerable and non-vulnerable populations	10 (10.9%)
Not vulnerable	2 (2.2%)
Not clear	65 (70.7%)
Intervention type	
Non-drug	39 (42.4%)
Drug	31 (33.7%)
Surgical	8 (8.7%)
Mix of the above intervention types	14 (15.2%)
Mode of follow-up	
Clinic visit	12 (13%)
Postal follow-up	6 (6.5%)
Use of routine databases/routine data	3 (3.3%)
Data collected via home/site visits	2 (2.2%)
Telephone follow-up	1 (1.1%)
All data collected while participant is in hospital	1 (1.1%)
Online follow-up	1 (1.1%)
Combinations of the above methods of follow-up	64 (69.6%)
Not clear from PIL	2 (2.2%)
Clinical speciality	**Number of PILs (% out of total of 92 PILs)**
Obstetrics and Gynaecology	14 (15.2%)

Oncology	13 (14.1%)
Nephrology and Urology	12 (13%)
Neurology	9 (9.8%)
Musculoskeletal disorders/illnesses	8 (8.7%)
Cardiology	7 (7.6%)
Vascular diseases	5 (5.4%)
Public Health	4 (4.3%)
Infectious Disease	3 (3.3%)
Gastroenterology	3 (3.3%)
Respiratory illnesses	2 (2.2%)
Immunology	2 (2.2%)
Ophthalmology	2 (2.2%)
Dermatology	2 (2.2%)
Diabetes and Endocrinology	2 (2.2%)
Dental Health	1 (1.1%)
Mental Health	1 (1.1%)
Genetic Conditions	1 (1.1%)
Sexual Health	1 (1.1%)

[1]Commerial trials were defined as a trial that has any type of funding or donation from a private for-profit company/organisation for example partly funded by pharma or product provided by a commercial company was classified as a commercial trial. [2]Vulnerable populations were defined via local ethics committee definition (140) and ICH-GCP definition (79) these included; infants and children aged 17 years and under, pregnant women, institutionalised individuals (prisoners, in nursing homes, mental health institutions), critically ill/ICU patients/patients on ventilators unable to provide consent so deferred consent is gained, where stated in the protocol deferred consent is obtained, adults aged 60 and over, participants with learning disabilities, suffers of dementia, adults with terminal illness, homeless individuals and refugees, adults with mental illness, and members of the armed forces and medical/nursing/dental/pharmacy students where there is a hierarchy in the trial that would influence the decision to take part voluntarily.

Communication of plans to use strategies to promote participant retention in PILs.

Proactive plans to use strategies to promote participant retention (results in Table 6.4)

SPIRIT item 18b(i) "plans to promote participant retention" were communicated in 81.5% (n=75/92) of PILs. The categories and examples of the strategies to promote participation retention are outlined in Table 6.4. We found 57.3% (n=43/75) of PILs communicated plans to use 'combined strategies' to promote participant retention. The joint most common 'combined strategies' were 'supporting participation' combined with 'data collection location and method', and 'data collection location and method' combined with 'data collection scheduled with routine care' (14%; n=6/43). 'Data collection location and method' encompasses activities such as providing pre-paid return envelopes and choice of data collection methods. See a full breakdown of all 'combined strategies' in Supplementary File 1.

In terms of individual strategies to promote retention, the most common was telling the participants that data collection for the trial would be scheduled during routine care visits (16%; n=12/75). Methods of supporting participation such as covering the cost of travel to trial appointments, was next most frequently used (12%; n=9/75). The use of reminders and collecting additional contact information were the least popular strategies (1.3%; n=1/75).

Table 6.4: Frequency and quotes from the PILs of SPIRIT item 18b(i) plans to promote participant retention.	
Does the PIL report SPIRIT item 18b(i) "plans to promote participant retention"	**Number of PILs (% out of total of 92 PILs)**
Yes	**75 (81.5%)**
No	17 (18.5%)
Examples from the PILs of plans to use strategies to promote participant retention. Percentage out of the number of PILs with a retention strategy (n=75)	
'Combined strategies' 43 (57.3%)	"Filling out the diary will take about five minutes at the end of each day. This can either be on paper form or over the internet. We will send you a brief text message or phone you every week to remind you complete this". – "Reasonable travel expenses will be reimbursed for all research visits".
	"We will provide you with a £10 high street voucher each time you complete the package of questionnaires as a thank you. If two parents from each family take part in the study, the second parent will be given a £15 high street voucher as a thank you for each time the questionnaire package is completed" – "You will have the choice to complete these questionnaires yourself by post, or with a researcher during a visit to your home or over the telephone".
	"We ask that you complete and return this to the Research team in the stamped addressed envelope provided. We will remind you with a letter and via telephone if you do not return your questionnaires". – "Travel expenses for your research appointments will be refunded by the Research team. We are not able to pay travel expenses for your physiotherapy treatment".
Data collection scheduled with routine care 12 (16%)	"The study visits fit into your normal clinical care".
	"You will be followed up as you normally would at your hospital so there are no extra visit".

Supporting participation 9 (12%)	"All travel costs will be reimbursed and parking will be provided free of charge. For patients unable to drive, taxi transfers can be provided free of charge to and from the hospital".
	"You will not be paid for taking part in this trial. However, we will reimburse you for any travel expenses you incur for visits resulting from your participation in the trial, as by participating in the trial, you will be asked to attend more clinics at your GP surgery. If independent travel is difficult for you and might preclude your participation in the trial, you can contact the trial team directly who will discuss alternative arrangements for travel with you".
Data collection location and method 6 (8%)	"You will be asked to complete these, and then post them back to BCTU in the freepost envelope they will send you".
	"Completing 6 short questionnaires on your muscle symptoms every 2 months. There are a few ways in which you can choose to complete the questionnaires; via the web, verbally over the phone, mobile phone app or conventional paper form".
Monetary incentives 3 (4%)	"You will receive £40 in shopping vouchers for completing the study".
Reminders 1 (1.3%)	"The study team will telephone you to remind you to return your questionnaires".
Contact information 1 (1.3%)	"With your permission, we may also contact your General Practitioner (GP) prior to contacting you, or if we are not able to reach you directly".

SPIRIT item 18b(ii) and item 18b(iii); Reactive plans to continue collecting follow-up data for participants who discontinue and deviate from trial protocols

SPIRIT item 18b(ii) "Plans to complete follow-up including lists of any outcome data to be collected for participants who *discontinue* from intervention protocols" (21:3) were communicated in 44.6% (n=41/92) of PILs, e.g., "You can withdraw from the study at any time without giving a reason. However, we would like to keep in contact with you to let us know your progress". SPIRIT item 18b(iii) "plans to complete follow-up including list of any outcome data to be collected for participants who *deviate* from intervention protocols" (21:3) were not communicated in any of the PILs.

The importance of retention in the trial and the impact of missing data (results in Table 6.5)

Quotes relevant to the importance of retention in the trial and the impact of missing data are shown in Table 6.5. The importance of retention in the trial was explained in 6.5% (n=6/92) of PILs. Explaining the impact that missing or deleted data (deleting data collected prior to withdrawal) has on the ability of the trial to answer the research question (81), was mentioned in 5.4% (n=5/92) of PILs. These explanations focused on explaining that the data collected in the trial is valuable to the research/study.

Table 6.5: The importance of retention in the trial and the impact of missing data on the ability to answer the research question	
Does the PIL explain the importance of retention in the trial/the importance of continued follow-up in the trial?	
	Number of PILs (%)
Yes	**6/92 (6.5%)**
	Examples from PILs "It is really important that you try to complete all follow-up assessments, whichever group you are allocated to, and even if you stop making use of the online sites. This ensures we have all the information we need to properly test how well each site works in improving outcomes for relatives (or close friends)"
	"For *[trial name]* to produce the best results it is important that participants stay in the study for the entire time."
No	86/92 (93.5%)
Does the PIL explain the impact of missing or deleted trial data* on the ability to answer the clinical question?	
	Number of PILs (%)
Yes	**5/92 (5.4%)**
	Examples from PILs "Even if you stop taking part in the study, the information we have recorded about you and the samples you have provided whilst you were in the study may still be used. You can ask for these to be destroyed but please consider, and perhaps discuss with us, how valuable these are to our research before making your decision".
	"The questionnaires will be completed when you attend for your treatment or follow-up appointments and will take approximately five minutes to complete. It is very important for you to answer all the questions in the questionnaire for us to accurately assess the impact of the treatment upon you".
No	87/92 (94.7%)

***Deleting participant data collected prior to withdrawal (81)

Patient and public involvement outlined in the PIL.

In terms of Patient and Public Involvement (PPI), 7.6% (n=7/92) of the PILs communicated that there was PPI involvement in the trial. One example is as follows "A group of patients and members of the public helped to develop this

research topic and the research questions that should be asked. The group helped to design the study and develop this leaflet. They will continue to be involved throughout the study". See Supplementary File 1 for more examples.

Comparison of strategies to promote participant retention in the PILs and their corresponding protocols (results in Table 6.6)

Overall, 81.5% (n=75/92) of PILs report "plans to promote participant retention"; these 75 PILs correspond to 74 protocols (two PILs correspond to one protocol). Of these 75 PILs and 74 corresponding protocols, there are 59 PILs corresponding to 58 protocols where both the PIL and the protocol communicate plans to use strategies to promote participant retention.

Out of the 59 PILs and 58 matching protocols, 18.6% (n=11/59) communicated the same information relevant to the participant, the remaining 81.4% (n=48/59) of PILs either only partially communicated (45.8%; n=27/59) the same information or did not communicate the same information (35.6%; n=21/59) as the protocol regarding the retention strategy(ies). In 21.3% of PILs (n=16/75) that outlined a plan to promote participant retention, this plan was not communicated in the corresponding protocol. Examples are shown in Table 6.6. A full list of all protocol and corresponding PIL content is in Supplementary File 1.

Table 6.6: PIL content compared to protocol content; plans to use strategies to promote participant retention	
Communication the same information	
PIL content	**Protocol content**
We will send you up to two reminders and will aim to contact you by post, email and/or telephone, taking into account which communication method is best for yourself	At six weeks after surgery, participants will complete a questionnaire to measure Pain Numerical Rating Scales (NRS), time to return to normal activities and acceptability, EQ5D and SF12. At six months after surgery and at 15 months following randomisation, participants will complete the SF12, MMAS, EQ5D, satisfaction with treatment and questions about healthcare utilisation. Participants will receive up to two reminders by post, email or phone, taking into account any preferences they may have for mode of communication
These follow up appointments will coincide with your usual regular clinic appointments	Patients will be assessed at 3 monthly intervals from baseline to 3 years in the patient's routine outpatient clinic visit as per the trial schedule of assessments
Partially communicate the same information	
PIL content	**Protocol content**
We will ask you for your name, email address and alternative telephone numbers so that we can contact you to find a suitable time to conduct these questionnaires. In the event that we are unable to contact you, for example your contact details change, we may request further information about you from your Local Authority so that we can reach you - For your time and contribution to the study we would like to provide you with a voucher worth £20 for each questionnaire you take part in as a thank you for taking part	We will make every effort to ensure retention. At enrolment, participants will be asked to provide alternative telephone numbers, email addresses and any other forms of communication that may be helpful to contact them. Researchers will endeavour to build a positive rapport with each participant for subsequent follow-up. Participants will also be emailed/posted vouchers as a reimbursement for their time after each questionnaire. **Finally, a third-party text messaging platform**

	(Esendex) will be used to send text messages to participants to keep in touch, or remind them of their follow-up contact
We will provide you with a £10 high street voucher each time you complete the package of questionnaires as a thank you. If two parents from each family take part in the study, the second parent will be given a £15 high street voucher as a thank you for each time the questionnaire package is completed - You will have the choice to complete these questionnaires yourself by post, or with a researcher during a visit to your home or over the telephone	Retention strategy To maintain engagement, encourage retention and to thank family caregivers for their time, primary carers will be provided with a £10 high street voucher when contacted to complete follow-up data collection, as has previously been shown to be effective. **Contact details will be collected during recruitment, and participants will be reminded by email and text message when a data collection follow-up is due and to complete questionnaires when posted. Participants will also receive a study newsletter at approximately 9–10 months post randomisation to maintain participant engagement**. Participants will be offered three methods of data collection: via telephone, postal or face-to-face at a convenient location. **For non-responding participants, a minimum data set (consisting of 3 prioritised outcome measures (Warwick Edinburgh Well-Being Scale, EQ-5D and Parenting Sense of Competence Scale) aligning with the intervention logic model and taking into consideration participant burden) will be offered to reduce participant burden and maximise follow-up rates.**
Do not communicate the same information	
PIL content	**Protocol content**
We will offer you a total of £20 in vouchers as a thank you for taking part. We will	All participants will be provided with study progress updates at 3

offer £10 for completing the first set of questionnaires and another £10 when you complete the third set of questionnaires at 12 months - Initial postal questionnaire sent with a pre-paid return envelope	and 9 months via a newsletter to maintain engagement with the trial and encourage response rates of follow-up questionnaires. The newsletter does not provide any detail on the *[study name]* intervention - All participants complete self-reported outcome measures in the form of questionnaires (IPSS, ICIQ-UI-SF,EQ-5D-5 L and B-IPQ) at baseline (postal), 6 and 12 months (postal, online or phone) post enrolment. Participants are sent one reminder to return their baseline materials, and up to three reminders to return their 6- and 12-month questionnaires.
You will not be paid for taking part in this trial. However, we will reimburse you for any travel expenses you incur for visits resulting from your participation in the trial, as by participating in the trial, you will be asked to attend more clinics at your GP surgery. If independent travel is difficult for you and might preclude your participation in the trial, you can contact the trial team directly who will discuss alternative arrangements for travel with you	Where questionnaires are not validated for use on a tablet computer, or where individuals are not comfort able using one, paper copies will be made available for completion
Examples of plans to use strategies to promote participant retention communicated in the PILs but not outlined in the trial protocol	
"All travel costs will be reimbursed and parking will be provided free of charge. For patients unable to drive, taxi transfers can be provided free of charge to and from the hospital"	
"To collect the information we need, everyone in the study will be sent questionnaires by post approximately 1, 3, 6, 18 and 27 months after you join the study. The questionnaires ask about your vision and general health. We will send you up to two reminders and will aim to contact you by post, email and/or telephone, taking into account which communication method is best for you"	

Discussion

This study has demonstrated that a high proportion of PILs outlined plans to use strategies to promote participant retention (81.5%; n=75/92) but not all corresponding protocols outlined or transparently communicated plans to use strategies to promote retention. Information was either partially communicated or completely different information was communicated in the PIL when compared to the protocol. Among PILs and corresponding protocols that both outlined a retention strategy(ies); there was a miscommunication regarding the retention strategy(ies) in 81.4% (n=48/59 PILs) of PILs compared to their corresponding protocol. Not all participant relevant information about plans to use retention strategies outlined in the protocol were communicated in the PIL, for example participants were not informed about reminders, newsletters or the option for paper-based questionnaire completion via PILs despite these plans being outlined in the corresponding protocol (see Table 6.6 and Supplementary File 1 for more examples). Miscommunication may potentially cause issues, if participants are not aware and do not expect to receive, for example, reminders if they miss data collection points. This could negatively impact their feelings towards remaining in the trial and lead to drop out. Poor trial expectation setting may be a reason why participants no longer remain in trials (17). Prior research shows that among participants who failed to return trial questionnaires at least once, the trial activities did not meet their initial expectations. They did not expect to receive the same questionnaire more than once and therefore did not send it back (65). Trial expectation setting should involve clearly communicating information regarding retention strategies that will be used in the trial via PILs. We have shown there is a

lack of follow-through when communicating this information in PILs. It is unclear why this is the case. Trial teams may fear that providing too much information may deter participation and negatively impact recruitment. Conversely though, improving knowledge and setting expectations regarding retention may lead to more meaningful participation and improve retention, but this is only speculation (74).

Using newsletters, pre-paid envelopes for returning questionnaires, telephone reminders and collecting data during routine care visits, are all within the top 10 most routinely used retention strategies in the UK (68). This finding is reflected in the PILs e.g., the most popular individual retention strategy was 'data collection scheduled with routine care' (16%; n=12/75). These routinely used retention strategies are also seen in the 'combined strategies'. There are signs that trial teams are planning to tackle the issue of poor retention during the early stages of the trial and communicating these plans with potential trial participants during recruitment, as evidenced by the inclusion of retention strategies in protocols from previous work (19) and protocols and PILs in this work. There is, however, no high-quality supporting evidence to show that the majority of retention strategies that are being used in trials improve participant retention rates (3). Based on cost estimates, these strategies can be very expensive to implement (18) and the cost effectiveness of retention strategies is yet to be shown (71). Early planning of strategies (ideally during grant application and subsequent protocol development) to improve retention may increase the likelihood of successful implementation of these plans. Certainly, if planned for early, the resources that are needed will be budgeted from the outset. Without supporting evidence however, resources are still potentially

being wasted implementing activities that may or may not improve participant retention rates.

In 21.3% (n=16/75) of PILs that communicated plans to use retention strategies to promote participant retention, these retention strategy plans were not included in the corresponding trial protocols. This would indicate that although trial teams plan to use retention strategies during the planning stage of the trial, they do not communicate this information in the trial protocols. We know very little as to why this is the case, and we plan to do a follow-up qualitative interview study with members of trial teams to tease this out. We know that the SPIRIT 2013 guidelines recommend the inclusion of plans to promote participant retention (21, 127) but do not know why trial teams fail to do so. Our findings here lead us to believe it is a reporting issue rather than a planning issue. This poses issues for the replication of plans to promote participant retention, which is needed to produce evidence to evaluate the effectiveness of the retention strategy in the future. Evaluating retention strategies is essential considering the lack of existing evidence to support their use in trials (3). While it is encouraging that trial teams are considering retention during the early stages of trial development and communicating plans to use strategies to promote retention, reporting it in the protocol is essential for good practice.

Although trial teams are reasonably good (81.5% of PILs; n=75/92) at informing potential trial participants about their intention to promote participant retention,

the value and importance of ongoing participation to the trial results is not well communicated in PILs (6.5%; n=6/92). This is a well-known phenomenon, whereby the potential harms are well communicated but potential benefits receive less attention (159). Even less information is provided on the impact that missing or deleted (deleting data collected prior to withdrawal), data has on the ability of the trial to answer the research question in the PILs (5.4%; n=5/92). These findings are reflective of previous research (12, 81). Without providing information regarding the importance of retention/the consequences of leaving to the trial, participants may be unaware of the value of their ongoing participation. Interviews with trials participants who had discontinued trial participation by either not returning for at least one follow-up clinic visit or not returning at least one follow-up questionnaire found some participants could not identify the negative consequences of not returning follow-up data. A reason for this cited by authors was due to the fact participants expected the trial team to send another questionnaire or reschedule the appointment, further adding to the need for clearer communication regarding what is involved in trial follow-up and ongoing participation requirements. Additionally, some participants were unsure their contributions made much of a difference to the trial (74). Other research has found that sometimes participants are not aware they are considered as non-retainers by trial teams (17, 74). This raises questions about how much trial participants understand about the requirements for and value of remaining in the trial. It may be valuable to retention rates to explain this information in PILs; potential participants will be better informed about the importance of continuing to provide follow-up data to the trial. Granted, providing information on the value and importance of remaining in the

trial may be difficult as it may be perceived as coercive (81) but a balance needs to be achieved between information on withdrawal and the importance of retention, as participants want to know what is expected of them when they participate in a trial (160).

Strengths and Limitations

It is a significant strength in this study that we compared the content regarding plans to use strategies to promote participant retention communicated in the PILs with the corresponding protocol as it allowed for a more detailed analysis of the communication process between trial teams and potential trial participants. We also recognise some weaknesses. Although we aimed to include PILs from both Ireland and the UK, our eligibility criteria meant only PILs and protocols from trial units in the UK were included. However, the sample is representative of PILs from the UK, as it includes PILs from more than 20 CTU's and a variety of populations, clinical specialities, and intervention types. Additionally, the findings of this piece of work may not be generalisable to PILs for children and the corresponding parent PILs, PILs for legal/personal representatives and PILs for adults in research without prior consent, as these PILs have not been included in the sample.

PILs are only one source of information that is provided to potential trial participants during the informed consent stage. We are aware that participants may be verbally informed about plans to use strategies to promote participant retention during conversations with trial staff during the consent stage of the trial. This information has not been captured. However since retention is seldom discussed in

consent consultations (12) it is likely that plans to use strategies to promote participant retention are also seldom mentioned.

Recommendations

We recommend and advocate for PILs to be transparent and include information specifically regarding retention strategies, and information on the value and importance of remaining in a clinical trial, as we feel it is important to set trial expectations with the hope of leading to improved retention rates. We acknowledge, however, that existing PILs are exceptionally long and that a balance needs to be struck between providing potential participants with information on retention and the risk of information overload. Potential trial participants have outlined that they want to know what is expected of them if they take part in a clinical trial, and this includes information on follow-up and retention requirements (160). Additionally, most people only access the minimum required information that provides a broad understanding of a project and what would be required if they chose to participate (161); this again speaks to retention. Trial teams may not want to outline certain retention strategies such as the option of collecting the minimum dataset needed for the primary outcome, as it may mislead participants to what is expected in terms of ongoing trial participation. It is understandable why this information is not included in the PIL but in these scenarios we advocate for participation to be made as burden free as possible from the outset of the trial. For retention strategies such as reminders, prompts, incentives, and other activities that participants may be receiving we recommend trial teams to outline these from the outset of the trial. Additionally, it is also recommended that trial teams make it clear

to participants if trial withdrawal can be nuanced. Depending on the trial, participants may be able to continue participating with less commitment if they are struggling to meet all trial requirements, or if they decide to stop receiving the intervention, that their follow-up data can still be collected and valuable to the trial results (50).

Despite the communication of plans to use retention strategies to promote retention in the PILs, there is still a lack of evidence to support the use of many strategies that trial teams are planning (3). We recommend that if trial teams are planning on using strategies to promote retention that they also plan to evaluate these strategies to add to the evidence base to either support or not support the use of retention strategies going forward. Trialist can evaluate retention strategies by using a SWAT (study within a trial) on which there is lots of guidance (72) and the Northern Ireland SWAT repository (SWAT Store | The Northern Ireland Network for Trials Methodology Research (qub.ac.uk)) contains protocols for SWATS that are focused on improving retention in trials that need to be evaluated in order to determine if they are effective or not at improving retention rates. We encourage trialists to look at these resources if they are interested in formally evaluating retention strategies. Clear communication of plans to use retention strategies in the trial protocol will also allow for replication of these methods for future evaluations.

We recommend that when choosing a retention strategy, the suitability of the strategy to the target population should also be considered. Similar to findings of

our recent scoping review (19), among the PILs most retention strategies were generic retention strategies that did not specifically target groups more 'at risk' of dropping out, for example participants who actively withdraw from the trial. Research using individual patient data within specific contexts has been able to identify participants most at risk of leaving the trial, for example participants with co-morbidities (76), these groups may need to be specifically targeted going forward depending on clinical context. Participant demographic characteristics may need to be considered by trial teams going forward as there may also be cultural and generational differences in terms of preferences for retention strategies and what different groups find acceptable. Having PPI input on retention strategies may help with this decision, although evidence as to whether PPI aids in participant retention is uncertain (142). Irrespective of this, participants want to know how patients and members of the public have been involved in the design of the study (160). Perhaps, going forward this is a piece of information that trial teams should try to include in PILs.

Conclusion

Retention strategies are often communicated in PILs, but information provided to the potential trial participant is different from the information outlined in the protocol. This miscommunication may negatively impact on participants trial expectations. Furthermore, without explaining the importance of retention in the trial, it is hard to expect potential participants to understand the reasons why these activities are conducted. Providing this information sets trial expectations and provides participants with a more well-rounded understanding of participation and

withdrawal in a trial. Additionally, in some cases plans to promote retention outlined in the PIL are not included at all in the corresponding protocol. While results indicate that trial teams appear to be considering participant retention at the early stages of the trial, they do not always communicate this information in the trial protocol nor communicate the same information in the PIL as outlined in the protocol.

Abbreviations

Randomised Controlled Trials (RCTs)

Participant Information Leaflets (PILs)

Clinical Trial Units (CTUs)

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

Patient and Public Involvement (PPI)

Online Resource for Research in Clinical Trials (ORRCA)

Study Within A Trial (SWAT)

Declarations

Ethics approval and consent to participate

Not applicable to this project.

Consent for publication

Not applicable as this project does not contain any individuals personal data in any form.

Availability of data and materials

The dataset created, used, and analysed during this project is available from the authors on reasonable request.

Competing interest

All authors confirm that they have no competing interests

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Author's contributions

EM carried out the data extraction, coding, results synthesis and write up of this manuscript. FS carried out data extraction checks. All authors reviewed the manuscript.

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End of Publication

6.5 Reflections and learnings

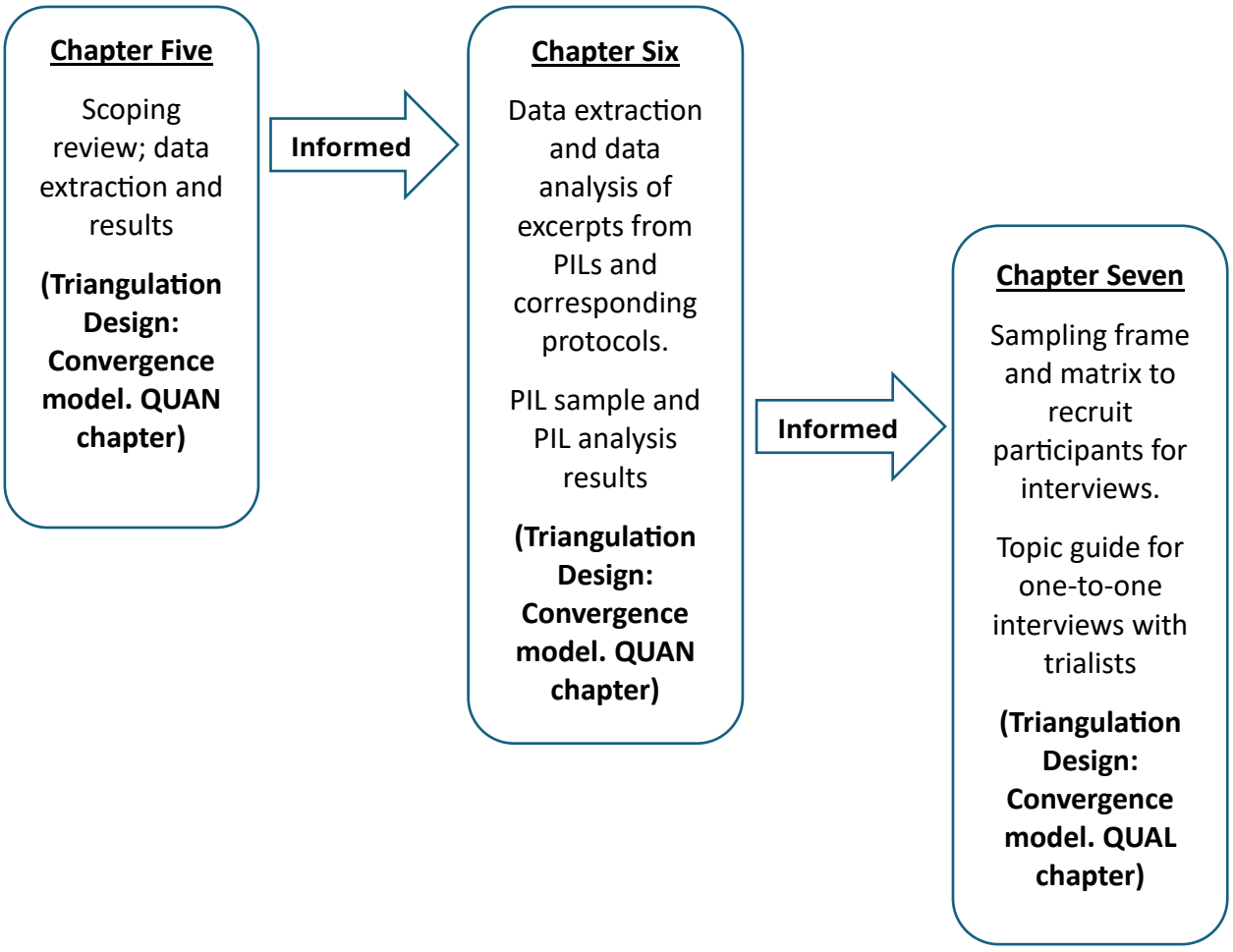
I have two key reflections. Firstly, retention strategies are often outlined in PILs, which indicates that trial teams are clearly considering and planning these strategies proactively during the trial design, and planning stages. Results from the scoping review, however, would indicate otherwise. In some cases, perhaps, these plans are in place but just not reported in trial protocols. This raises questions about the formal documentation of these strategies. If retention strategies are not outlined in trial protocols, where are they documented?

Secondly, there is a lack of information about the importance of retention. The PILs rarely outlined how important continued participation is for the trial, and the impact that missing data has on the trials' ability to answer the research question. Although not a key objective of the analysis, it adds to existing literature on the communication of the importance, and relevance, of continued participation in trials (81). This information should be communicated during informed consent, via PILs or verbally, for participants to be fully informed about what their ongoing participation means for the outcome of the trial, the validity and reliability of the trial results. It may cause participants to reconsider their commitment to the trial, and make them more aware of how their participation can impact the wider applicability of the trial results, rather than only considering the benefits and risks involved for themselves as individuals.

6.6 How this chapter links in with other chapters

Data extraction in this chapter was informed by the scoping review (Chapter Five). In the scoping review we extracted retention strategy information from trial protocols in line with SPIRIT 2013 guideline item 18b. We used the same data extraction approach in this chapter. Additionally, the retention strategies identified in the scoping review informed the deductive nature of the PIL analysis (details in published paper). The PILs informed the sampling frame and the sampling matrix to recruit participants for the interviews conducted in Chapter Seven. Results informed the topic guide for these interviews (Appendix 11 – Topic guide).

Figure 6.2. Diagram of how Chapter Six links with other chapters.



6.7 Summary of key points from the chapter

Summary of key points from the chapter

- There is no existing literature on whether retention strategies are outlined in PILs. We conducted a content analysis of PILs and their corresponding protocols to contribute to this evidence gap.
- In our sample, retention strategies are frequently outlined in PILs (81.5%; n=75/92). The importance of retention (6.5% (n=6/92)), and the impact that missing, or deleted, data has on the trial's ability to answer the research question (5.4% (n=5/92)), were rarely explained.
- In this sample, the information communicated in PILs and corresponding protocols about retention strategies was inconsistent. PILs either partially communicated (45.8%; n=27/59) or did not communicate retention strategy information (35.6%; n=21/59) outlined in their corresponding protocol.
- To clearly set trial expectations, PILs should make potential participants aware of planned retention strategies, and the importance and value of continued trial participation.
- Retention strategies should be considered during the trial design and planning stages, with input from PPI to help ensure the suitability of the chosen strategy.
- Formal evaluation of retention strategies via SWATs is needed to contribute evidence to whether these strategies are effective, and should be used to promote retention.

Chapter Seven. Planning and communicating retention strategies in clinical trials; a qualitative interview study.

7.1 Introduction

This chapter presents one-to-one interviews with trialists in the UK and Ireland. The chapter outlines the rationale for the interviews, and the analysis method. The paper will be submitted for publication in April 2025, an extended version of this is presented. The chapter continues with my statement on reflexivity, reflections and learnings, and concludes with a summary of key points.

7.2 Rationale for the interviews

Results from the scoping review (Chapter Five) and the PIL analysis (Chapter Six) raise questions about whether trialists, i.e., anyone whose role includes the design, delivery, analysis in clinical trials e.g., trial managers, principal investigators, statisticians, research nurses, study co-ordinators etc., proactively plan retention strategies during the design and planning stages of the trial. Questions also remain regarding how these strategies are documented and communicated within trials. Existing research conducted by Daykin et al. (70) and Brueton et al. (69) has explored trial staff perspectives on the types of retention strategies used in trials, their perceived appropriateness, and the factors that influence retention. Our study builds on this work by focusing more specifically on the planning and communication of retention strategies, providing complementary findings but also offering new insights, particularly regarding the communication of retention strategies in trial documents. This chapter provides insights on when during the trial retention strategies are planned and implemented, what strategies are chosen, how

choices are made, and how strategies are communicated in trial documents, to others involved in delivering the trial, and trial participants. Answering these questions will help provide evidence to help address question 10 of the PRioRiTy II study, "how should people who run trials plan for retention during their funding application and creation of the trial (protocol development)" (4). This chapter addressed research objective four *"to get a more in-depth understanding of trialists' views and opinions on retention strategy planning and communication in trials"*.

7.3 Methods

7.3.1 Why we chose Framework analysis

The Framework method is a systematic and flexible approach to analysing qualitative data. It is not tied to a specific epistemological standpoint (162); therefore, it fits into our overarching research paradigm of pragmatism (The paradigm of pragmatism - Chapter Three, section 3.3). Framework analysis is a comparative approach to thematic analysis due to the use of a matrix framework. The matrix allows researchers to identify any patterns, differences, and similarities between cases across identified themes (163, 164). This approach helped identify similarities and differences in patterns in the data within and between different groups of trialists we interviewed, e.g., trial managers, research nurses, principal investigators etc.

7.3.2 Framework analysis

In this section a detailed description of the stages of Framework analysis are outlined while a summary is provided in the paper below in section 7.4.

The Framework analysis developed by Ritchie and Spencer was used to analyse the data (164). Guidance from Ritchie and Spencer (164) as well as Gale et al. (162) were followed. Stage one; Transcription. Interviews were transcribed by a third-party transcription service; NJC Secretarial (165). Stage two; Familiarisation. EM listened to all interview recordings and read all the transcripts to carry out anonymisation and become familiar with the data. The Rapid Research Evaluation and Appraisal Lab (RREAL) sheets, a document summarising each interview (RREAL sheets - section 7.3.3), were also revisited to help with familiarisation. Stage 3; Coding. Retention strategies were defined as an action/activity conducted for the purpose of retaining participants in a trial, to reduce missing data and improve data completeness. We did not ask about or include information about activities aiming to improve adherence or compliance to the trial intervention (3, 21). EM manually conducted line-by-line open coding on three transcripts from (non-pilot) interviews with different trialists (a Trial Manager, a Study Co-ordinator, and a Clinical Trial Unit Director), this generated a list of open codes. All RREAL sheets were then re-read to ensure that the list of open codes was reflective of all interviews. During this process more open codes were added to the list. After this was completed the list of open codes was summarised and initial descriptions of the data content were created by EM. KG and SM open-coded three further transcripts prior to developing the coding framework. EM, KG, and SM met to discuss the list of open-codes and

initial descriptions of the data. Stage 4; Developing a working analytical framework. After reviewing and discussing the open codes and descriptions of the data, EM, KG and SM developed a coding framework. EM applied the framework to four of the six initial open coded transcripts. This coding was done using NVivo software (version 14). KG and SM reviewed the coding summaries generated by NVivo for each code across the four transcripts. After this, EM, KG, and SM met again to discuss the coding framework and to further refine, merge and collapse codes where links/similarities were identified. Illustrations of code brainstorms are included in Appendix 9. Iteration of the coding framework continued until agreed upon by EM, KG, and SM. Stage 5; Applying the analytical framework. The final coding framework was then applied to all transcripts. Data within each of the codes were summarised, ensuring that any differing viewpoints within and across trialist role groupings were noted. KG and SM reviewed the summarised data. The findings were subsequently written up by EM and reviewed KG, SM and FS. Stage 6; Charting data into the framework matrix. EM created a framework matrix and charted the data into the matrix. A framework matrix is a table that organises and summarises coded data across key themes and cases to allow for comparison. The matrix was formatted to indicate if a finding was present for each interview conducted to identify any differences in responses within and across the different trialist roles. Brief summaries of interviewee responses were included in the matrix (Appendix 10). Stage 7; Interpretation of the data. Data interpretation started during the coding of the data among EM, KG, and SM, for example, where it was decided to merge codes. Data interpretation was influenced by the research question and by the information from the interviews. Themes were generated by reviewing the data and

through discussions between EM, KG, and SM. These themes remained descriptive (162, 164).

7.3.3 RREAL Sheets

Rapid qualitative research is becoming increasingly popular, particularly in the field of healthcare (166). Researchers have developed different approaches to this type of research such as, rapid qualitative evidence syntheses, rapid appraisals and rapid ethnographies, among others (166, 167). These rapid research methods rely on using iterative cycles of data collection and analysis, e.g., identifying emerging findings that can be shared in real-time with stakeholders (167). A way in which to facilitate these iterative cycles and maintain consistency in data collection and analysis is by using a Rapid Research Evaluation and Appraisal Lab sheet 'RREAL sheet' (167). A RREAL sheet is a document that facilitates the summary of the most important findings from interviews as well as other data sources (167, 168). These sheets are made up of two columns. The left column contains the topic guide questions and the right column contains the key points and answer summaries to the questions (167, 168). EM created a RREAL sheet for the interviews and completed one after each interview. The RREAL sheet is an iterative document and therefore as the topic guide was developed through multiple iterations, (Topic guide – section 7.4), so too was the RREAL sheet. The RREAL sheets highlighted questions and information gaps that needed to be explored more in further interviews. They were useful when trying to identify and capture potential differences in experience/perceptions between different trialists (167). They were also helpful in

the familiarisation and coding stage of data analysis as it provided a structured summary of each interview. A blank version of the RREAL sheet is included in Appendix 11.

7.4. Thesis Paper Four (to be submitted for publication)

Start of paper

Title: Planning retention strategies in clinical trials; a qualitative interview study.

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Abstract

Background

To address poor participant retention, trial teams often use retention strategies. Evidence on the planning of retention strategies in trials is limited. Based on our previously conducted research, and other existing literature, it is unclear whether retention strategies are prospectively or retrospectively planned by trialists. Our objective was to investigate this.

Methods

One-to-one semi structured interviews, online or in-person, were conducted with trialists in the UK and Ireland. Data were analysed using Framework analysis.

Results

Trialists interviewed were Trial Managers, Study Co-ordinators, Principal Investigators, Research Nurses, a Head of Trial Operations, a Clinical Trial Unit Director, a Clinical Trial Monitor, a Co-Investigator, and a Clinical Trials Practitioner. Findings show that the development of retention strategies in trials is mostly done proactively during the design and planning stages of the trial, i.e., during trial design and protocol development. Participant retention, however, is an ongoing process and if retention rates are problematic additional strategies are reactively planned and implemented. Strategies tend to be chosen by the core trial management team, and the choice of strategy is mainly guided by prior experience. A variety of different formal strategies, (explicitly and intentionally planned strategies that are often more structured, such as, reminders or incentives), are used to facilitate ongoing participant retention. Informal strategies (not explicitly or intentionally

planned) such as, building rapport with participants, and having motivated and invested trial staff, are also highlighted as being important to facilitating retention in trials.

Conclusion

Most trialists proactively plan and implement retention strategies during the design and planning stages of the trial but are also responsive to poor retention rates as the trial is ongoing. Currently retention strategies are chosen based on prior experience of using the strategy. More research is needed to improve evidence-based decision-making.

Keywords: retention strategies, qualitative, interviews, randomised controlled trials.

Background

Retaining participants for the duration of a randomised controlled trial, (hereafter referred to as trial(s)), can be a significant challenge for trial teams (3, 4, 10). Between 60-89% of trials have some level of missing data (6). Substantial loss-to-follow-up can lead to both under and overestimation of the intervention treatment effect (6). Even low rates of loss-to-follow-up may introduce bias if there are higher rates of loss-to-follow-up in one trial arm, which can interfere with the balance of participant characteristics created via randomisation (6, 7). Inadequate retention of participants can have negative implications for the accuracy, validity, and generalisability of trial results (6-9). These issues, along with time delays, and inflated trial costs associated with poor retention, contribute to research waste (13). Due to the issues posed by poor retention rates, improving participant retention in trials has been prioritised as a key area of methods research (4).

A range of retention strategies are often used by trial teams to facilitate participant retention (3, 68). There is ambiguity within the literature on whether retention strategies are effective, as high-quality evidence to support these strategies is lacking, raising questions about what informs retention strategy decision making (3). We previously established that trial protocols don't often outline retention strategies, suggesting these activities are not proactively considered by trial teams during trial design and protocol development (19). On the other hand, participant information leaflets (PILs) often outline retention strategies, indicating that plans are in place during these initial stages of the trial to promote retention (20). Questions remain regarding the planning process for retention strategies in trials

including, when retention strategies are planned, how retention strategies are selected and when they are implemented. The aim of this paper was to provide a more in-depth understanding of the decision-making processes behind the planning of retention strategies in trials.

Methods

Study Design

The interviews conducted in this study were guided by a pragmatic research paradigm. Pragmatism focuses on practical outcomes and real-world applicability. This was suited to our aim of providing a more in-depth understanding of the decision-making processes behind the planning of retention strategies in trials. One-to-one semi-structured interviews were conducted with trialists in the UK and Ireland. This research was approved by the Social Research Ethics Committee at University College Cork (Reference number; 2023-149). All interviewees provided informed consent online prior to the interview and verbally at the start of the interview. The Standards for Reporting Qualitative Research (SRQR) checklist was used to report the qualitative study (Supplementary File 1; Appendix 12)

Overview of interview process

Interviews were conducted online via Microsoft Teams or in-person. Interviews were conducted in-person only when geographically feasible to do so. Three pilot interviews were conducted with a Trial Manager, a Research Nurse, and a Research Manager in January 2024. These interviews were used to train the researcher, EM, and refine the topic guide. The data from pilot interviews were not included in the

analysis. Interviews included in the analysis were conducted between March and June 2024.

Sampling method and recruitment process

Potential interview participants were identified from trial PILs included in a previous study by the lead author (20). A purposive sampling approach was applied. A sampling matrix was developed to ensure the trial teams contacted represented the diversity of trials, including clinical area, intervention type, year and sample size, represented in a previous study analysing PILs for information on retention strategies (20). We used the concept of information power to guide judgement on how many interviews to conduct (169). Information power informs the planning of qualitative interview recruitment figures, whereby the sample size is influenced by study aim, sample specificity, use of established theory, quality of dialogue, and the analysis strategy (169).

We contacted trial teams through the generic trial email on the PIL from our earlier study (20) or on the trial website. We directly emailed the Trial Manager, Principal Investigator, or Study Co-ordinator rather than using the generic email in the first instance. All emails included an information pack which incorporated an information leaflet and an infographic about the study. In addition to purposive sampling, we used snowball sampling to recruit specific individuals who had a role in participant retention, or the decision-making process on retention strategies in the trial. We did not aim to recruit all members of each trial team (170). If there was no initial response, we sent two email reminders. If there was still no response, we selected another trial from the sample that best matched the characteristics of the

non-responders or those that declined, and invited a member of the team to interview. Due to poor response rates, we emailed all remaining trials from the entire sample of PILs. Further, we contacted Irish Clinical Trial Units (CTUs) and professional contacts in the Irish setting to extend our sample to include perspectives from trialist in Ireland.

Interested individuals who contacted EM were provided with an online information leaflet (the same information leaflet provided in initial email) and informed consent form, which was completed prior to all interviews. Verbal consent was additionally sought at the beginning of each interview. EM conducted all interviews. Interviews were conducted with trialists, that provided a broad range of experience and different perspectives, and continued until authors agreed no new data were being generated by additional interviews.

Topic Guide

The topic guide was developed by the research team and informed by existing literature (19, 20). The topic guide was also refined after the pilot interviews. The topic guide included open questions on retention generally, e.g., if interviewees felt retention was important in a trial and how they conceptualised retention. There were specific questions and probes used to encourage interviewees to expand on the topic of planning retention strategies, e.g., if they use retention strategies, how strategies are chosen, and by whom. As the interviews progressed, the topic guide was iterated with further probes added as required. The final version of the topic guide is presented in Supplementary File 2.

Data Analysis

The Framework analysis guidance outlined by Ritchie and Spencer (164), and Gale et al. (162) were used to analyse the data. The interviews were transcribed verbatim. Once EM was familiar with the data, she began coding. Retention strategies were defined as an activity/action that is conducted, for the purpose of retaining participants in a trial, to reduce missing data and improve data completeness. We did not ask about or include information about activities aiming to improve adherence or compliance to the trial intervention (3, 21). Six transcripts were manually coded using line-by-line open coding, RREAL sheets were reviewed, and initial open codes and descriptions of the data were generated. Through discussions between EM, KG, and SM an initial coding framework was developed. This framework was applied to four of the six initial transcripts. This coding was done in NVivo software. Subsequent to this, EM, KG, and SM met again to discuss and refine the coding framework. The final coding framework was then applied to all transcripts. Table 7.1 provides the various definitions of retention strategies used throughout the manuscript, i.e., formal proactive, formal reactive, and informal retention strategies. Data within each of the codes were summarised, ensuring that any differing viewpoints within and across trialist roles were noted. EM created the framework matrix and charted the data into the matrix (Supplementary File 3). The matrix was formatted to indicate if a finding was present for each interview conducted, to allow for any differences in responses to be seen within and across the different trialist roles. Brief summaries of interviewee responses were included in the matrix. To illustrate key findings, interviewee quotes are presented, followed

by ID number and professional role, e.g., Interview 6, Trial Manager. Additional supporting quotes are outlined in Supplementary File 4.

Table 7.1. Retention strategy definitions.

Retention strategy definitions
Formal strategies - Formal retention strategies may be proactive or reactive and are explicitly and intentionally planned to improve retention rates. They often include more structured activities, such as reminders, incentives, or offering different follow-up methods. ● **Proactive -** Proactive strategies are planned during the initial stages of the trial, i.e., during trial design, planning, and protocol development and implemented from the start of the trial to minimise attrition rates throughout. ● **Reactive -** Reactive retention strategies are only considered once retention became an issue or once follow-up had started. These strategies are not planned during the initial stages of the trial, during trial design, planning, and protocol development.
Informal strategies - Informal retention strategies, are not explicitly planned, less structured, and revolve around building good relationships with trial participants, trying to create a good research culture, having motivated and invested trial staff and participants.

Trustworthiness

To ensure credibility of the qualitative analysis, EM read and re-read the interview transcripts and listened back to the interviews to enhance familiarity and understanding of the data. To minimise the influence of personal bias and preconceptions during coding and interpretation, EM regularly discussed codes and themes with KG and SM who were most distanced from the data but had read three transcripts. These robust discussions helped ensure that a range of perspectives and potential interpretations of the data were considered and reflected in the findings.

Confirmability was supported through these robust discussions as it helped to ensure a degree of objectivity when interpreting the data. Additionally, a reflexivity statement outlining EM's positionality and potential biases is included as an Additional File, contributing to the confirmability of the findings.

The dependability and the transferability of the findings was strengthened by the purposive sampling method chosen, which ensured that interviewees were able to provide relevant and rich data. The sample of interviewees (N=24) were recruited from a range of CTUs across the UK and Ireland, held various roles in the trial team, and had a large amount of experience in these roles. As a result, we are confident that the findings are not going to be very different in another sample from this context. A description of the study context, including detailed information about the roles, clinical areas, and experiences of interviewees is provided. In addition, illustrative quotes from interviewees are used throughout the findings section to demonstrate how conclusions were grounded in the data, allowing readers to assess the relevance and applicability of the findings to their own settings.

Results

Eighty-five trial teams, across the UK and Ireland, were contacted to take part in the interviews. Of these two trial teams declined to take part, and 60 trial teams were non-responders. Twenty-three trial teams responded and 24 trialists from these teams were interviewed (28% response rate). Twenty-four interviews were conducted via MS Teams and two interviews were conducted in-person.

Interviewee Characteristics

The characteristics of those interviewed are presented in Table 7.2. The mean age of interviewees was 44 years and the majority were female (n=19). Trialists held various roles within the trial team, which included Trial Managers (n=10), Study Co-ordinators (n=4), Principal Investigators (n=3), Research Nurses (n=2), Head of Trial Operations within a Clinical Trials Unit (n=1), a Clinical Trials Unit Director (n=1), a Clinical Trials Monitor (n=1), a Co-Investigator (n=1), and a Clinical Trial Practitioner (n=1). Experience in these roles ranged from 1 to 20 years, with an average of 9.5 years. Most trialists provided insights from working across several different trials, three reported experiences of working on a singular trial. The clinical fields in which the participants worked included, Cardiology, Musculoskeletal, Nephrology, Obstetrics and Gynaecology, Oncology, Ophthalmology, Respiratory, Rheumatology and Women's Health.

Table 7.2. Interviewee Characteristics.

Interviewee Characteristics	**n=number (percentage)**
Gender	
Female	n=19 (79%)
Male	n=5 (21%)
Age (mean)*	44yrs
Years of experience (mean)	9.5yrs
Job Role	
Trial Manager	n=10 (42%)
Study Co-ordinator	n=4 (17%)
Principal Investigator	n=3 (13%)
Research Nurse	n=2 (8%)
Head of Trial Operations	n=1 (4%)
Clinical Trial Unit Director	n=1 (4%)
Clinical Trial Monitor	n=1 (4%)

Co-Investigator	n=1 (4%)
Clinical Trials Practitioner	n=1 (4%)
Clinical Area	
Obstetrics and Gynaecology	n=6 (25%)
Oncology	n=3 (13%)
Cardiology	n=3 (13%)
Nephrology	n=2 (8%)
Respiratory	n=1 (4%)
Musculoskeletal	n=1 (4%)
Public Health	n=1 (4%)
Rheumatology	n=1 (4%)
Ophthalmology	n=1 (4%)
Women's Health	n=1 (4%)
Trauma	n=1 (4%)
Surgical	n=1 (4%)
Did not provide specific disease area	n=2 (8%)

*One participant did not provide their age

Overall findings

Trialists were asked about their views on participant retention in trials, what they do to promote retention, and how such activities are planned and implemented within the trial. Eight key themes and four sub-themes were identified. Key themes were as follows: 1. 'Conceptualisation and perceptions of participant retention', 2. 'Retention against competing trial priorities', 3. 'Retention responsibility and decision-making', 4. 'Proactively planning for retention', 5. 'Reactively planning and implementing retention strategies', 6. 'Influences on the choice of retention strategy', 7. 'Challenges with planning and implementing retention strategies' and 8. 'Informal ways to improve retention'. These themes are elaborated on below.

1. Conceptualisation and perceptions of participant retention

Trialists conceptualise participant retention in trials broadly under two key areas; keeping trial participants engaged for the trials' full duration, and simultaneously ensuring collection of outcome data and data completeness. One research nurse and the head of trial operations conceptualised retention solely as *"keeping participants on the study as per the protocol and informing them of the results after" (Interview 18, Research Nurse)* and that participants remain in the trial until they meet withdrawal criteria.

Trialists were asked how they judge whether retention rates in a trial are acceptable, e.g., whether rates are in line with projected attrition rates. Most make this judgement by comparing retention rates to the attrition rate accounted for in the sample size calculation.

"Every couple of weeks, we'll look at the percentages for the seven and 90-day follow-up…I think we've adjusted for 20% loss to follow-up in our sample size so we're high performing against the sample size calculation." (Interview 10, Study-Co-ordinator)

A range of other factors influence perceptions of the acceptability of retention rates for trialists interviewed. For example, comparison to similar trials/research in the field, the opinions of more experienced trialists, the views of the lead site staff, trial experience and personal beliefs around what is an acceptable rate, aspects of trial design, e.g., whether the trial is decentralised, the length of follow-up and the types of participants, e.g., elderly participants,, are individually mentioned by some trial

managers, a co-investigator, the clinical trial practitioner, a principal investigator, and the head of trial operations.

2. **<u>Retention against competing trial priorities</u>**

All interviewees acknowledge that participant retention in a trial is important and many outline that poor retention leads to bias, underpowered trials, and that without good participant retention the ability to answer the research question is jeopardised, ultimately contributing to research waste. However, in practice those interviewed feel that retention is not the top priority, as recruitment usually takes precedence. This is because funders focus on and reward sites for recruitment, as described by two trial managers and the clinical trial practitioner.

"There is a cohort of researchers who are interested in the recruits, not the retention. Because we are pushed to recruit not to retain, and our funding is really based on it…. There is a massive over-bias from the NIHR to recruit numbers" (Interview 23, Clinical Trial Practitioner)

Others feel retention comes into focus when it becomes problematic or when recruitment is complete. One trial manager feels that since trial teams compensate for attrition during trial design, it is not a priority.

"There's a lot of thought that does go into the retention, but I don't think it's a priority… I think some of the time because they build in into the stats some loss to follow up. They [Trial Teams] feel that they've compensated for it in that way" (Interview 5, Trial Manager)

3. Retention responsibility and decision-making

Many explain that participant retention is a shared responsibility across the trial team. Some state that ultimately the responsibility is with the sponsor or principal/chief investigator. In practice, when it comes to decision-making about how to retain participants, interviewees list that the core trial management team, such as the trial manager, data/study/trial co-ordinator, the principal/chief investigator and patient and public partners are usually involved. Site staff are commonly one step removed from this decision-making process, as they are not often involved in participant follow-up, or are only included when their assistance is required if retention rates become problematic, as outlined by some trialists. When the trial is managed by a lead site or sponsor, the trial site has less ability to implement their own retention strategies, as often they are provided with a finalised protocol to implement, as explained by the clinical trial practitioner, the clinical trial unit director and both research nurses.

"So essentially when we're looking at a study we get a fully fledged protocol. We can have a little bit of input into it, but not really. It's kind of fait accompli by the time we get it. And then it's us enacting that" (Interview 19, Clinical Trial Unit Director)

Sometimes the trial site has a standard in-house follow-up protocol they implement if there is nothing specific in the trial protocol to enhance response rates, or they adapt to make the protocol work to facilitate retention. The clinical trial unit director outlines that even though they receive the completed protocol, they often negotiate with the funder to include participant reimbursement.

Retention strategies

Trialists were asked if they use strategies to facilitate ongoing participation in trials they work on. Responses reflect retention strategies that are formal proactive, formal reactive, and informal (see Table 7.1).

4. Proactively planning for retention

4.1 Planning for power

A proactive first step in ensuring participant retention in a trial is to incorporate attrition rate considerations during the calculation of the sample size. Most provided insights on how attrition rates are calculated, however, none of the interviewees were statisticians. The attrition figure is primarily influenced by the trial statistician's experience and existing literature from similar trials.

"There is sometimes a bit of background behind that [attrition rate], like where it will refer to previous trials. Quite often there might not be that information so that 20% seems to be what I've seen, actually, taken across the board" (Interview 16, Trial Manager)

The chosen attrition percentage is often a standard figure used, especially if there is no literature to base the calculation on or when trial teams are not familiar with the research area, as suggested by some trialists interviewed. One trial manager questions the science behind the figure and feels it is *'quite arbitrary' (Interview 4).*

Aspects of trial design, such as length of follow-up, level of personal contact with participants, how the outcome data is collected (e.g. during vs outside of routine

care), the level of benefit for participants, and the type of participants (e.g. elderly population) are also reported as influencing attrition rate calculations. One trial manager also highlights that the sample size can only be inflated to a certain level and a balance must be struck between *"what lost-to-follow-up would be and what the funders are willing to fund" (Interview 6)*. Whereas another trial manager and a principal investigator report there is a need to err on the side of caution and inflate the expected attrition rate, so that the trial is not left underpowered.

"we actually assumed 18% loss to follow up…. I wanted to ensure that if I'd got my assumptions wrong, I've been very generous. I would expect only 10% loss to follow up, but [what I] do not want is an underpowered trial" (Interview 8, Principal Investigator)

4.2 Implementing retention strategies

Most trialists said they plan and implement formal retention strategies (prompts, reminders, newsletters, incentives, pre-paid envelopes) proactively from the beginning of the trial to maximise retention rates (see Table 7.1). The importance of being prepared and pre-empting retention issues, and being able to respond proactively is highlighted.

"Well it's to be prepared, it's because, can we do something different in the early stages to prevent us getting there, yeah, rather than have people withdraw and then think, "Oh we should have tried this or we should have done that or we should have known that might happen." So it's about trying to predict what the challenges

might be for participants and how we can mitigate them" (Interview 17, Research Nurse)

In recent years, proactive planning of such strategies and early consideration of retention during the design stage is becoming more common practice, in the opinion of two trial managers. One of these trial managers no longer submits protocol amendments for retention strategies and now plans retention strategies at the grant application stage.

"I do remember, going back 15, 16 years, putting amendments in to say we will now do this, we will now potentially phone a participant if they've not returned… But for the last few years, no…"

R- To clarify usually at what stage of the trial are you planning retention strategies?

"Very much at the grant application stage..." (Interview 16, Trial Manager)

A range of formal retention strategies are reported, for example, prompts, reminders, financial incentives, travel reimbursements, and providing pre-paid return envelopes for questionnaires. Other strategies include providing participants choice on mode of data collection, being flexible when providing clinic appointments and scheduling clinic visits with routine care. Most retention strategies target trial participants but strategies that target site staff are also mentioned by some trialists. These strategies involve training site staff about the importance of retention, how to communicate this to trial participants, and how to handle conversations about trial withdrawal. Strategies used to maintain site engagement include rewarding sites for retention of participants/full datasets,

regular site meetings and sending sites trial merchandise like stationery. When proactively implementing formal strategies, it is usually a standardised approach where all participants receive the planned strategy.

A few trialists mention aspects of recruitment that are linked to retention. A trial manager describes how trial follow-up is conducted, where possible, by the same staff that recruit the participants. Additionally, recruiting participants that interviewees believe will remain in the trial is a strategy used by the clinical trial practitioner, a principal investigator, and the clinical trial unit director.

"The patients are often being followed up by members of staff who don't have a clinical background, so if they're asked anything clinically or even just their manner, it's all very businesslike and the retention is not as great there and often is passed back to the research nurses. So when I design a trial we always try to have the follow up by the team who recruited the patient at the site." (Interview 3, Trial Manager)

"I'm very clear with people, when I'm recruiting them, what that requirement is. I work quite hard to make sure that whoever I recruit can complete the study." (Interview 23, Clinical Trial Practitioner)

Clearly setting participants expectations about trial follow-up during recruitment is seen to be particularly important to facilitate participant retention by both research nurses, the clinical trial practitioner, and the clinical trial unit director. Linked to setting expectations, interviewees were asked whether participants are informed about the importance of retention and completing follow-up. According to the trialists interviewed, this communication sometimes occurs during informed

consent, mainly verbally, or via the PIL. Others communicate this information during the follow-up stage, or when participants express they wish to leave the trial, as explained by some trial managers, study co-ordinators and a principal investigator. A couple note that this information needs to be balanced with information about trial withdrawal, and one trial manager feels the importance of retention is not emphasised enough.

5. **<u>Reactively planning and implementing retention strategies</u>**

While most of those interviewed state they proactively plan and implement retention strategies, two trial managers and the co-investigator report being mainly reactive to retention challenges and did not consider retention strategies until retention rates became problematic, or until follow-up was underway (see Table 7.1).

"We've kind of started looking at plans as we go.… for situations where things might not be going as well in terms of retention, maybe we could've had, well contingency plans in place, whereas they've kind of just come about as we go" (Interview 20, Trial Manager)

Most report that retaining participants is a dynamic process and that whilst trials have proactive strategies, some trials also require real-time intervention. If negative retention trends are identified, often additional strategies are implemented in a reactive manner. The need to be reactive is mostly in response to continuously monitoring retention rates and assessing how these rates compare with the predefined attrition rate.

"So it's kind of an ongoing rolling process. I wouldn't say we have a particular threshold that we all of a sudden start getting concerned, I think it's really an ongoing process" (Interview 24, Principal Investigator)

If the trial hits "*a risk assessment trigger" (Interview 6),* often when calculated attrition rates are exceeded, then additional action is taken, as mentioned by one trial manager. The need to be reactive is more of a *"gut feeling" (Interview 21)* for one principal investigator, who has limited experience of what is likely to happen in terms of attrition in one of their trials.

The reactive approach to addressing retention issues reported by many, is to contact and work with sites to see if sites can provide insights to address the problem. According to the interviewees, reactive strategies are used target sites struggling with retention, e.g., those that target participants within struggling sites, such as, building in more prompts, reminders, newsletters and one trial manager reactively implemented monetary vouchers.

"then you hit, oh something's going wrong here [with follow-up rates]. This is, what can we do? Is it the site? Do they need more help? Do they need more support? Is it the participants? Can we engage with them in some way?... We wouldn't at that point look at anything around participant fees if that wasn't already implemented. But we would try and speak to sites and see if there was something that we weren't aware of" (Interview 5, Trial Manager)

6. Influences on the choice of retention strategy

In terms of influences on the choice of retention strategy, many outline that the decision is mainly based on experience of working in the field, and having used/seen the strategy used in other trials. Factors mentioned alongside experience include, budget and resource, scientific literature, the participant population, the mode of follow-up data collection, time point for primary outcome data collection, and input/feedback from PPI. The influence that other relevant parties, such as funders, and the ethics committee, have on the choice of strategy, is also highlighted by several trialists. For example, participant reimbursement depends on whether the funder is willing to provide the necessary funds. Additionally, the perception of what ethics committees will approve also influences considerations about the frequency of reminders, and what is seen as the "*not hassling approach*" *(Interview 16, Trial Manager)*.

"Sometimes Ethics Committees do allow you to do news[letters], well some will allow you to do kind of more fluid newsletters but not all. Because everything needs to go through an Ethics Committee it means that you can't, you're very restricted. Everything has to be pre-planned. It has to be written in advance. Has to go through an Ethics Committee. Have to have 35 days approval so you can't be, you can't be quick in what you're doing. That severely I think restricts what we do" [follow-on quote] "It will be very common that we'll say we can't do that because we have to go to ethics." (Interview 6, Trial Manager)

An acknowledgement of retention issues is observed as a few interviewees mention that ethics committees are providing feedback and encouraging the use of

monetary incentives or reimbursements for participants. One trial manager, however, still has issues getting incentives approved, as they had a lot of discussion with their ethics committee on the topic for one trial.

"Our most recent ethics committee suggested that we did offer shopping vouchers or some sort of payment for people's time for a study that's potentially going to be quite a lot of work in term of filling in data on an app. So that's something that we hadn't put in and actually the ethics committee said, "We think you should be acknowledging how much time people put into this"" (Interview 21, Principal Investigator)

7. **<u>Challenges with planning and implementing retention strategies</u>**

Challenges with planning and implementing strategies, particularly in a reactive manner, were outlined by some trialists. For example, changing the primary outcome measure is not possible, so instead more participants are being recruited, one trial manager explained. Changes to the randomisation ratio are a consideration for the head of trial operations, to combat poor retention. Limited scope to make changes while still ensuring participants' trial experience remain comparable, before and after any changes are made, is a difficulty to being reactive according to one trial manager. Two other trial managers mention repurposing other funding within grants to implement retention strategies, if reactive approaches are needed. Other challenges include, the need for ethical amendments and associated time delays, and limitations on what can be done in the middle of a trial due to budget and staff time constraints.

"It requires going to ethics and things like that. So that's why I'm saying contingency plans at the beginning would've made more sense in my eyes……ethics in every country seems to be a time-consuming process, a back-and-forth process. So yeah, it would delay things and it's just more of a frustration for the trial" (Interview 20, Trial Manager)

Contrastingly two trial managers and a study co-ordinator feel that having to additionally implement retention strategies is just part of what comes with conducting trials. One of these trial managers, however, feels that being reactive is *"like you're playing catch up" (Interview 4),* and that having the strategy from the start may facilitate better retention throughout the trial.

Some report challenges using certain retention strategies regardless of when they are implemented including, for example, the challenge of following-up participants via General Practices due to increased associated costs, issues with routine data caused by the dated nature of the systems, and difficulties ensuring sites are following-up participants as per the protocol due to the inability to monitor this robustly.

8. Informal ways to improve retention

8.1 Motivation and investment

When discussing ways to optimise retention, many highlight the importance of having motivated and invested staff working on the trial. Different staff members have different levels of investment in the trial, and this influences their motivation

to follow-up participants and see the trial succeed, according to one trial manager and principal investigator.

"We're [the trial team] motivated to make it succeed but if you have clinical staff who are just rotating in to cover the intervention, they don't have had the same motivations to keep people and doing the intervention. They don't care as much, say, if people aren't showing up for their classes, their appointments…. you need to I suppose generate more of a research culture in clinicians so that they are passionate about it and as motivated as the researcher is to make it succeed" (Interview 13, Trial Manager)

Some mention having trial participants in the trial that are keen to find an answer to their health issues, contributes to facilitating retention. One research nurse believes that giving participants the feeling of ownership of aspects of the trial also contributes participant retention.

8.2 Relational aspects of retention

Developing a good rapport with trial participants is seen to be important to retention rates by trialists interviewed. It feels personal to trial staff when someone leaves the trial, according to a research nurse and a principal investigator, "*it's very sad when someone drops out part way*" *(Interview 8).* Additionally, a good relationship between the lead site, and the site staff working on the ground, is important for retention, one trial manager and both research nurses report.

Staff qualities seen as influencing retention are: empathy, being approachable, having a good manner, making trial participants feel appreciated, as well as staff who chat, listen, and answer participant queries, and go "*the extra mile" (Interview*

9, Study Co-ordinator) to assist participants attending follow-up clinics. These were listed by, trial managers, study co-ordinators, principal investigators, research nurses and the clinical trial practitioner. Research nurses, or staff who have more direct contact with trial participants, mention personalising the strategy to the participants. These staff explained that as they become more familiar with participants, they can identify participants who may need more retention support through, for example, individualised follow-up.

"If I knew the patient very well and I knew they were going to fill it in, I might just say, "Just a reminder your survey is in your inbox". Or, if I knew it was someone that needed a bit more coaxing or it was unusual that they wouldn't have filled it in at this stage, I would pick up the phone and talk to them. Again, it was that human contact, and they knew if they didn't fill it in that the nurse was going to be contacting three days later. That gave them a little incentive" (Interview 18, Research Nurse)

Having face-to-face contact, or regular follow-up calls with participants, is felt to facilitate building good rapport, by some trial managers, study co-ordinators, and the clinical trial practitioner. Less participant contact possibly hinders retention, as participants do not have a relationship built with trial staff, and consequently may not feel as obliged to complete follow-up, some trialists speculate. Trial staff consistency also facilitates relations with participants and may enhance retention, a trial manager and principal investigator report.

Discussion

Overall, trialists usually plan retention strategies proactively during the design and planning stages of the trial, i.e., during trial design and protocol development, and implement strategies from the trial outset, to maximise retention throughout the trial. Trialists, however, aim to be adaptive and responsive to poor retention rates. If issues are detected with participant retention, additional strategies are planned and implemented reactively. Only a couple of trialists mention being mainly reactive to poor retention rates. Prior research by Daykin et al. (70) explored trialists' perceptions and experiences of operationalising retention strategies. Similar to our findings, this research showed that some trial teams proactively plan ways to promote retention and other teams plan strategies reactively when needed. Our research goes beyond this and furthers our understanding of the planning process, as our findings highlight that for most trial teams planning strategies happens both proactively and reactively, and highlights the influences and challenges with implementing retention strategies.

A wide range of formal strategies are used, such as using prompts, reminders, newsletters, monetary incentives, pre-paid envelopes for questionnaire return, being flexible with clinic appointments and scheduling appointments with routine care. These strategies are reflective of retention strategies previously reported by trial staff interviewed by Daykin et al. (70) and Brueton et al. (69). These findings also align with routinely used trial retention strategies in the UK, where popular strategies include newsletters, using pre-paid envelopes for questionnaire return,

telephone reminders, scheduling trial data collection with routine care, and having flexible appointment times (68). These strategies were also evident in the Cochrane review of strategies to improve retention in trials and in a recent systematic mapping review of retention strategy reporting in National Institute for Health and Care Research Health Technology Assessment (NIHR HTA) trial protocols (3, 171). Despite their routine use, there is very limited high-quality evidence to show they are effective (3). Additionally, these strategies can potentially be expensive, with little evidence of cost-effectiveness (18, 71). Therefore, we do not know whether these strategies improve participant retention rates or if they are a waste of trial resources. Formal evaluations of these strategies are needed to ensure trial resources are not wasted on strategies that are expensive and ineffective.

Ultimately while trialists report participant retention is important to the trial, participant recruitment is prioritised because funding bodies place emphasis on hitting recruitment targets. This finding supports previous work by Daykin et al. (70) and Coffey et al. (77) which, according to the trialists interviewed, found that participant retention is often not a top priority, particularly, during the initial stages of the trial. This has also been reported in previous literature (70, 77). Since recruitment is often the top priority, the responsibility of participant recruitment is assigned to specific members of the trial team (77). Participant retention is typically not treated the same. Our findings indicate that there is no specific individual responsible for the retention of trial participants, rather, it is a whole team responsibility. Despite this, only a handful of interviewees report that they train site staff on the importance of retention, how to communicate this to participants, and how to engage in withdrawal conversations effectively. In practice, as a result site

staff may be unaware of ways they can support retention efforts. Those interviewed report that building a good relationship with trial participants plays a role in facilitating participant retention. The influence of interrelationships between trial participants and staff in the context of trial retention has been described previously (70). Interviewees also outlined that having staff with empathy, who are friendly and engaging is important for retention. This is reinforced by research showing trial retention is influenced by the friendliness and helpfulness of research staff (74), and by participants who outlined leaving trials when relational support from trial staff is not present (172). Irrespective of the role site staff play in follow-up data collection, emphasising the importance of the sites' role in fostering good rapport with participants during site initiation training may be a valuable tool to help aid trial retention efforts.

Our findings show that the decision-making process behind planning and choosing the retention strategy is mostly influenced by experience of having used the strategy previously. A small number of trialists interviewed mention the choice of strategy being influenced by the types of participants in the trial. Once chosen however, the strategy is typically implemented in a standardised fashion, without considerations for tailoring strategies to specific participants that may need assistance remaining in the trial. Existing literature has suggested when it comes to retention strategies and retaining participants, a one-size-fits all approach might not be sufficient (75). Tailoring retention strategies and targeting participants more likely to leave the trial, may help teams focus retention efforts on specific subsets of individuals. More work is needed to understand how best to retain participants

from specific disease cohorts and cultural backgrounds to ensure inclusive, representative, results.

Some aspects of participant retention is linked to the recruitment process. For example, clearly setting participants expectations of what the trial involves or training sites to do so. The importance of expectation setting has also been previously outlined by trial staff responsible for recruitment and retention (77). Whether setting expectations about trial retention happens routinely in practice is unclear, as existing evidence suggests that expectation setting does not often occur (12, 77). Results from reviewing audio recordings of consent consultations, show retention information is not frequently outlined to potential trial participants and if it is, there are inaccuracies in the follow-up information being communicated to potential trial participants (12). Previous research highlights that staff with more of an active role in participant retention, believe that recruitment staff do not often provide participants with information about follow-up during consent, and those tasked with retention faced the repercussions (77). Participants want to know what is involved in a trial (160). This may encompass information about retention strategies, if the participants are not fully aware of what they may receive from the trial team, e.g., if they miss data collection they will get a certain number of reminders, it may interfere with their expectations about the trial. Additionally, when participants' expectations about a trial are not met, it can contribute to participants deciding to no longer remain in the trial (64). This further highlights the potential value and importance of informing recruitment staff, and site staff, on clearly communicating information about trial retention and follow-up, as trial teams are relying on these staff members to ensure participants' expectations about

the trial are set correctly. An intervention to facilitate and support trial staff discussing retention during recruitment has been developed (173), but is yet to be tested, but perhaps a starting point to guide trial teams how to best enable such conversations to happen.

Recommendations

While trialists report proactive planning of retention strategies commonly occurs, and a wide range of strategies are used across trials, trialists' experiences of planning retention strategies proactively, typically relying on past experiences of having used a particular strategy or existing templates to select and report strategies. A factor as not commonly considered is the evidence to indicate whether strategies are effective or not. More research and awareness of the evidence is needed to support trialists to make evidence-based choices when planning retention strategies to ensure that the strategies chosen are effective at improving participant retention rates. To achieve this, formal evaluations of the effectiveness of these strategies are needed using the Studies Within A Trial (SWATs) design. Trial Forge has a range of guidance on how to conduct such evaluations and the PRESS project has prioritised those that need evaluation (72, 174-176).

Strengths and Limitations

Using a sample of PILs from a wide range of trials to recruit potential interviewees, helped to capture a range of different experiences and approaches to retain participants across different clinical settings, as well as insights from trialists with different roles and responsibilities. This provided a more comprehensive

understanding of different dynamics when planning retention strategies. Snowball sampling may have introduced selection bias, as interviewee recruitment relied on the trial team contact's subjective judgement to forward the recruitment email to trialists they believed were best suited to answer questions about retention strategies. However, this could also be seen as a strength. Additionally, the sample may have been affected by self-selection bias, as those who agreed to be interviewed may have been more likely to have had positive experiences with retention and successful retention strategies. EM knew three interviewees, posing the risk of social desirability bias in responses. While we recruited trialists that held various roles, we may be lacking in different viewpoints held by for example patient and public contributors, or research assistants. Interviewees shared experiences across a range of different trials, therefore, the trials discussed may not fully reflect the sampling matrix used for recruitment. In some cases, experiences may be in relation to trials that included vulnerable populations, but it was not possible to disentangle this across all the interviews.

Conclusion

Trialists outlined how they navigate planning and implementing retention strategies in trials. Findings from the interviews suggest that trialists mostly take a dynamic approach, where both proactive strategies are planned and implemented from the trial outset, and additional action is taken during the trial if issues with retention rates are identified. According to trialists the use of retention strategies is mainly

guided by previous experience of using the strategy. More work is needed to to overcome challenges when planning and implementing strategies in practice.

Abbreviations

Participant information leaflet (PIL)

Patient and Public Involvement (PPI)

Clinical Trial Unit (CTU)

Informed Consent Form (ICF)

Studies Within A Trial (SWATs)

Declarations

Availability of materials

Currently selected quotes from interview transcripts that support the study's findings are available upon reasonable request. An ethical amendment is being sought to allow anonymized transcripts to be shared upon reasonable request.

Patient and Public Involvement

Two patient and public partners were involved in reviewing and providing feedback on the interview topic guide and involved in providing feedback on result dissemination.

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Competing interests

All authors confirm that they have no competing interests.

Consent for publication

This paper does not contain any individual person's data as the data has been appropriately anonymised.

Ethical approval and consent to participate

This study was approved by the Social Research Ethics Committee at University College Cork, reference number 2023-149. Participants provided e-consent prior to the interviews. Consent was also verbally provided at the start of each interview.

End of paper

7.5 Additional findings

Research objective four aimed to *"to get a more in-depth understanding of trialists' views and opinions on retention strategy planning and communication in trials"*. The interviews conducted focused on both the planning and communication of retention strategies. However, due to the quantity of data generated through the interviews, it was decided to focus on the planning aspects of retention strategies in the paper to be submitted for publication. As a result, the findings about the communication of retention strategies are presented here.

7.5.1 How are retention strategies communicated and documented in trials

After interviewees were asked about how they facilitate retention in their trials, they were asked whether, and how, they communicate these plans to the trial team, and participants, and whether they document these retention plans in protocols and PILs.

7.5.1.1 Communication within the trial team and documentation in trial protocols

Team meetings with core trial staff were outlined by a range of different trialists, as the main mechanism of communicating information about retention strategies within the trial team. Whether site staff are informed about retention strategies is variable.

When asked about documenting retention strategies, a range of different trialists stated that their protocols include this information, while others said this information is documented in standard operating procedure documents. Reasons for not reporting retention strategies in protocols include: they are not planned during the trial design or protocol development stage, inclusion is not a mandatory requirement from sponsor/funder, there is not a specific section in protocol templates, and some strategies are done without much formal planning and thus not formally documented. The head of trial operations said that setting participants' expectations about the trial is *"a given as part of the standard, the ICF process" (Interview 22)* so it is not something outlined in the protocol. Retention strategies are not presented in a separate section of the protocol. Instead, retention strategies, and considerations for keeping participants involved, are built into the overall trial design, a view expressed by two trial managers, one study co-ordinator and the head of trial operations.

"I don't think we've actually got, trying to think, a specific section of plans for retention…. I suspect it's sort of in the way we plan it in terms…. the way we state the follow up visits. For example, I suppose we worded it in a way which makes it sound like we've minimised the burden for patients. I don't think we've actually got like a specific retention section in our protocol….it will be into the design" (Interview 9, Study Co-ordinator)

One trial manager and a principal investigator felt that retention strategies do not belong in a protocol, especially not in a detailed manner, as it would lead to lack of flexibility and possible protocol deviations if the retention strategy does not end up

being followed for all participants. Retention strategies are *"quite obtuse" (Interview 12)* in the protocol, as described by another trial manager. A way to facilitate better planning and documentation of retention strategies, is by having mandatory requirements or "*more of a framework or guidance*" *(Interview 13, Trial Manager)* to include this information in protocols, as it would ensure that trial teams are considering retention right at the beginning of the trial, as one trial manager and study co-ordinator suggested.

7.5.1.2 Communication with trial participants and documentation in PILs

Most trialists interviewed feel that communicating information about retention strategies is important during the informed consent meeting, to set participants' expectations about trial participation. This occurs either verbally, or via the PIL. Interviewees report that incentives, reimbursements, or aspects that the participants must consent to, such as receiving communications from the trial team, are often outlined in PILs, though it is not made explicit these are retention strategies. Others outline that strategies may not be outlined or loosely outlined in PILs.

"If they get incentives, it will be in the patient information leaflet. Again, in the patient information leaflet, we might be quite obtuse in what we say. Yeah. We probably would say that we might keep in touch with them while we have newsletters or similar so it's not really clear." (Interview 12, Trial Manager)

One trial manager and principal investigator said that trial participants do not need to know this level of detail about trial activities and that it should be expected by

the participants that they will receive certain strategies, like reminders, as it is part of the trial process. For retention strategies implemented in a reactive manner, whether participants need to be reconsented, and thus informed about the retention strategy, depends on the strategy, the existing ethics application, and the sponsor/ethics committee, as explained by some trialists.

Documenting information about retention strategies in PILs varies. Reasons for not including this information in PILs include: it is not a template requirement, trying to reduce PIL length, and it may deter trial participants initial participation if they are told they will receive lots of follow-up communications. A study co-ordinator feels that perhaps outlining information on activities that are intended to change behaviour, such as reminders, may affect the impact of these retention strategies. One research nurse feels the PIL is *"... a very standard PIL, you know the way. It did all the necessities, tick box from a legal point of view…yeah, the standard unfriendly patient template, yeah, didn't have that kind of information [about retention strategies], no"* and instead they provide information about retention strategies in *"other information that we gave them outside of the PIL that had their schedule and would have mentioned about their reminders on that." (Interview 18).*

7.5.2 Insights into PIL analysis results (Chapter Six)

In the PIL analysis in Chapter Six, a key result was that there were often inconsistencies in the information about retention strategies outlined in PILs and their corresponding protocols (Results – Chapter Six, section 6.4). Trialists interviewed were asked why such inconsistencies may occur between these trial

documents. Answers provided mainly included human error, issues in document version control, and tight timelines to submit documents for ethical approval.

"Probably because at the point that we're trying to get all the paperwork together. It's a bit of a crazy time. As much as you try to make sure everything matches, there's always that push to get the submission in and to get the process started so it's just something that's missed." (Interview 12, Trial Manager)

Other reasons include, streamlining to minimise PIL length, and that the same level of detail in the protocol is not needed in the PIL since it is a patient facing document.

7.5.3 Communication findings in the context of existing literature

The qualitative interviews provide valuable new insights that explain and advance our understanding of results from the scoping review (Chapter Five) and the PIL analysis (Chapter Six).

The scoping review conducted in Chapter Five, clearly highlighted the lack of reporting of retention strategies within protocols. Despite the guidance that exists from SPIRIT, and the Health Research Authority, to outline information about retention strategies in protocols, evidence shows us that this is not the case. We speculated previously that this may be a reporting issue rather than a planning and implementation issue. The interviews were able to provide further insights and add to our understanding on the lack of reporting. While some trialists interviewed state that they include retention strategies in trial protocols, others reported that this does not occur for reasons such as: concerns about increasing protocol deviations if

the strategy is not followed exactly by all participants; it is not a requirement to provide this information; it is not within the templates for protocol development.

In Chapter Six, the PIL analysis highlighted retention strategies are often outlined in PILs. However, the importance of retention and the impact any missing data has on the trials ability to answer the research question were rarely outlined, strengthening existing similar findings by Kearney et al (81). Our interview study provide more context on this. Trialists explained that certain retention strategies are reported in PILs when participant consent is required, e.g., for incentives or to receive communications from the trial team. Reasons trialists were reluctant to outline strategies in PILs included: avoiding excessive detail; lack of template requirements; efforts to reduce PIL length; or concerns about deterring participation. Information around the importance and value of retention in the trial was not something commonly outlined in PILs according to the trialists, but instead this information is communicated verbally during consent or in later follow-up communications from the trial team.

While some trialists saw value in documenting these strategies in protocols and PILs, others expressed concerns about reporting information about retention strategies in protocols and PILs as it may cause potential rigidity in trial processes or excessive PIL length. These concerns are at odds with the current reporting guidance. These interviews have provided new insights into the potential barriers that need to be addressed to improve uptake of guidance from SPIRIT 2013 and the HRA to include such information in trial protocols and to ensure we keep potential trial participants fully informed. Working with ethics committees and funders to

address these concerns may facilitate better reporting of retention strategies in protocols in the future. Further qualitative research with trial participants/potential trial participants to gain insights into communication preferences may be very beneficial for trial teams to improve communication practices on this topic during the consent process (Further discussed throughout Chapter Eight).

End of Findings

7.6 Reflexivity and positionality

Reflexivity and positionality are commonly mentioned when undertaking qualitative research, as researchers need to think critically about their own positionality and how it can shape the research (96, 177).

"Reflexivity communicates to readers our recognition that knowledge claims are conditioned… Often, being reflexive means exploring the question of how our social positions may influence our knowledge claims" (178:2).

Positionality requires researchers to reflect and disclose how their views and characteristics, e.g., gender, race, socio-economic and education status, might have either directly or indirectly influenced the research. This allows the reader to assess the effects of the researchers' personal characteristics and perspectives in relation to the research being undertaken (96, 179, 180). The Social Identity Map outlined by Jacobson and Mustafa (181), was a helpful guide to consider the different aspects of my identity, allowing me to consider how these may have influenced data

collection and analysis. Being a young, white, middle-class, Irish, female PhD student may have influenced interviewees' perceptions of me and thus the answers given in the interviews.

I have not directly worked on a clinical trial, however from working as a research assistant in the field of trial methodology, completing a Postgraduate Certificate in Clinical Trials and conducting the original studies in Chapters Four to Six of this thesis, I have a very good understanding of trials and their retention strategies. Prior knowledge and understanding may have been beneficial in facilitating more-in depth conversations and probing about the topics discussed by interviewees. Equally, having set pre-existing knowledge may have unknowingly closed off certain lines of enquiry, perhaps preventing different relevant information being discussed in the interviews. The topic guide and prompts were informed by my previous research on retention strategies in trials and common practices in retaining participants, again possibly influencing responses. I may have been more inclined to explore topics brought up by the interviewees, that I deemed significant based on my prior understandings.

Interviewees may have not been comfortable sharing retention practices with an early career researcher, particularly if these differed from best practice guidance or scientific literature, on how to retain trial participants and the documentation of such information. Conversely, interviewees may have been more open and honest about retention practices, as I may be perceived as less threatening being an early career researcher. Many interviewees outlined that their trials had retention rates that were in line with projected attrition rates. If retention rates in trials were poor,

interviewees may not have discussed these challenges because perhaps, they felt I may be judgemental due to lack of practical experience of conducting trials. Additionally, I knew a handful of the interviewees, this may have caused more desirable answers.

My existing knowledge inevitably means that the data will be viewed from a specific perspective, emphasising certain information over other details provided in the interviews. For example, I may have focused more on challenges with implementing retention strategies, viewing these as barriers that need to be overcome, and areas of recommended improvements, rather than focusing on examples of successful retention strategies. Being aware and reflexive of these factors throughout conducting the interviews and analysing the data, has made me aware of these possible scenarios.

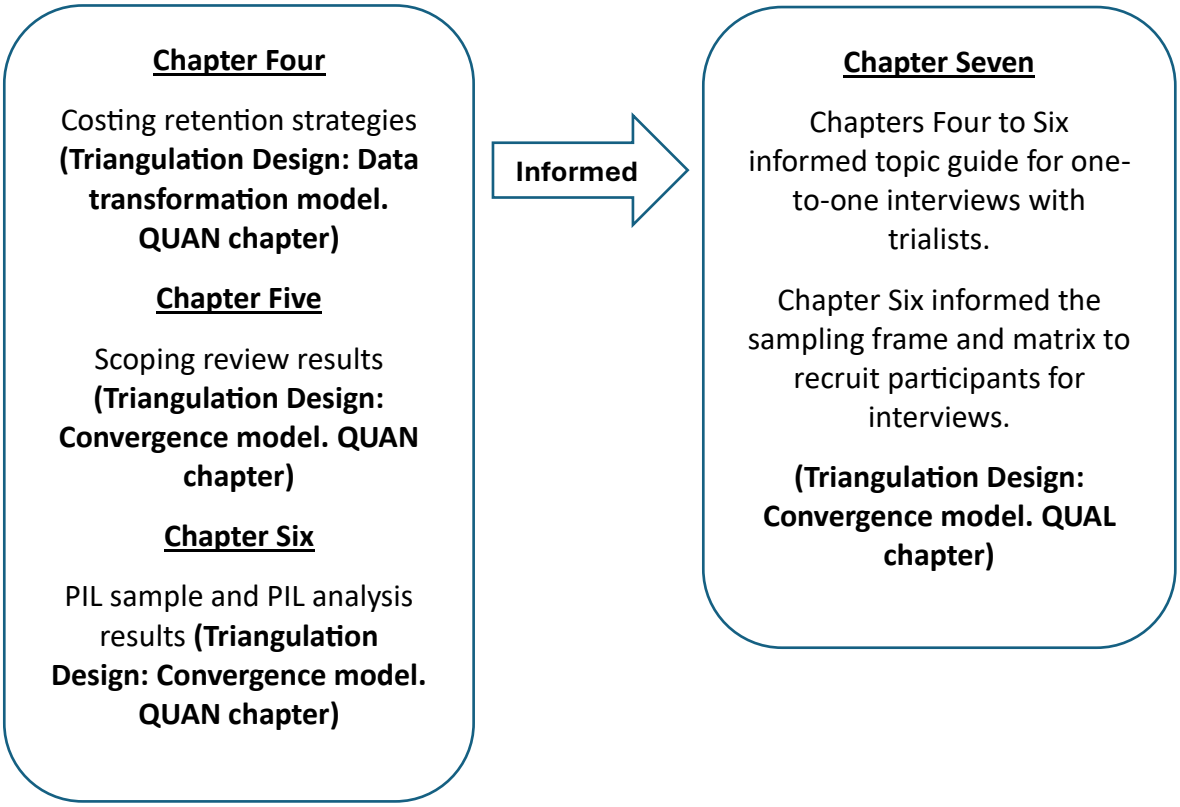
7.7 Reflections and learnings

This is the first time I conducted one-to-one interviews, and I have one key reflection. Interviewing people is challenging. I had to remain aware of my own interests and assumptions about participant retention throughout the interviews, to avoid asking leading questions. Learning how to phrase questions to elicit rich answers, and when, and how, to probe and prompt interviewees to expand on responses, was also challenging. As I conducted more interviews, I gained confidence and found the interviews easier to navigate, and it became easier to be flexible in the order of questioning based on information provided.

7.8 How this chapter links in with other chapters

The topic guide for the interviews was informed by Chapters Four, Five and Six. The sampling frame and sampling matrix to recruit interviewees was informed by the PILs used in Chapter Six.

Figure 7.1. Diagram of how this Chapter Seven links with other chapters.



7.9 Summary of key points from the chapter

Summary of key points from the chapter

- Twenty-four trialists in the UK and Ireland were interviewed to gain a more in-depth understanding of the planning and communication of retention strategies in trials.
- Planning retention strategies often occurs proactively during the design and planning stages of the trial, and strategies are implemented from the outset of the trial to minimise attrition. If retention becomes problematic, additional retention strategies are reactively planned and implemented.
- A variety of different formal retention strategies are used, having used the strategy previously is the main factor that influences choice.
- To improve retention rates, ensuring participants' expectations about the trial are clearly set, and building rapport with participants are important.
- The documentation of retention strategies varies in trial protocols and PILs.

Chapter Eight. Discussion

8.1 Overview

This concluding chapter provides an overview of the research aim, objectives, and associated chapters, along with a discussion of integrated findings from Chapters Four to Seven. It presents recommendations for practice and future research, and the overall strengths and limitations of the research presented in this thesis. Finally, I conclude with my personal reflections on my PhD journey.

8.2 Summary and interpretation of integrated findings

The aim of this doctoral thesis was to gain a better understanding of the costing, planning, and communication of retention strategies in trials, during the design, planning, and consent stages. An overview of the research objectives and the associated chapters are presented in Table 8.1, along with an interpretation of integrated findings across the chapters (Integration of findings – Chapter Three, section 3.6)

Table 8.1. Integration of results from individual research objectives.

Research Objectives	Chapter Four; Costing approach	Chapter Five; Scoping review	Chapter Six; PIL analysis	Chapter Seven; Interviews	Interpretation of integrated findings
Research objective one; To estimate how much routinely used retention strategies might be costing trial teams in Ireland and the UK.	**Key finding:** Retention strategies can range from being less expensive to very expensive. Regardless of cost, however, these resources may be wasted since there is no high-quality evidence to show strategies are effective.			**Key finding:** Cost and resource influence choice of retention strategy, particularly reactive strategies. Retention strategies are believed to be effective but not often formally evaluated to assess effectiveness (Framework matrix – Table A7.8 - Appendix 10, Supporting quotes included in Appendix 13)	It is important to proactively plan retention strategies during the trial design and planning stages to ensure that the strategies are resourced and budgeted for properly (discussed throughout section 8.3) Strategies need to be formally evaluated to ensure that resources are spent on strategies that will improve participant retention (discussed in section 8.3.3)
Research objective two; To identify if, and how, trial teams document plans for participant retention in trial protocols, reflecting the		**Key finding:** Trial protocols do not often include retention strategies, indicating trial teams do not plan strategies during the trial	**Key finding:** PILs often include retention strategies and so did their corresponding protocols – indicating trial	**Key findings:** Planning and implementing strategies usually occurs during the initial trial design and planning stage of the trial. The documentation in protocols varies for a	The proactive planning of retention strategies is better in practice than it is reported in trial protocols. Therefore, in this context, the lack of retention strategies in protocols is likely a reporting issue, rather than a planning and implementation issue,

extent of retention planning during the protocol development stage of the trial.		design and planning stage and/or do not outline retention strategies in trial protocols. Among protocols that outline retention strategies, a wide range of different strategies are documented across the protocols.	teams plan for retention during the trial design and planning stages. A range of different retention strategies are outlined across the PILs.	range of reasons and some strategies are instead outlined in standard operating procedures. Reasons for not outlining strategies in protocols were reported. Such reasons include: strategies are not planned during the trial design or protocol development stage; inclusion of retention strategies is not a mandatory requirement from sponsor/funder; inclusion of strategies may lead to lack of flexibility and possible protocol deviations if the retention strategy is not followed for each participant. Trialists report using various formal and	during trial design and planning (discussed in section 8.3.1). A wide range of retention strategies are used in trials to promote retention, across Chapters Four to Seven similar strategies are seen such as monetary incentives, prompts, reminders, newsletters, pre-paid envelopes, covering clinic visit transportation, and scheduling visits in line with routine care (discussed in section 8.3.2) Working with sponsors and funders to mandate retention strategy planning may be warranted. Further understanding of reporting barriers in trial protocols is essential and working with stakeholders to overcome these barriers is important to improve reporting practices.

				informal strategies to promote retention.	Training with trial teams to provide insight into the importance of planning and reporting retention strategies is also needed.
Research objective three; To establish if trial teams communicate retention strategies in participant information leaflets (PILs), and if they do, to establish if this was pre-planned in the trial protocol.			**Key finding:** PILs often outline retention strategies. There are inconsistencies regarding information about retention strategies outlined in corresponding protocols and PILs. The importance of retention is rarely outlined in PILs.	**Key finding:** The documentation of retention strategies in PILs varies. Some strategies are outlined or vaguely outlined PILs. Some trialists felt there is no need to communicate such information to participants. Reasons for not outlining strategies in PILs are reported. Reasons for not including this information in PILs include: it is not a template requirement; trying to reduce PIL length; it may deter trial participants initial participation if they are	Different practices are taken by trialists to communicate information about retention strategies in PILs. Participants are often told verbally by trial staff about the importance and value of retention in the trial, rather than in written format via the PIL. More research is needed to understand participants' perspectives on whether, and how, participants would prefer communications about retention strategies and about the importance of retention. This may help trial teams overcome concerns with providing participants with information on retention strategies via PILs (discussed in section 8.4.3)

				told they will receive lots of follow-up communications; participants do not need to be told about certain strategies as they should expect to receive for example reminders. Inconsistencies between corresponding documents, regarding retention strategies, are hypothesised to be caused mainly by human error and issues in version control. The importance of retention is often verbally communicated during consent or written in follow-up communications.	
Research objective four; To get a more in-depth understanding of				**Key finding:** Trialists are mainly proactive in their approach to planning and implementing retention	Planning and implementing retention strategies is a dynamic process that requires both proactive and

trialists' views and opinions on retention strategy planning and communication in trials.				strategies but are also reactive when issues arise. Interviews provided insights into influences on the choice of strategy, challenges with implementation, and decisions around the communication of retention strategies in trials.	reactive approaches to facilitate retention. A variety of different factors are considered when choosing a retention strategy, but experience of using the strategy previously is the main influence on choice. There is not a standard approach taken when communicating and reporting information about retention strategies in trial documents or to trial participants. Barriers and reasons as to why strategies are not reported in trial documents may need to be addressed, though education and training to improve understanding on why reporting of this information in protocols and during the informed consent process is important.

8.3 Key findings and recommendations for practice

8.3.1 Retention strategy planning and implementation better than reporting

My overall findings indicate that, the proactive planning and implementation of retention strategies are better than the reporting of retention strategies. While proactively planning and implementing retention strategies seems to be common practice by trialists (Chapter Seven), routinely, and consistently, documenting these plans is less common, based on the findings from our scoping review (Chapter Five), PIL analysis (Chapter Six), and according to trialists themselves (Chapter Seven).

The SPIRIT 2013 guidelines recommend the inclusion of information on retention strategies under item 18b (21, 127). The Declaration of Helsinki recommends that protocols should include information on incentives for participants (22). The Health Research Authority (HRA) protocol template for Clinical Trials of Investigational Medicinal Products (CTIMPs), has a section for participant payments, including "reasonable travel expenses for any visits additional to normal care", and within the "long term follow-up assessments" section, it outlines the protocol "should" describe "retention strategies" (80:24,32). The HRA also endorse, and recommend, the use of the SPIRIT 2013 guidelines when writing protocols. Similarly, a wide range of journals endorse the use of the SPIRIT 2013 guidelines (141). Our scoping review found that protocols did not often include retention strategies. Even among protocols that claimed to follow the SPIRIT 2013 guidelines, item 18b (retention strategy) was often not reported, highlighting poor adherence to the guidelines and incomplete application of the guidelines when developing trial protocols. Our study included protocols published up to 2019, the same year the PRioRiTy II study was

published, which highlighted the need for, and priority areas of, research required to help improve retention in trials. Since this publication, there may be improvements in reporting practices on retention strategies in trial protocols. We must at least allow for that possibility, however, our more recent qualitative study of trialists would indicate that reporting of retention strategies in protocols is still variable. For example, many trialists outline that the reporting of retention strategies is not a requirement within protocols, nor is there a specific section in the protocol template, they use within their units, to include such information (Chapter Seven). My findings indicate that there is a need for greater awareness and enforcement of the use of the SPIRIT 2013 guideline item 18b, as there seems to be a disconnect between the guidance and its implementation, i.e., reporting of SPIRIT item 18b.

8.3.1.1 Recommendations for practice; improved reporting of retention strategies

Reporting of retention strategies is likely to remain poor until there is greater priority placed on participant retention during the initial trial design and planning stages, forcing trial teams to proactively plan, and report retention strategies in protocols. From the outset of the trial less priority is placed on participant retention from stakeholders such as funders, compared to recruitment, a view held by trialists (Chapter Seven) which is supported by existing literature (70, 77). A couple of trialists in my study suggest that there is a need for more guidance and mandatory requirements to facilitate better planning and documentation of retention strategies, as it would ensure trial teams are considering retention during trial design and when writing protocols (Chapter Seven). This indicates there may be a

need to increase the awareness of the SPIRIT 2013 guidance, and the HRA protocol template, which both include sections for retention strategies (21, 80, 127). A top-down approach may be needed. A requirement from funders and ethics committees for retention strategies to be included in trial protocols may facilitate greater awareness of existing guidance, and place greater emphasis on the importance of proactively planning, and reporting, retention strategies. Additionally, involving publishing journals to enforce the use of and check application of the SPIRIT 2013 guidance, ensuring item 18b is reported, may help increase the reporting of retention strategies in published protocols. Although the retention strategy does not need to be finalised at this stage, since protocols must only be published before recruitment of participants is completed (182), it may be helpful for journals to remind protocol authors of the importance of such strategies. This could encourage trial teams to consider such strategies during the design and planning stages of the trial.

Placing a larger priority on retention would not only benefit the trial itself, but it would also be of benefit to trial funders. Requiring protocol amendments, additional ethical approvals, and implementing additionally required retention strategies, all add to time delays and resource costs (183, 184). Improved participant retention may lead to fewer trial extension requirements and recruiting fewer participants to compensate for loss, all of which save the funder further investment in the trial. Additionally, collaboration is needed with publishing journals and peer-reviewers to facilitate and ensure protocol submissions are checked for retention strategy inclusion and flagged for inclusion to authors. Working with trial stakeholders is needed to understand how best to facilitate the prioritisation of

participant retention during the trial design and planning stages. Early prioritisation of retention should improve proactive planning of retention strategies, which may, in turn, improve awareness of the reporting guidance. This, in turn, could encourage trial teams to integrate retention strategy sections into standardised templates used by trial units, ultimately leading to improved reporting in published protocols. Additionally, the new knowledge generated in this thesis on the reasons why trialists don't report retention strategies in protocols and PILS will help address these barriers in collaboration with key stakeholders—such as trial teams, ethics committees, and funders. This may further support the uptake of the SPIRIT 2013 guideline item 18b and ultimately lead to more complete and transparent reporting of retention strategies in protocols.

Complete reporting of intended trial activities increases transparency in trial conduct, and this should encompass retention strategies (21, 127). Clearly disclosing retention strategies in protocols may inspire the use and replication of the strategies among other trial teams. This is particularly useful for replicating much needed retention strategies, (i.e., retention interventions), in formal evaluations (3). Additionally, reporting information about the cost and resources involved in implementing planned retention strategies, may help trial teams make more informed choices about the resources and the budget they need to allocate for such activities.

While it is positive that recommendations exist for reporting retention strategies in trial documents, it is not a mandatory requirement to follow the existing guidance.

Placing greater value on the importance of participant retention, in a top-down approach, may lead to trial teams integrating sections for retention strategies into protocols, and adhering to the existing guidance and recommendations. Additionally, increasing awareness of existing guidance among trial teams and the trial community, who are likely peer reviewers, may also facilitate greater inclusion of strategies in published protocols. This should lead to improved proactive planning of retention strategies, improved reporting of retention strategies in trial documents, and ultimately improved participant retention rates in trials.

8.3.2 A variety of retention strategies are implemented

Chapters Four to Seven present data showing that a broad array of retention strategies were identified in trial protocols, PILs, and reported by trialists. Retention strategies included: prompts, reminders, newsletter, pens, pre-paid return envelopes, monetary incentives (both conditional and unconditional), offering participants different options of methods to complete follow-up activities, organising and covering transportation to clinic visits, and the list continues. The types of strategies identified are consistent with the most routinely used strategies in the UK (68). Overlap in strategies also align with the Cochrane review of strategies to improve retention in trials and a systematic mapping review of NIHR HTA protocols (3, 171). The Cochrane review identified and included formal evaluations of strategies that have been implemented in practice, including: offering different options of data collection location/method, monetary incentives, rewards, prompts, newsletters, and offering participants to receive the results of the trial (3). Among the NIHR HTA protocols, the three most popular strategies were, flexibility

with data collection method/location, participant diaries, and the use of routine data. Other strategies included: participant telephone reminders, participant postal reminders, flexibility with timing of data collection, and monitoring approaches (171). My findings align with the existing evidence base, showing that trial teams take similar approaches to improving participant retention. Given this, these commonly used strategies are in urgent need of formal evaluation to understand which strategies improve retention rates because evidence is currently lacking (further discussed; recommendations for practice; formal evaluations of retention strategies, section 8.3.3.1).

My findings are not tied to a specific clinical context, population type, or resource setting. When compared to trials conducted in more specific settings, our findings reveal both similarities and differences in the types of retention strategies used. For example, in paediatric trials, monetary incentives are popular, similar to our findings, but are mostly provided to parents/carers. Often retention strategies in the form of non-monetary incentives, such as: stickers, stamps in a visit passport when children attend visits, toys for younger children, and colouring pictures, are used to facilitate engagement in these trials (185). These types of strategies differ from the results of my research. In the specific context of paediatric trials, several factors must be considered when planning to improve retention. These include the age of the participant, as well as the involvement of families/parents/carers and teachers in school-based trials (185). This demonstrates that in different trial contexts, different retention strategies, and different retention influences, need to be considered when targeting and retaining different participant populations.

Different considerations for retention and different retention strategies may be required in trials among under-served groups. Although some trialists we interviewed noted that the type of population is considered when planning retention strategies, none specifically discussed the retention of under-served groups. For example, existing literature shows in specific cultural contexts, factors such as partners, a woman's role in the family unit, and cultural traditions, such as bereavement traditions, influence continued trial participation (64). As a result, retention considerations, and thus different retention strategies and different communication practices may be seen within these contexts compared to my findings. Different considerations for retention, and retention strategies, may also be needed for trials that include adults who lack capacity to consent, as other stakeholders, such as family members or friends, may be involved in decision making for these trials (186). For example, do these stakeholders need to be targeted with strategies, to enable and support participation and data collection from the trial participant (187).

Trials in low resource settings can lack core infrastructure to support trial delivery (188). Trial teams may be more limited in what they are able to do to facilitate ongoing participant retention, and popular retention strategies may vary in this context compared to our findings. There may be less funding, and resources, available to implement retention strategies. In low resource settings, the strategies that teams might use are perhaps more focused on providing transportation to

clinic visits, conducting home visits, or collecting multiple forms of participant contact information (189, 190). Research investigating remote assessment of surgical wounds, found that telemedicine/telephone follow-up may have a strong potential in reducing attrition, in surgical RCTs in low and middle income countries (191). More research is needed in such settings to understand the nuances of trial retention, and the use of retention strategies. Trialists conducting trials across various resource settings need to consider the practicality and suitability of implementing retention strategies, ideally during the design and planning stage of the trial.

8.3.2.1 Recommendations for practice; considerations when planning retention strategies.

When planning and choosing retention strategies, we recommend that trial teams critically consider, during the design and planning stages of the trial, which strategies they will implement during trial conduct. Within the wider trial methodology context, there are several key factors we recommend should be considered.

8.3.2.2 Patient and Public Involvement

Involving patients and the public (PPI) in trials is very important, as having input from these individuals can help maximise the relevance of the research to the trial participants (143, 192, 193). We recommend that patients and the public be routinely involved in the retention strategy decision-making process. The measurable impact of PPI on participant retention rates is limited, and requires

more research to understand the impact of PPI on improving retention (142). However, involving patients and the public in the development and decision-making process on how best to retain participants, as well as the overall trial design process, may help to ensure that the trial design is maximised to retain its enrolled participants. It may additionally help ensure that the chosen retention strategies are likely to be deemed appropriate and suitable for the trial participants. Having PPI involved as part of the retention strategy itself may also be beneficial. For example, one trial involving minority and under-represented women, evaluated a community-based PPI led retention strategy. The strategy involved the PPI partners phoning participants, reminding them about follow-up visits, helping participants overcome participation barriers, and comply with follow-up. This strategy led to an approximate 22% increase in retention rates of participants in the intervention group when compared to the control group that did not receive the support (194). This type of strategy may, however, be costly compared to other strategies, as the PPI partners were reimbursed for their time, and, additionally, our findings show that phoning participants can be expensive (194)(Chapter Four). Further research is needed to see if the strategy is cost effective, but PPI involvement in retention strategies may be very valuable. Having input from patients and the public, may help trial teams to best understand the needs and requirements of participants to be retained in trials in specific clinical contexts, resource settings, or among under-served populations. Additionally, PPI input may provide insight into sub-groups of the trial cohort that might need to be targeted with additional/different strategies compared to most participants. Meaningful PPI needs to be planned, and considered by trial teams during the trial design, and planning stages, to maximise

PPI input to facilitate retention rates, and budget needs to be allocated for PPI contributions at this stage (148, 195).

8.3.2.3 Inclusive trials

There have been increased efforts to make trials more inclusive, to ensure that traditionally under-served populations are being recruited, and naturally being retained in trials, such as the NIHR INCLUDE project (149, 187, 196-200). Under-served populations include: Black, Asian, and Ethnic Minorities, older people (those >75 years), pregnant women, people with mental health conditions, people who lack capacity to consent, and those from socio-economically disadvantaged groups, among many others (200). All these groups may need specific attention when planning retention strategies, to ensure they are retained in the trial, as research suggests that current strategies to recruit and retain participants, might not be fit for purpose among under-served groups (149). The INCLUDE project is an example of work in progress to make trials more inclusive. It currently has three developed frameworks to support wider inclusion in trials: the INCLUDE Ethnicity, the INCLUDE Impaired Capacity to Consent, and the INCLUDE Socio-economic Disadvantage Framework (187, 196, 201). These frameworks highlight key considerations for improving the retention of under-served groups in trials. For example, trial teams should assess how data collection locations may create barriers to ongoing participation for participants facing socio-economic disadvantage, such as, limited disposable income for transport to clinics, and poor transport links. Remote data collection may also pose challenges due to digital literacy or access issues (201).

Additionally, enabling participants to nominate a study partner may support retention in trials involving adults who lack capacity to consent (187). Teams should also consider whether data collection methods may exclude certain ethnic groups, such as by requiring appropriate language translation (196). Additionally, Trial Forge Guidance 3 has specifically focused on the recruitment and retention of ethnic minority groups, and provides guidance and recommendations on how best to facilitate their recruitment and retention in trials (149). Such recommendations include, ensuring staff are culturally competent to increase their confidence to engage with different ethnic groups, and building trust with participants. Including such information during site initiation trainings could facilitate cultural competency (149). Ensuring that trial materials and information are developed to facilitate inclusion is important. This includes effective translation to ensure trial information is understood by participants, which supports expectation setting - a factor shown to be important to retention (17, 64, 65, 77, 149).

We recommend that when planning retention strategies, trial teams need to consider whether the strategy is suitable and appropriate for all intended participants, to avoid the strategy indirectly hindering the retention of participants from different under-served groups. Tailored approaches to retention that are designed to be inclusive are likely to facilitate retention (149). This may help facilitate the follow-up and retention of participants from groups that are traditionally under-served in trials. For this to occur, the trial team needs time to consider these factors and to plan, budget, and allocate resources for such activities. Ideally, all of these steps should happen proactively during the trial design and planning stages.

8.3.2.4 Greener trials

When determining the choice of retention strategies, trialists cited a wide range of factors. Only one trialists in our study mentioned considering the environmental impact of retention strategies when deciding what strategy to implement (Chapter Seven). With the increased interest and focus on making trials 'greener', perhaps it is a factor that should be considered more by teams when planning retention strategies. Estimates show, the carbon footprint produced per trial can range from around 80 to over 2000 tonnes of carbon dioxide emissions (CO_2e) (202-205). To put this in perspective, 80 tonnes of CO_2e is equivalent to the greenhouse gas emissions produced by 6 UK citizens annually (203), or 49 return flights from London to New York (204). Going forward, the carbon impact of retention strategies may need to be considered, to reduce the carbon emissions produced by trials. Some retention strategies, such as scheduling study visits at the same time as routine care visits, may reduce carbon emissions. Remote data collection methods may reduce emissions, however, the energy of remote data collection technologies has to be considered (202, 204). Other strategies, however, can significantly add to carbon emissions. Sending Christmas cards to 1,617 participants produces roughly 226kg of carbon dioxide – the equivalent of flying 230 miles (73). We also know that this retention strategy is not effective (73), a double whammy. Future research should prioritise strategies that have a low carbon output, and consider these in line with effectiveness, to help trial teams make more informed and 'greener' choices when it comes to choose retention strategies. For now, trial teams should try considering

taking a ‘greener’ approach when decision which strategy to implement when planning retention strategies, ideally during the initial stages of the trial.

8.3.2.5 Decentralised trials

Trial teams need to consider the impact that decentralised trials, or decentralised aspects of data collection, can have on participant retention. While decentralised trials are becoming more popular due to benefits such as, reducing burden of trial participation, reducing trial costs, as some argue making trials ‘greener’ (39, 41, 204, 206, 207), aspects that facilitate participant retention may suffer. For example, participants may have limited communication opportunities with the trial team, and lack in-person support (206). Additionally, there is a lack of evidence to determine whether decentralised trials improve retention (206). A handful of trialists felt that participants that had less regular contact with trial staff, were more likely to not be retained in the trial, as they did not have a relationship with trial staff (Chapter Seven). The importance of the relationship between trial staff and participants is previously reported by both trial staff and trial participants (69, 70, 74, 77). How best to facilitate developing, and maintaining, rapport with participants in trials where follow-up is remote and participants have less contact with trial staff, should be a key consideration during the trial design and planning stage for trial teams involved in such trials.

8.3.3 Evaluating retention strategies

To improve the evidence-base for effective retention strategies, formal evaluations of such strategies need to be integrated in routine practice. Few trialists reported looking at the literature when choosing retention strategies (Chapter Seven). This is not surprising considering the lack of high-quality evidence to support their use (3). Yet, differences between the evidence base and current practice are prevalent. For example, some trialists mentioned sending seasonal cards but, based on recent evaluations, Christmas cards are not effective at improving retention (73). A systematic mapping review of retention strategies in protocols for NIHR HTA trials, identified the use of participant diaries as popular among trial teams (171). The existing evidence suggests, that compared to usual follow-up, using diaries has a negative effect on retention rates, this is supported by evidence of moderate certainty as assessed by GRADE (3).

Most trialists believed the strategies they used were effective, despite not having conducted formal evaluations (Chapter Seven). Some mentioned challenges implementing SWATs (Studies Within A Trial). Concerns included: the additional time, resources and workload, the perceived risks associated with conducting a SWAT, and the perceived challenge of getting ethical approval for conducting such evaluations. More work is needed in the trial methodology community to both improve awareness of the existing literature, (albeit limited), and to facilitate formal evaluations of retention strategies.

8.3.3.1 Recommendations for practice; formal evaluations of retention strategies

8.3.3.2 Evaluating the effectiveness of retention strategies

Formal evaluations of the effectiveness of retention strategies are needed, to help trial teams make informed, evidence-based, decisions when planning retention strategies. Not only this, but due to the costs and resources associated with implementing retention strategies (Chapter Four), the results of these evaluations are needed to ensure, limited trial resources are not wasted on strategies that are both expensive and ineffective. The Cochrane review outlines key priority evaluations that are needed (3). It is recommended not to reinvent the wheel, but instead replicate and evaluate existing strategies that have little supporting evidence, to gain high certainty evidence as to whether the strategy is effective at improving participant retention (175). The PRESS project has also produced a list of retention SWATs that should be prioritised when trial teams are considering implementing and evaluating retention strategies. Priority retention SWAT questions include for example: 'What is the most effective way of using participant reminders to support retention?' and 'What is the most effective way to use financial incentives to support retention?'. Including cost effectiveness analysis is also recommended (176). Research has been conducted to facilitate the implementation of SWATs to evaluate strategies, and guidance is available for the reporting of such evaluations (72, 174, 175, 208, 209). For example, the PROMETHUS project has outlined solutions to challenges when implementing SWATs (210, 211). Funding streams have also been made available for SWATs, within the UK NIHR funding process (212), and via the Health Research Board Trial Methodology Research Network (213).

In practice, more awareness may be needed to facilitate the implementation of SWATs, as often they are not conducted by trialists (Chapter Seven). A barrier mentioned was expected pushback from ethics committees for these types of evaluations, additionally a few trialists mentioned ethics committees can influence and pushback on the types of retention strategies used in a trial. Engaging with ethics committees to improve understanding of retention strategies, understanding of SWATs, and the importance of such evaluations for retention strategies, may help facilitate the review, and approval of such evaluations. For example, informing ethics committees about the PRESS project, may help facilitate the evaluation of priority retention strategy SWATs to gather enough evidence to be able to say with certainty a strategy is effective or not. Working with ethics committees, funding bodies, and the trial methodology community to raise more awareness of the supports, and resources available to facilitate SWAT implementation could be beneficial.

Furthermore, existing literature has found that despite the potential impact that recruitment and retention strategies can have on the alternate outcome, i.e., the impact of recruitment strategies on retention rates and vice-versa, the opposite outcome is very seldom evaluated in studies evaluating the effectiveness of these strategies (214, 215). Therefore, it is recommended that the impact of recruitment/retention strategies on the opposite construct should be investigated, to ensure that one strategy does not hinder the opposite process, and to see which strategies may improve both recruitment and retention (214, 215). This is something that needs to be considered during the trial design stage. Firstly, however, trial teams need to start formally evaluating retention strategies, to

generate evidence to show which strategies work at improving retention rates and which do not. These evaluations will help ensure that trial resources are being invested into strategies that will improve participant retention. Trial teams, again, need to be planning and budgeting such evaluations during the initial trial design and planning stages, another key reason why trial teams need to be considering retention during these initial stages of the trial.

8.3.3.3 Evaluating the cost effectiveness of retention strategies

Linked to evaluating the effectiveness of retention strategies on improving participant retention rates, the cost-effectiveness of such strategies should also be considered by trial teams, if planning on implementing a retention strategy. Retention strategies impact trial budget and resource allocation, as we have shown commonly used strategies can be very expensive (Chapter Four). While the cost of retention strategies may be small compared to the overall cost of the trial, understanding which strategies can maximise retention rates while minimising the costs involved may be very beneficial for trial teams when deciding what strategy to implement. As more high-quality evidence on the effectiveness of retention strategies is generated, trial teams can compare the cost-per-participant retained, (cost of a retention strategy divided by the number of participants successfully retained), across different strategies, as we did in Chapter Four. Identifying effective strategies with lower cost-per-participant retained can also help inform the choice of strategy and budget allocation.

Currently, it is difficult for teams to consider cost-effectiveness due to the limited evidence to indicate whether strategies are cost-effective but research is being

conducted in this area (216). Strategies such as giving participants £10 during follow-up, and providing trial-branded pens, may be cost-effective based on the limited evidence. Whether electronic prompts, pre-notification cards, or unconditional (versus conditional) monetary incentives, are cost effective is yet to be seen (71). Existing research recommends the economic evaluation of retention strategies alongside retention strategy SWATs, through using, for example cost-benefit analysis (71). As previously highlighted such evaluations need to be considered during the trial design and planning stages. Organising trainings for trial teams on how to carry out cost-effectiveness/economic evaluations, working with funding bodies to provide funding for this type of evaluation, and with ethics committees to encourage trial teams to include a cost-effectiveness/economic evaluation when implementing a retention strategy, all may help facilitate gathering evidence on retention strategy cost-effectiveness.

8.4 Recommendations for future research

An overview of the key recommendations for future research from this thesis are outlined in Table 8.2.

Table 8.2. Overview of recommendations for future research.

Research in specific trial contexts	Targeting trial staff	Exploring trial participants views
This thesis has provided a broad overview of planning and communicating retention strategies across a range of trial contexts. Different or additional retention considerations may need to be accounted for when working in specific clinical areas, with specific participant population types or for specific trial design types, and as a result findings may be different in these contexts compared to what we have identified.	The findings of the thesis outline that most retention strategies used by trial teams target trial participants. Trial staff, however, play a key role in participant retention. As a result, **f**uture research should investigate effective ways to engage, and support, trial staff to improve participant retention rates.	Based on previous literature, participants have views on the use of certain types of retention strategies. Exploring these preferences may facilitate better planning. Additionally, exploring participants' preferences for the timing and amount of information they wish to receive about retention strategies, and the importance of retention in the trial, could help trial teams better communicate such information.

8.4.1 Research in specific trial contexts

This thesis has provided an overview when it comes to the current practices of planning and communicating retention strategies, and the costs involved, across the trial landscape. As discussed in the above sections, different or additional retention considerations may need to be accounted for when working in paediatric trials, trials in low resource settings, among under-served populations, and specific trial design types. There is scope for further research into retention practices in these contexts, which may offer new insights into the strategies used. Such research could

lead to improved recommendations for costing, planning, and communicating retention strategies in trials.

8.4.2 Targeting trial staff

Trial staff play a key role in facilitating participant retention. Building rapport and relationships with participants is deemed to be an important aspect of participant retention (70, 74, 172). Trialists interviewed in Chapter Seven, held the same beliefs. Site staff need to provide sufficient information to participants to set their expectations about trial involvement when taking informed consent, which is another crucial aspect of participant retention (77). Aspects of retention, however, are often not outlined during informed consent (12, 81). As a result participants' expectations about the trial may not be correctly set, contributing to participants leaving the trial (64). It is clear that trial staff play a key role in the retention of trial participants. However, my research findings indicate that very little is planned to target trial staff to improve retention, most strategies are targeted at trial participants. The Cochrane review of strategies to improve retention in trials includes 69 studies, only two of which target trial staff (3). Despite the importance staff play in retaining participants, very little has been done to implement staff focused retention strategies. Future research should investigate effective ways to engage, and support, trial staff to improve participant retention rates. An improved understanding of how best to train and support staff to retain participants could provide trial teams with more options when planning on how to facilitate participant retention.

8.4.3 Exploring trial participants views

Existing literature shows that participants have mixed views in terms of the use of retention strategies in trials (65, 74). Participants have opinions on the use, and acceptability, of retention strategies. Exploring these preferences may facilitate better planning of retention strategies among trial teams, and one way to do this is through engaging with PPI as discussed above. Participants may also have preferences around when, and how, information about retention strategies, and the importance of retention is communicated. We have found that the communication of retention strategies in PILs is variable. Trialists noted there are mixed views and practices when it comes to communicating information about retention strategies in PILs. We found the importance of retention is rarely outlined in PILs, complimenting previous research findings on the topic (81). The trialists reported that the importance of retention is more commonly communicated verbally during consent, contradictory to existing literature (12). Exploring participants' preferences for the timing and amount of information they wish to receive about retention strategies, and the importance of retention in the trial, could benefit expectation setting. This exploration may also enhance the successful communication of such information. This research will further help address question 10 and nine set out by PRioRiTy II "how should people who run trials plan for retention during their funding application and creation of the trial (protocol development)? and "What information should trial teams communicate to potential trial participants to improve trial retention?" (4).

8.5 Contributions to the existing evidence base

The research conducted as part of this thesis has contributed new insights and understanding of the costing, planning, and communication of retention strategies in trials. These contributions are outlined in Table 8.3 below. The research has helped address gaps in the literature and contributed to answering priority question 10; “How should people who run trials plan for retention during their funding application and creation of the trial (protocol development)?” (56).

Table 8.3. Overview of contributions to the literature.

Chapter	Contribution to the literature
Chapter Four; Costing approach	● Creation and application of a costing approach to estimate the costs of implementing retention strategies in trials (Published).
Chapter Five; Scoping review	● Synthesis of existing practices in the documentation of retention strategies in trial protocols (Published).
Chapter Six; PIL analysis	● Outlining existing practices in the documentation of retention strategies in PILs and their corresponding protocols. ● Contributions to existing literature further highlighting the lack of communication about the importance and value of remaining in a trial, via PILs (Published).
Chapter Seven; Interviews	● Exploration of the views of trialists on the planning and communication of retention strategies in trials, to allow for a more in-depth understanding of the nuances behind current practices (Being prepared for submission).

8.6 Strengths and limitations of the research

In Chapters Four to Seven the strengths and limitations of the individual chapters are detailed. In this section the overall strengths and limitations of the research are discussed.

A strength of the research is it encompasses trials conducted in a wide range of different clinical specialities, intervention type, and includes the viewpoint of various trialists with different roles in the trial team. The scoping review included 824 protocols, we analysed 92 participant information leaflets and interviewed 24 trialists. This has provided a broad high-level understanding of the costing, planning, and communication of retention strategies in trials during the trial design, planning and informed consent stages. The scoping review included published trial protocols across a wide range of geographical areas and thus a range of resource settings are included. Additionally, included were trial protocols for trials conducted among all population types, including vulnerable populations such as children and adults that lack capacity to consent.

Another key strength of the research is that each chapter builds on the prior one. This approach allowed learnings from the previous chapter to be used in the next chapter. For example, the data extraction and results of the scoping review informed how we analysed the PILs and their corresponding protocols. The topic guide for the interviews was informed by all previous chapters allowing for the interviews to provide us with insights into previous findings.

The costing approach, PILs, and interviews were associated with the UK and Ireland only. This is a limitation. However, given the large number of protocols included,

and the fact several studies were multinational, we do not believe the findings would be any different in other countries. However, we cannot be sure of that. We make a similar case about our PIL analysis. In terms of the interview study, it is possible that approaches taken to the planning of retention strategies may be different in countries other than the UK and Ireland. This is because anecdotal evidence from our interviews and the fact the PIL template in a given CTU is similar for all trials in that CTU. Thus, trial teams in CTUs tend to practice similar behaviour across each CTU and or/region. This behaviour could differ internationally, but further research is needed to establish this.

Another limitation is that the protocols reviewed in both the scoping review and the PIL analysis may not to be the finalised version of the protocol. A general rule for publishing protocols is that the document must be published before recruitment of participants is completed (182), i.e., the protocol that is published versus the finalised protocol may differ in terms of outlining information on retention strategies. Additionally, if the follow-up period is long, this leaves room for amendments to be made to counter poor participant retention rates. The PILs analysed, however, could be the finalised version of the document. Therefore, inconsistencies and differences in reporting of retention strategies seen across the documents, could be due to comparisons between different versions of the documents.

We were not able to recruit trial PPI partners to interview, which may be a limitation of our research. Having input from the perspectives of PPI partners involved in trials might have highlighted additional or different relevant findings. PPI partners could

have provided first-hand accounts of their experience in trial involvement, helping to confirm whether trialists described PPI involvement in the choice of retention strategy accurately. Direct input from PPI partners could have validated or challenged claims made by trialists in how the retention strategies are chosen and the level of input from the partners themselves.

8.7 Reflections from my PhD

8.7.1 Reflections on conducting PPI

As part of Chapter Seven we decided to incorporate patient and public involvement partners as part of the research project. This was my first time conducting research with PPI contributors and it was more difficult than I was expecting.

Recruiting interested individuals was challenging. We advertised the research on the PPI Ignite Ireland noticeboard, but engagement was slow. The PPI partners we recruited were lay members of the public who had prior experience of being PPI contributors in healthcare research. However, since we were recruiting trialists to the interviews, perhaps restricting the PPI partners to people who held roles with a trial team would have been more beneficial and suitable for the aim of the project. Making sure the PPI are more reflective of the target audience of the research is something I will take into consideration going forward.

The PPI partners were asked to provide feedback on the interview topic guide. They suggested asking about PPI involvement in making choices about retention strategies to make sure they are relevant to trial participants. This was added in to

determine who is involved in the decision-making process. As the interviews progressed, I regularly updated the partners. The PPI partners suggested the results of the interviews be translated into a graphic. Through discussions it was decided that a graphic of my entire PhD would be more beneficial. This required informing the partners of the other PhD research. The PPI provided feedback to ensure the graphic is engaging and lay friendly (Appendix 14, PhD Infographic).

It was challenging to manage the relationship with the PPI partners. Once the partners were recruited, the project was put on hold as I decided to take a lecturing role for six months. I was unsure how to keep up communication with the partners during this time. Thankfully they were patient and remained happy to be involved once the project resumed. Due to the nature of the research, there were long periods of time, (during recruitment and interviewing stages), where the partners were not directly involved. I was worried about keeping the PPI partners engaged and making them feel engaged and valued in the project during these stages. One of the PPI partners felt I could have done more to involve them in the project. This feedback made my reflect on whether I had meaningfully engaged with the partners or whether their involvement was more tokenistic. This was very valuable feedback and great learning for future work with PPI partners. Clearly setting expectations of what involvement would look like from the outset and perhaps more clearly throughout the project may have facilitated better management of expectations. Involving PPI in this research was a learning curve and taught me a lot about conducting PPI in research projects, and as a first experience, despite the couple of challenges I think overall it was successful.

8.7.2 Reflections on my PhD journey

My PhD started in October 2021. Due to the COVID-19 pandemic, working was still mostly remote and as a result it was difficult to meet other PhD students. Thankfully, I was part of an incredibly supportive group of Health Research Board Trial Methodology Research Network (HRB-TMRN) students who met online once a month, which was an amazing support particularly during the initial stages of my PhD. After completing two years of my PhD full time, I had the opportunity to take a 6-month lecturing position within the School of Public Health in University College Cork, lecturing on the online Postgraduate Certificate in Clinical Trials. This also coincided with the opportunity to move to Aberdeen and start placement with the Aberdeen Centre for Evaluation (ACE). Lecturing online was a fantastic opportunity to see what the role entails, and it showed me that in the immediate future my interest lies in trial methodology research. Starting placement in ACE allowed me to expand my research network and get involved in research outside my PhD. Doing this taught me new research skills and gave me a better understanding of the wider literature in which my PhD lies. Becoming a co-lead of the MRC TMRP Retention Working Group also facilitated learning about other research on retention in trials. Being in an office environment surrounded by researchers all working in trial methodology was majorly helpful when I needed advice and support, and it expanded my understanding of different career possibilities after my PhD. Over the past three years I have also enjoyed presenting my work at various conferences and events (Appendix 15, PhD in Pictures).

While I would describe my PhD journey as a positive experience, it was not without its challenges. The scoping review was a major undertaking, due to the volume of work required to review the 824 included protocols. I had to amend my ethics application prior to starting the recruitment process for the interviews and the recruitment process was also slower and more difficult than expected, causing time delays. Transitioning back to my PhD full-time after lecturing presented an unexpected challenge. While the lecturing experience highlighted that I wanted to pursue a career as a full-time researcher, being in Aberdeen also made me realise that I was interested in exploring research topics outside the scope of my PhD. Being in the final year of my PhD, balancing the demands of completing the thesis, with maintaining motivation and managing stress, was a rollercoaster of an experience. Overall, however, I have thoroughly enjoyed my time as a PhD student, and it has been a rewarding experience full of both personal and professional growth and development.

8.8 Concluding remarks

This thesis has provided a better understanding of the costing, planning, and communication of retention strategies in trials, focusing on the design, planning, and consent stages of the trial. We have added to the existing evidence base on the topic and provided insights to help address PRioRiTy II question 10; “How should people who run trials plan for retention during their funding application and creation of the trial (protocol development)?” (44). Trial teams should be planning retention strategies during the trial design and planning stages, as such activities are costly and resource intensive and therefore need to be proactively considered and

budgeted for by the trial team. Additionally, proactive planning allows teams more time to critically consider the strategy that will be most suitable for their trial. Based on existing evidence formal evaluations of retention strategy effectiveness and cost-effectiveness are needed, such evaluations, again, need to be planned for during trial design. Placing a greater importance and emphasis on participant retention within the research system, may facilitate better proactive planning and reporting of retention strategies among trial teams and ultimately, may lead to improvements in participant retention rates in trials.

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Appendix 1. Thesis Chapter Four. Additional File 1: Costing retention strategies; Breakdown of assumptions in the costing model for each trial.

Preface

We acknowledge that the assumptions that we have made regarding the use of the ten retention strategies may not be truly representative of how these activities are or were actually conducted, and that others may make different assumptions.

We have sought input from clinical trial professionals such as trial managers, clinical research nurses, and professionals working in clinical research facilities in the UK and Ireland as well as from the authors of Kearney et al paper (68) for information to inform our assumptions and costing model. Although we have tried to be as realistic and accurate as possible, the overall aim of our project is rather to highlight the lack of evidence to support the use of retention strategies that are being routinely used by CTUs in the UK and that none of these strategies is without cost.

However, to help to address this limitation, we have made the costing spreadsheet available as an additional file, which means readers can modify it to suit their own trial.

Assumptions about the retention strategies and additional activities that were made regarding the implementations of strategies listed in Kearney et al., (68)

In the Kearney et al., (68) paper CTUs were able to reply to the survey outlining strategies to mitigate missing data that they routinely use. However, responses lacked detail as to how the trial team conducted the activities, which meant we had to make assumptions as to how the top 10 most routinely used retention strategies

are likely to be carried out, in discussion with trial managers, research nurses and others.

- "Newsletter" - we calculated the costs of both electronically and manually posting out newsletters.
- "A timeline of participant visits for sites" – the nature of the strategy itself was unclear from the Kearney paper (68), therefore we created two assumptions. Firstly, we interpreted this strategy as the Data Management team developing reminder schedule software to send out to each site in the trial. The reminder schedule software can be modified to suit the trial follow-up schedule and used to notify site staff of participants' visits. Secondly, from correspondents with trial staff we integrated a participant reminder schedule stemming from the site reminder, this involves the Trial Manager/Research Nurse contacting the participants to remind them of their visit and failed contact attempts are also costed. We costed both of these assumptions. The cost of developing and sending site the reminder schedule software was costed separately but also had to be included in the reminder schedule for participants.
- "Inclusion of pre-paid envelopes (questionnaires)" – We costed sending out pre-paid return envelopes with a questionnaire to all participants. We decided to include the costs of a pre-paid return reminder schedule for the questionnaires that are sent out. This reminder schedule is sent to 30% of participants (non-response rate of 30%).
- "Telephone reminders" - we included costs for telephone reminders for trial visits, telephone reminders for questionnaire response for 30% of trial

participants and additionally for one of the “real-life” trials (MAMI trial)(115) we included telephone reminders for at home data collection for 30% of trial participants. We also included costs for failed telephone reminder attempts for trial visits, for questionnaire response and additionally for the MAMI trial we included failed telephone reminder attempts for at home data collection, as it is likely multiple attempts may be needed to contact non-responding participants.

- “Data collection scheduled with routine care” is costed as the time it takes for research nurses to collected trial related data from participants during their routine care visit.
- “Site initiation training on missing data”/ “Investigator meetings face-to-face”/ “Routine site visits by CTU staff” – we made the same assumption across all three of these retention strategies – based on input from clinical trial professionals in Ireland these activities are charged at a flat rate plus travel costs and other expenses. In the UK the Trial Manager is paid per hours work plus travel costs and other expenses.
- With regards to “targeted recruitment of GPs/site” there was no clear explanation as to what this entailed outlined in the Kearney et al., paper (68), therefore we interpreted this as trial teams targeting sites that would be most likely to participate/sites that had the facilities and experience to participate/sites that have conducted similar trials previously, we costed the time taken to conduct background research into which sites these would be and associated investigation into recruitment.

- Flexibility in appointments – we made the assumption that only 10% of patients need out of hours appointments which would take 1.5 hours to conduct.

Further detail on the assumptions for each retention strategy in each trial is outlined below

Mailchimp electronic newsletter costs

- Based on the standard package for up to 500 recipients the cost is $14.99 per month which works out as $179.88 per year. Based on the conversion rates of 1 GBP = 1.16279 EUR,
- 1 EUR = 0.860001 GBP, 1 USD = 0.843802 EUR and 1 USD = 0.725647 GBP,
- Taken from Xe Currency Converter - LIVE Foreign Exchange Rates on the 7th of September 2021.
- This works out as €151.78 per year and £130.53 per year.

Tables display the trial information and strategy assumptions applied to each of the trials used in the study. The "real-life" trials were sourced out of convenience from Trials | Home page (biomedcentral.com) published between 2016 and 2020.

Hypothetical trial – Ireland

Trial Characteristics	
Number of participants	500
Number of sites	10 sites
Duration of participant follow-up	1 year
Number of trial visits	3
Data collection	1 questionnaire is sent out and 3 trial visits
Location of the trial	Ireland

Assumptions for costing application

Staff costs: Staff hourly salary was obtained from personal correspondence with Research Nurses and other professionals involved in the conduct and running of clinical trials in Ireland**.**

Research Nurse: €54 hourly

Research Assistant: €25 hourly

Data Manager: €25 hourly

Stamp cost: €1.10 E00127369-GuidePostalRatesA5-Final-AW_V4-2020_WEB.pdf (anpost.com)

Strategy Assumptions

Strategy	Assumptions made
Newsletter	→ 2 newsletters sent out over the 1-year trial period → 5 hours to develop the newsletter. → 2 hours work to electronically send out 500 newsletters (this includes time to deal with returned undelivered emails and re-sending) → 8 hours to manually post out 500 newsletters → Stamp costs in Ireland = €1.10 → Mailchimp subscription is €151.78 for 1 year → Developing the newsletter carried out by a Research Nurse. → Emailing/posting out the newsletter carried out by a Research Assistant.
A timeline of participant visits for sites	→ **Reminder schedule for site** → Data Manager develops reminder schedule software → 3 hours of work

	→ Electronically emails the reminder schedule software to the sites → 10 minutes work (0.167 hours) → Carried out once → This reminder schedule software can be modified to suit the trial follow-up schedule and used by trial sites to notify staff of upcoming participant trial visits. → **Built in reminder schedule for participants (this will include the cost of the site reminder schedule)** → Research Nurse contacts the participants directly – telephone call → 5 minutes/0.08hours per call per participant (500 participants) → Carried out three times (once for each visit) **Failed contact - telephone reminder attempts for *trial visits*** → Carried out by a Research Nurse → An average of 2 failed attempts are made to try contact each participant → Each attempt takes 1 minute so a total time of 2 minutes/0.033hrs per participant (500 participants) → Carried out three times (once for each trial visit)
Inclusion of pre-paid envelopes (questionnaires)	**Inclusion of pre-paid envelopes** → This activity is carried out once → Carried out by a Research Assistant → 8 hours work to manually stuff 500 envelopes. → Stamp cost €1.10 - stamp costs are doubled; one stamp for sending out the questionnaire and one stamp for the participant to return the questionnaire **Reminder schedule** → This activity is carried out once. → Carried out by a Research Assistant. → Initial response rate estimated at 70%. → Send out reminder schedule of 150 envelopes (30% non-response) → 2.4 hours to manually stuff 150 envelopes (30% of 500) → Stamp costs €1.10 - stamp costs are doubled; one stamp for sending out the

	questionnaire and one stamp for the participant to return the questionnaire
Telephone reminders	**Telephone reminders for *trial visits*** → Research Nurse contacts the participants directly → 5 minutes/0.08hours per call per participant (500 participants) → Carried out three times (once for each visit) **Failed telephone reminder attempts for *trial visits*** → Carried out by a Research Nurse → An average of 2 failed attempts are made to try contact each participant → Each attempt takes 1 minute so a total time of 2 minutes/0.033hrs per participant (500 participants) → Carried out three times (once for each trial visit) **Telephone reminder schedule for *questionnaire response*** → Carried out once → Carried out by a Research Assistant → Calling up 150 participants (30% non-responders) → 5 minutes/0.08hours per call **Failed attempts at a telephone reminder for *questionnaire response*** → Carried out once → Carried out by a Research Assistant → 150 participants (30% non-responders) contacted → An average of 2 failed call attempts per participant → Each failed call attempt lasts 1 minute – so total time is 2 minutes/0.033 hours
Data collection scheduled with routine care	→ Carried out by a Research Nurse. → Data is collected during a routine clinic visit. → Portion of routine visit spent on trial data collection: 15 minutes/0.25hrs → Activity carried out three times (once for each trial visit)

Site initiation training on missing data	→ This activity is carried out once for each site (10 sites) Assume: Training preparation, site training and report per site @€400 per day plus travel and overnight costs. → Cost per site is €400 which includes staff costs → Travel costs: €100 → Other expenses: overnight costs: €200
Investigator meetings face-to-face	→ This activity is carried out twice for each site (10 sites) Assume: Visit preparation, face-to-face meeting and report per site @€400 per day plus travel and overnight costs. → Cost per site is €400 which includes staff costs → Travel costs: €100 → Other expenses: overnight costs: €200
Routine site visits by CTU staff	→ This activity is carried out twice for each site (10 sites) Assume: Visit preparation, site visit and report per site @€400 per day plus travel and overnight costs. → Cost per site is €400 which includes staff costs → Travel costs: €100 → Other expenses: overnight costs: €200
Targeted recruitment of GPs/sites	→ Site selection and associated investigation into recruitment (1 hour work per site) → Assumed that 30 sites were targeted to recruit 10 sites (Recruitment to targeting ratio is 1:3) → Carried out by a Research Nurse
Flexibility in appointments	→ Carried out by a Research Nurse. → Length of appointment 1.5 hours → Carried out for a maximum of 10% of the study population which is 50 participants

Hypothetical trial – United Kingdom

Trial Characteristics	
Number of participants	500
Number of sites	10 sites
Duration of participant follow-up	1 year
Number of trial visits	3
Data collection	1 questionnaire is sent out and 3 trial visits
Location of the trial	United Kingdom

Assumptions for costing application

Staff costs: Staff hourly salary was obtained from personal correspondence with Research Nurses and other professionals involved in the conduct and running of clinical trials in the United Kingdom.

Trial Manager: £30.40 hourly

Research Nurse: £36 hourly

Research Assistant: £28.85 hourly

Data Manager: £30.40 hourly

Stamp costs: £0.66 Stamps | Royal Mail

Strategy Assumptions

Strategy	**Assumptions made**
Newsletter	→ 2 newsletters sent out over the 1-year trial period → 5 hours to develop the newsletter → 2 hours work to electronically send out 500 newsletters (this includes time to deal with returned undelivered emails and re-sending)

	→ 8 hours to manually post out 500 newsletters → Second class mail – 66p → Mailchimp subscription cost £130.53 for 1 year. → Developing the newsletter is carried out by a Trial Manager. → Emailing/Posting out the newsletter carried out by a Research Assistant.
A timeline of participant visits for sites	→ **Reminder schedule for site** → Data Manager develops reminder schedule software → 3 hours of work → Electronically emails the reminder schedule software to the sites → 10 minutes work (0.167 hours) → Carried out once → This reminder schedule software can be modified to suit the trial follow-up schedule and used by trial sites to notify staff of upcoming participant trial visits → **Built in reminder schedule for participants (this will include the cost of the site reminder schedule)** → Trial Manager contacts the participants directly → 5 minutes/0.08hours per call per participant (500 participants) → Carried out three times (once for each trial visit) **Failed contact - telephone reminder attempts for *trial visits*** → Carried out by a Trial Manager → An average of 2 failed attempts are made to try contact each participant → Each attempt takes 1 minute so a total time of 2 minutes/0.033 hours per participant (500 participants) → Carried out three times (once for each trial visit)
Inclusion of pre-paid envelopes (questionnaires)	**Inclusion of pre-paid envelopes** → This activity is carried out once

	→ Carried out by a Research Assistant → 8 hours work to manually stuff 500 envelopes. → Stamp costs = 0.66p - stamp costs are doubled; one stamp for sending out the questionnaire and one stamp for the participant to return the questionnaire **Reminder Schedule** → Reminder schedule sent out once → Carried out by a Research Assistant → Initial response rate estimated at 70%. → Send out reminder schedule to 150 participants (30% non-response) → 2.4 hours work to manually stuff 150 envelopes → Stamp costs = 0.66p - stamp costs are doubled; one stamp for sending out the questionnaire and one stamp for the participant to return the questionnaire
Telephone reminders	**Telephone reminders for *trial visits*** → Trial Manager contacts the participants directly → 5 minutes/0.08hours per call per participant (500 participants) → Carried out three times (once for each trial visit) **Failed telephone reminder attempts for *trial visits*** → Carried out by a Trial Manager → An average of 2 failed attempts are made to try contact each participant → Each attempt takes 1 minute so a total time of 2 minutes/0.033 hours per participant (500 participants)

	→ Carried out three times (once for each trial visit) **Telephone reminder schedule for *questionnaire response*** → Carried out once. → Carried out by a Research Assistant. → Initial response rate estimated 70% → Telephone reminder schedule for 150 participants (30% non-response), → 5 minutes/0.08hrs per call **Failed telephone reminder attempts for *questionnaire response*** → Carried out once → Carried out by a Research Assistant → 150 participants (30% non-responders) contacted → An average of 2 failed attempts are made to try contact each participant → Each attempt takes 1 minute so a total time of 2 minutes/0.033hrs per participant.
Data collection scheduled with routine care	→ Carried out by a Research Nurse. → Data is collected during a routine clinic visit. → Portion of routine visit spent on trial data collection: 15 minutes/0.25hrs → Activity is carried out three times (once for each trial visit)
Site initiation training on missing data	→ Trial Manager carries out preparation, carries out training and writes up a report → 11 hours of work in total → Hourly salary for a Trial Manager → Travel costs: £100 → Other expenses: overnight costs: £200 → Activity carried out once per site (10 sites)

Investigator meetings face-to-face	→ Trial Manager carries out preparation, carries out face-to-face meeting and writes up a report → 11 hours of work in total → Hourly salary for a Trial Manager → Travel costs: £100 → Other expenses: overnight costs: £200 → Activity carried out twice per site (10 sites)
Routine site visits by CTU staff	→ Trial Manager carries out preparation, carries out visit and writes up a report → 11 hours of work in total → Hourly salary for a Trial Manager → Travel costs: £100 → Other expenses: overnight costs: £200 → Activity carried out twice per site (10 sites)
Targeted recruitment of GPs/sites	→ Site selection and associated investigation into recruitment (1 hour work per site). → Assumed that 30 sites are targeted to recruit 10 sites (Recruitment to targeting ratio is 1:3) → Carried out by a Trial Manager
Flexibility in appointments	→ Carried out by a Research Nurse. → Length of appointment 1.5 hours → Carried out for a maximum of 10% of the study population which is 50 participants.

MAMI trial (115) The influence of timing of Maternal administration of Antibiotics during cesarean section on the intestinal Microbial colonization in Infants (MAMI-trial): study protocol for a randomised controlled trial.

Trial information

Trial Characteristics	
Number of participants	60
Number of sites	1 site (single centre)
Duration of participant follow-up	2 years
Number of trial visits	1
Data collection	Data collection takes place at an outpatient clinic prior to the birth of the child, takes places at the birth, and at home data collection takes place on day 1 (after birth), day 7, day 28 and when the child is 2 years old 1 postal questionnaire is sent out
Location of the trial	Amsterdam

Assumptions for costing application

Staff costs – estimates of average staff costs for a Research Nurse, Research Assistant and a Data Manager in the Netherlands -

https://www.salaryexpert.com/salary/job/research-assistant/netherlands

https://www.salaryexpert.com/salary/job/clinical-research-nurse/netherlands

Manager Clinical Data Salary Netherlands - SalaryExpert

Research Nurse: €30 hourly

Research Assistant €17 hourly

Data Manager: €32 hourly

Stamp costs - €0.96c - Domestic Mail | PostNL

Strategy Assumptions

Strategy	Assumptions made
Newsletter	→ 4 newsletters sent out over the 2-year trial period → 5 hours to develop the newsletter. → 0.24 hours to electronically send out 60 newsletters (2 hours work to electronically send out 500 newsletters, therefore 60 newsletters take 0.24 hours) → 0.96 hours of work to manually stuff and post 60 newsletters (8 hours to manually post out 500 newsletters, therefore 60 newsletters take 0.96 hours) → Stamp costs in the Netherlands = €0.96 → Mailchimp subscription for two years is €303.56 (€151.78 for 1 year) → Developing the newsletter carried out by a Research Nurse. → Emailing/posting out the newsletter carried out by a Research Assistant
A timeline of participant visits for sites	→ **Reminder schedule for site** → Data Manager develops reminder schedule software → 3 hours of work → Electronically emails the reminder schedule software to the sites → 10 minutes work (0.167 hours) → Carried out once → This reminder schedule software can be modified to suit the trial follow-up schedule and used by trial sites to notify staff of upcoming participant trial visits → **Built in reminder schedule for participants (this will include the cost of the site reminder schedule)** → Carried out once (1 trial visit) → Research Nurse contacts the participants directly → 5 minutes/0.08hours per call per participant (60 participants) **Failed telephone reminder attempts for *trial visits***

	→ Carried out once (1 trial visit) → Carried out by a Research Nurse → An average of 2 failed attempts are made to try contact each participant → Each attempt takes 1 minute so a total time of 2 minutes/0.033 hours per participant (60 participants)
Inclusion of pre-paid envelopes (questionnaires)	**Inclusion of pre-paid envelopes** → This activity is carried out once → Carried out by a Research Assistant → 0.96 hours work to manually stuff 60 envelopes. → Stamp cost €0.96 - stamp costs are doubled; one stamp for sending out the questionnaire and one stamp for the participant to return the questionnaire **Reminder schedule** → This activity is carried out once. → Carried out by a Research Assistant. → Initial response rate estimated at 70%. → Send out reminder schedule to 18 participants (30% non-response) → 0.288 hours to manually stuff 18 envelopes (30% non-response). → Stamp costs €0.96 - stamp costs are doubled; one stamp for sending out the questionnaire and one stamp for the participant to return the questionnaire
Telephone reminders	**Telephone reminders for *trial visits*** → Carried out once (1 trial visit) → Research Nurse contacts the participants directly → 5 minutes/0.08hours per call per participant (60 participants) **Failed telephone reminder attempts for *trial visits*** → Carried out once (1 trial visit) → Carried out by a Research Nurse → An average of 2 failed attempts are made to try contact each participant → Each attempt takes 1 minute so a total time of 2 minutes/0.033 hours per participant (60 participants)

	Telephone reminder schedule for *questionnaire response* → Carried out once → Carried out by a Research Assistant → Calling up 18 (30% non-responders) participants → 5 minutes/0.08 hours per call **Failed attempts at a telephone reminder for *questionnaire response*** → Carried out once → Carried out by a Research Assistant → 18 (30% non-responders) participants for the telephone reminder for questionnaire response → An average of 2 failed call attempts per participant → Each failed call attempt lasts 1 minute – so total time is 2 minutes/0.033 hours **Telephone reminder for at home data collection** → Carried out 4 times → Carried out by a Research Nurse → Calling up 18 participants (30% non-response) → 1 telephone reminder for each at home data collection event (day 1, 7, 28, 2 years old, 4 in total) → Each call last 5 minutes/0.08 hours per participant **Failed attempts at telephone reminder calls** → Activity is carried out 4 times → Carried out by a Research Nurse → 18 participants (30% non-response) → An average of 2 failed call attempts per participant → Each failed call attempt lasts 1 minute – so total time is 2 minutes/0.033 hours per participant
Data collection scheduled with routine care	→ Carried out by a Research Nurse. → Data is collected during a routine clinic visit.

	→ Portion of routine visit spent on trial data collection: 15 minutes/0.25hrs. → Activity carried out twice (outpatient clinic data collection and data collection at birth)
Site initiation training on missing data	→ This activity is carried out once for each site (1 site) Assume: Training preparation, site training and report per site @€400 per day plus travel and overnight costs. → Cost per site is €400 which includes staff costs → No travel costs because it is a single centre trial. → Other expenses: No overnight costs because it is a single centre trial
Investigator meetings face-to-face	→ Activity is carried out four times over a 2-year period for each site (1 site) Assume: Visit preparation, face-to-face meeting, and report per site @€400 per day plus travel and overnight costs. → Cost per site is €400 which includes staff costs → No travel costs because it is a single centre trial. → Other expenses: No overnight costs because it is a single centre trial.
Routine site visits by CTU staff	→ Activity is carried out four times over a 2-year period for each site (1 site) Assume: Visit preparation, site visit, and report per site @€400 per day plus travel and overnight costs. → Cost per site is €400 which includes staff costs → No travel costs because it is a single centre trial. → Other expenses: No overnight costs because it is a single centre trial.
Targeted recruitment of GPs/sites	→ Site selection and associated investigation into recruitment (1 hour work per site)

	→ Single centre study so assumed only 1 site was targeted for recruitment → Carried out by a Research Nurse
Flexibility in appointments	→ Carried out by a Research Nurse. → Length of appointment 1.5 hours → Carried out for a maximum of 10% of the study population which is 6 participants

MOON trial (116) Medial malleolus: Operative Or Non-operative (MOON) trial protocol - a prospective randomised controlled trial of operative versus non-operative management of associated medial malleolus fractures in unstable fractures of the ankle.

Trial information

Trial Characteristics	
Number of participants	154
Number of sites	1 site
Duration of participant follow-up	1 year
Number of trial visits	Outcome assessment at 2 weeks, 6 weeks and 1 year post intervention (3 trial visits)
Data collection	Postal questionnaires sent out a 3- and 6-month time marks (2 questionnaires)
Location of the trial	UK based trial

Staff costs: Staff hourly salary was obtained from personal correspondence with Research Nurses and other professionals involved in the conduct and running of clinical trials in the United Kingdom.

Trial Manager: £30.40 hourly

Research Nurse: £36 hourly

Research Assistant: £28.85 hourly

Data Manager: £30.40 hourly

Stamp costs: £0.66 Stamps | Royal Mail

Strategy Assumptions

Strategy	Assumptions made
Newsletter	→ 2 newsletters are sent over a 1-year trial. → 5 hours to develop the newsletter. → 0.616 hours to electronically send out 154 newsletters (2 hours work to electronically send out 500 newsletters, therefore 154 newsletters are 0.616 hours work) → 2.464 hours to manually post out 154 newsletters (8 hours to manually post out 500 newsletters, therefore 154 newsletters take 2.464 hours) → Second class mail – 66p → Mailchimp subscription cost £130.53 for 1 year. → Developing the newsletter is carried out by a Trial Manager. → Emailing/Posting out the newsletter carried out by a Research Assistant.
A timeline of participant visits for sites	→ **Reminder schedule for site** → Data Manager develops reminder schedule software → 3 hours of work → Electronically emails the reminder schedule software to the sites → 10 minutes work (0.167 hours) → Carried out once → This reminder schedule software can be modified to suit the trial follow-up schedule and used by trial sites to

	notify staff of upcoming participant trial visits → **Built in reminder schedule for participants (this will include the cost of the site reminder schedule)** → Trial Manager contacts the participants directly → 5 minutes/0.08hours per call per participant (154 participants) → Carried out three times (once for each trial visit) **Failed contact - telephone reminder attempts for *trial visits*** → Carried out three times (once for each trial visit) → Carried out by a Trial Manager → An average of 2 failed attempts are made to try contact each participant (154 participants) → Each attempt takes 1 minute so a total time of 2 minutes/0.033hours per participant
Inclusion of pre-paid envelopes (questionnaires)	**Inclusion of pre-paid envelopes** → This activity is carried out twice (2 questionnaires are posted out in this study) → Carried out by a Research Assistant. → 2.464 hours to manually stuff 154 envelopes → Stamp costs = 0.66p - stamp costs are doubled; one stamp for sending out the questionnaire and one stamp for the participant to return the questionnaire **Reminder Schedule** → Reminder schedule sent out twice (once for each questionnaire) → Carried out by a Research Assistant → Initial response rate estimated at 70%.

	→ Send out reminder schedule of 47 envelopes (30% non-response) → 0.752 hours of work to manually stuff 47 envelopes → Stamp costs = 0.66p - stamp costs are doubled; one stamp for sending out the questionnaire and one stamp for the participant to return the questionnaire
Telephone reminders	**Telephone reminders for *trial visits*** → Trial Manager contacts the participants directly → 5 minutes/0.08hours per call per participant (154 participants) → Carried out three times (once for each trial visit) **Failed telephone reminder attempts for *trial visits*** → Carried out three times (once for each trial visit) → Carried out by a Trial Manager → An average of 2 failed attempts are made to try contact each participant (154 participants) → Each attempt takes 1 minute so a total time of 2 minutes/0.033hours per participant **Telephone reminder schedule for *questionnaire response*** → Carried out twice (once for each questionnaire) → Carried out by a Research Assistant. → Initial response rate estimated 70% → Telephone reminder schedule for 47 participants (30% non-response), → 5 minutes/0.08hours per call per participant **Failed telephone reminder attempts for *questionnaire response***

	→ Carried out twice (once for each questionnaire) → Carried out by a Research Assistant → An average of 2 failed attempts are made to try contact each participant (47 participants) → Each attempt takes 1 minute so a total time of 2 minutes/0.033hours per participant.
Data collection scheduled with routine care	**Data collected scheduled with routine care** → Carried out by a Research Nurse. → Data is collected during a routine clinic visit. → Portion of routine visit spent on trial data collection: 15 minutes/0.25hrs → Activity is carried out 3 times (for each trial visit)
Site initiation training on missing data	→ Trial Manager carries out preparation, carries out training and writes up a report → 11 hours of work in total → Hourly salary for a Trial Manager → No travel costs since it is a single centre trial. → Other expenses: No overnight costs since it is a single centre trial → Activity carried out once per site (1 site)
Investigator meetings face-to-face	→ Trial Manager carries out preparation, carries out face-to-face meeting and writes up a report → 11 hours of work in total → Hourly salary for a Trial Manager → No travel costs since it is a single centre trial. → Other expenses: No overnight costs because it is a single centre trial

	→ Activity carried out twice per site (1 site)
Routine site visits by CTU staff	→ Trial Manager carries out preparation, carries out visit and writes up a report → 11 hours of work in total → Hourly salary for a Trial Manager → No travel costs since it is a single centre study. → Other expenses: No overnight costs because it is a single centre trial → Activity carried out twice per site (1 site)
Targeted recruitment of GPs/sites	→ Site selection and associated investigation into recruitment (1 hour work per site). → Single centre study so assumed only 1 site was targeted for recruitment → Carried out by a Trial Manager
Flexibility in appointments	→ Carried out by a Research Nurse. → Length of appointment 1.5 hours → Carried out for a maximum of 10% of the study population which is 16 participants.

CINNAMON trial (117) Assessment of the effeCt of lIfestyle iNtervention plus water-soluble ciNnAMon extract On loweriNg blood glucose in pre-diabetics, a randomized, double-blind, multicenter, placebo controlled trial: study protocol for a randomized controlled trial.

Trial information

Trial Characteristics	
Number of participants	428
Number of sites	5 sites
Duration of participant follow-up	2-years
Number of trial visits	9 trial visits
Data collection	Data collection takes place at each trial visit (9 visits)
Location of the trial	USA based trial

Staff costs - estimates of average staff costs for both a Research Nurse and a Research Assistant in the Netherlands -

https://www.salaryexpert.com/salary/job/clinical-research-nurse/united-states

https://www.salaryexpert.com/salary/job/research-assistant/united-states

Manager Clinical Data Salary the United States - SalaryExpert

Research Nurse: $40 hourly

Research Assistant: $20 hourly

Data Manager: $42 hourly

Stamp costs: 0.55$ - Stamps.com - Current Postage Rates, US Postage Stamp Prices

Strategy Assumptions

Strategy	**Assumptions made**

Newsletter	→ 4 newsletters are sent over a 2-year trial period. → 5 hours to develop the newsletter. → 1.712 hours work to electronically send out 428 newsletters (2 hours work to electronically send out 500 newsletters, therefore 428 newsletters take 1.712 hours work) → 6.848 hours to manually post out 428 newsletters (8 hours to manually post out 500 newsletters, therefore 428 newsletters take 6.848 hours) → Postage costs = 0.55$ → Mailchimp subscription cost $179.88 for 1 year, so two-year subscription is $359.76 → Developing the newsletter is carried out by a Research Nurse. → Emailing/Posting out the newsletter carried out by a Research Assistant.
A timeline of participant visits for sites	→ **Reminder schedule for site** → Data Manager develops reminder schedule software → 3 hours of work → Electronically emails the reminder schedule software to the sites → 10 minutes work (0.167 hours) → Carried out once → This reminder schedule software can be modified to suit the trial follow-up schedule and used by trial sites to notify staff of upcoming participant trial visits → **Built in reminder schedule for participants (this will include the cost of the site reminder schedule)** → Carried out 9 times (once for each trial visit) → Research Nurse contacts the participants directly

	→ 5 minutes/0.08hours per call per participant. → 428 participants **Failed contact - telephone reminder attempts for *trial visits*** → Carried out 9 times (once for each trial visit) → Carried out by a Research Nurse → An average of 2 failed attempts are made to try contact each participant → Each attempt takes 1 minute so a total time of 2 minutes/0.033 hours per participant (428 participants)
Inclusion of pre-paid envelopes (questionnaires)	**Inclusion of pre-paid envelopes** → This activity is carried out once. → Carried out by a Research Assistant. → 6.848 hours to manually stuff 428 envelopes → Stamp costs = 0.55$ - stamp costs are doubled; one stamp for sending out the questionnaire and one stamp for the participant to return the questionnaire **Reminder Schedule** → Carried out by a Research Assistant → Reminder schedule sent out once → Initial response rate estimated at 70%. → Send out reminder schedule to 129 participants (30% non-response) → 2.064 hours of work → Stamp costs = 0.55$ - stamp costs are doubled; one stamp for sending out the questionnaire and one stamp for the participant to return the questionnaire
Telephone reminders	**Telephone reminders for *trial visits***

	→ Carried out 9 times (once for each trial visit) → Research Nurse contacts the participants directly → 5 minutes/0.08hours per call per participant. → 428 participants **Failed telephone reminder attempts for *trial visits*** → Carried out 9 times (once for each trial visit) → Carried out by a Research Nurse → An average of 2 failed attempts are made to try contact each participant → Each attempt takes 1 minute so a total time of 2 minutes/0.033 hours per participant (428 participants) **Telephone reminder schedule for *questionnaire response*** → Carried out once → Carried out by a Research Assistant. → Initial response rate estimated 70% → Telephone reminder schedule for 129 participants (30% non-response), → 5 minutes/0.08 hours per call per participant **Failed telephone reminder attempts for *questionnaire response*** → Carried out once → Carried out by a Research Assistant → An average of 2 failed attempts are made to try contact each participant (129 participants) → Each attempt takes 1 minute so a total time of 2 minutes/0.033 hours per participant
Data collection scheduled with routine care	**Data collection scheduled with routine care**

	→ Carried out by a Research Nurse. → Data is collected during a routine clinic visit. → Portion of routine visit spent on trial data collection: 15 minutes/0.25hrs → Activity is carried out 9 times (for each trial visit)
Site initiation training on missing data	→ Activity is carried out once per site (5 sites) Assume: Training preparation, site training and report per site @€400 per day plus travel and overnight costs. → Cost per site is $400 which includes staff costs → Travel $100 average estimate. → Other expenses: Overnight costs $200 average estimate.
Investigator meetings face-to-face	→ Activity is carried out four times over a 2-year period for each site (5 sites) Assume: Visit preparation, face-to-face meeting, and report per site @€400 per day + travel + overnight. → Cost per site is $400 which includes staff costs → Travel $100 average estimate. → Other expenses: Overnight costs $200 average estimate.
Routine site visits by CTU staff	→ Activity is carried out four times over a 2-year period for each site (5 sites) Assume: Visit preparation, site visit and report per site @€400 per day + travel + overnight → Cost per site is $400 which includes staff costs → Travel $100 average estimate. → Other expenses: Overnight costs $200 average estimate.

Targeted recruitment of GPs/sites	→ Site selection and associated investigation into recruitment (1 hour work per site). → 5 sites were recruited so assumed 15 sites were initially targeted for recruitment (Recruitment to targeting ratio is 1:3) → Carried out by a Research Nurse
Flexibility in appointments	→ Carried out by a Research Nurse. → Length of appointment 1.5 hours → Carried out for a maximum of 10% of the study population which is 43 participants.

References

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Appendix 2. Thesis Chapter Four. Additional File 2: Costing retention strategies; Costing approach application

Hypothetical Trial Ireland

Newsletters costing (both paper and electronic newsletters)

		Staff hours	Research Nurse	Staff costs			
Newsletter	Developing newsletter	5	€ 54.00	€ 270.00			
			Research assistant		Postage costs	Number of participants/years	Total postage costs
	Emailing newsletter	2	€ 25.00	€ 50.00	€ 151.78	1	€ 151.78
	Manually stuffing 500 envelopes and posting	8	€ 25.00	€ 200.00	€ 1.10	500	€ 550.00

Costs of developing and electronically posting					
	Staff costs	Mailchimp (electronic emailing)		Frequency of activity	Total cost (staff costs x 2) plus flat charge of the 12 month mailchimp
	€ 320.00	€151.78		2	€ 791.78
Costs of developing and manually posting					
	Staff costs	Postage costs	staff and postage costs	Frequency of activity	Total costs
	€ 470.00	€ 550.00	€ 1,020.00	2	€ 2,040.00

A timeline of participant visits for sites – site reminder and participant reminder

			Hourly rate (Ireland)	
A timeline of participant visits for sites -Site Reminder		**Staff hours**	**Data Manager**	**Staff costs per 1 site**
	Developing reminder schedule software	3	€ 25.00	€ 75.00
	Emailing the reminder schedule software to the sites for the sites to use (10minutes/0.167 hours)	0.167	€ 25.00	€ 4.18
Total costs for site reminder schedule				**€ 79.18**

A timeline of participant visits for sites - Participant Reminder		**Staff hours**	**Research Nurse**	**Staff cost per 1 participant**	**Number of participants**	**Staff cost per 500 participants**	**Frequency of activity (done for each trial visit which is 3)**	**Total costs = total staff costs x frequenct of acitivty**
	Research Nurse directly contacts patient - 5 mins/0.08hrs per participant	0.08	€ 54.00	€ 4.32	500	€ 2,160.00	3	€ 6,480.00
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2	0.033	€ 54.00	€ 1.78	500	€ 891.00	3	€ 2,673.00
Cost for particpant remdiner schedule								€ 9,153.00
Cost of site reminder schedule								€ 79.18
Total cost of Participant reminder schedule								**€ 9,232.18**

Inclusion of pre-paid envelopes (initial mail out and reminder schedule)

		Staff hours	Hourly rate (Ireland) Research assistant	Total staff costs	Stamp costs (sending out)	Stamp cost (return pre-paid)
Inclusion of pre-paid envelopes	Manually stuffing the 500 envelopes	8	€ 25.00	€ 200.00	€ 1.10	€ 1.10
Reminder schedule	Manually stuffing the 150 envelopes	2.4	€ 25.00	€ 60.00	€ 1.10	€ 1.10
Total costs for pre-paid and reminder						

Total stamp costs	Number of participants	Total postage costs	Frequency of activity	Total costs = (staff costs + postage costs) x frequency of activity
€ 2.20	500	€ 1,100.00	1	€ 1,300.00
€ 2.20	150	€ 330.00	1	€ 390.00
				€ **1,690.00**

Telephone reminders (for trial visits and for questionnaire reminder schedule)

		Staff Hours	Hourly rate (Ireland) Research Nurse	Staff cost per 1 participant	Number of particpants	Staff costs per 500 participants
Telephone reminders (for trial visits)	Calling participants (5mins/0.08hrs per participant	0.08	€ 54.00	€ 4.32	500	€ 2,160.00
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	€ 54.00	€ 1.78	500	€ 891.00
			Research assistant		**Number of participants**	**Staff costs per 150 participants**
Telephone reminder schedule for questionnaire response	Calling 150 participants	0.08	€ 25.00	€ 2.00	150	€ 300.00
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	€ 25.00	€ 0.83	150	€ 123.75

Frequency of activity	Total costs = total staff costs x frequency of activity
3	€ 6,480.00
3	€ 2,673.00
	€ 9,153.00

Frequency of activity	Total cost = total staff costs x frequency of activity
1	**€ 300.00**
1	**€ 123.75**
	€ 423.75

Data collection scheduled with routine care, site initiation training on missing data, investigator meetings face-to-face, routine site visits by CTU staff

			Hourly rate (Ireland)						
Data collection scheduled with routine care		Staff hours	Research Nurse	Staff costs per 1 participant		Number of particpants	Staff costs per 500 participants	Frequency of activity	Total costs = staff costs x frequncy of acitvity
	Collecting participant data during routine clinic visit (15 minutes/0.25hrs for trial related data collection)	0.25	€ 54.00	€ 13.50		500	€ 6,750.00	3	€ 20,250.00
Site initiation training on missing data									
		Cost per 1 site	Travel costs	Other expenses e.g. overnight expenses	Number of sites	Frequency of activity	Total costs		
	Prep, site training and report per site @€400 per day + travel + overnight.	€ 400.00	€ 100.00	€ 200.00	10	1	€ 7,000.00		
Investigator meetings face to face									
		Cost per 1 site	Travel costs	Other expenses	Number of	Frequency of	Total costs		
	Prep, meeting and report per site @€400 per day + travel + overnight.	€ 400.00	€ 100.00	€ 200.00	10	2	€ 14,000.00		
Routine site visits by CTU staff		Costs per 1 sites	Travel costs	Other expenses	Number of sites	Frequency of activity	Total costs		
	Prep, site visit and report per site @€400 per day + travel + overnight.	€ 400.00	€ 100.00	€ 200.00	10	2	€ 14,000.00		

Targeted recruitment of sites/GPs, and flexibility in appointments,

			Hourly rate (Ireland)			
Targeted reruitment of sites/GPs		**Staff hours**	**Research Nurse**	**Total staff costs per 1 site**	**Number of sites**	**Total costs = staff cost x number of**
	Site selection and assosiated investigation into recruitment (1hour of work per site))	1	€ 54.00	€ 54.00	30	€ 1,620.00
Flexibility in appointments - out of hours appointments -		**Staff hours**	**Research Nurse**	**Number of participants needing out of hours appointments**		**Total costs = staff hours x staff wage x number of appointment**
	Length of appointment (per appointment)	1.5	€ 54.00	50		€ 4,050.00

Total cost of interventions

	Total costs of each intervention	
Newsletters		
Manually sending out newsletters	€	2,040.00
Emailing out newsletters	€	791.78
A timeline of participant visits for sites		
Reminder schedule for sites	€	79.18
Reminder schedule for participants	€	9,232.18
Inclusion of pre-paid envelopes	€	1,690.00
Telephone reminders for trial visits	€	9,153.00
Telephone reminder schedule for questionnaire response	€	423.75
Data collection scheduled with routine care	€	20,250.00
Site initiation training on missing data	€	7,000.00
Investigator meetings face to face	€	14,000.00
Routine site visits by CTU staff	€	14,000.00
Targeted reruitment of sites/GPs	€	1,620.00
Flexibility in appointments - out of hours appointments -	€	4,050.00

Hypothetical trial United Kingdom

Newsletter costing (both paper and electronic newsletters)

			Hourly Rate (United Kingdom)					
		Staff Hours	Trial manager	Staff costs				
Newsletter	Developing newsletter	5	£ 30.40	£ 152.00				
			Research assistant			Postage Costs	Number of participants/years	Total postage costs
	Emailing newsletter	2	£ 28.85	£ 57.70		£ 130.53	1	£ 130.53
	Manually stuffing 500 envelopes and posting	8	£ 28.85	£ 230.80		£ 0.66	500	£ 330.00

Costs of developing and electronically posting	Staff cost	Mailchimp (electronic emailing)		Frequency of activity	Total cost (staff costs x 2) plus flat charge of the 12 month mailchimp
	£ 209.70	£ 130.53		2	£ 549.93
Costs of developing and maunally posting					
	Staff costs	Postage costs	staff cost and postage cost	Frequency of activity	Total costs
	£ 382.80	£ 330.00	£ 712.80	2	£ 1,425.60

Timeline of participant visits – site reminder and participant reminder

			Hourly rate (UK)	
A timeline of participant visits for sites -Site Reminder		**Staff hours**	**Data Manager**	**Staff costs per 1 site**
	Developing reminder schedule software	3	£ 30.40	£ **91.20**
	Emailing the reminder schedule software to the sites for the sites to use (10minutes/0.167 hours)	0.167	£ 30.40	£ **5.08**
Total costs for site reminder schedule				£ **96.28**

A timeline of participant visits for sites - Participant reminder		Staff hours	Trial Manager	Staff costs per 1 participant	Number of participants	Staff cost per 500 particpants	Frequency of activity	Total costs = staff costs x frequency of activity
	Trial Manager directly contacts patient - 5	0.08	£ 30.40	£ 2.43	500	£ 1,216.00	3	£ 3,648.00
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2	0.033	£ 30.40	£ 1.00	500	£ 501.60	3	£ 1,504.80
Cost of participant remdiner							Cost of participant remdiner	£ 5,152.80
Cost of site reminder							Cost of site reminder	£ 96.28
Total cost of Participant reminder schedule							Total cost of Participant reminder schedule	£ **5,249.08**

Inclusion of pre-paid envelopes (initial mail out and reminder schedule)

			Hourly rate (United Kingdom)				
		Staff hours	Research assistant	Staff costs	Stamp costs (sending out)	stamp cost (returning pre-paid)	total stamp cost
Inclusion of pre-paid envelopes	Manually stuffing the 500 envelopes	8	£ 28.85	£ 230.80	£ 0.66	£ 0.66	£ 1.32
Reminder schedule	Manually stuffing the 150 envelopes	2.4	£ 28.85	£ 69.24	£ 0.66	£ 0.66	£ 1.32
Total costs for both pre-paid envelopes and reminder schedule							

number of participants	Total postage costs	frequency of activity	Total costs = staff cost plus postage cost x frequency of activity
500	£ 660.00	1	£ 890.80
150	£ 198.00	1	£ 267.24
			£ 1,158.04

Telephone reminders (for trial visits and for questionnaire reminder schedule)

			Hourly rate (United Kingdom)				
		Staff hours	Trial Manager	Staff costs per 1 participant	Number of participants	Staff cost per 500 participants	Frequency of activity
Telephone reminders (for trial visits)	Calling participants (5mins/0.08hrs per participant	0.08	£ 30.40	£ 2.43	500	£ 1,216.00	3
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	£ 30.40	£ 1.00	500	£ 501.60	3
			Research assistant				
Telephone reminder schedule for questionnaire response	Calling participants (5mins/0.08hrs per participant	0.08	£ 28.85	£ 2.31	150	£ 346.20	1
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	£ 28.85	£ 0.95	150	£ 142.81	1

Total costs = total staff costs x frequency of activity
£ 3,648.00
£ 1,504.80
£ 5,152.80
£ 346.20
£ 142.81
£ 489.01

Data collection scheduled with routine care, site initiation training on missing data, investigator meetings face-to-face, routine site visits by CTU staff.

			Hourly rate (United Kingdom)					
Data collection scheduled with routine care		Staff hours	Research Nurse	Staff cost per 1 participant	Number of participants	Staff costs per 500 participants	Frequency of activty	Total costs = total staff costs x frequency of activity
	Collecting participant data during a routine clinic visit (15 minutes/0.25hrs for trial related	0.25	£ 36.00	£ 9.00	500	£ 4,500.00	3	£ 13,500.00

			Hourly rate (United					
Site initiation training on missing data		Staff hours	Trial Manager	Staff costs per 1 site	Travel costs	Other expenses e.g. Overnight	Number of sites	Frequency of activity	Total costs
	Trial Manager carries out preparation travels to the sites and carries out training and writes up a report. 11 hours of work in total, travel costs: £100, other expenses: overnight costs: £200	11	£ 30.40	£ 334.40	£ 100.00	£ 200.00	10	1	£ 6,344.00

			Hourly rate (United					
Investigator meetings face to face		Staff hours	Trial Manager	Staff costs per 1 site	Travel costs	Other expenses e.g. Overnight	Number of sites	Frequency of activity	Total costs
	Trial Manager carries out preparation travels to the sites and carries out training and writes up a report. 11 hours of work in total, travel costs: £100, other expenses: overnight costs: £200	11	£ 30.40	£ 334.40	£ 100.00	£ 200.00	10	2	£ 12,688.00

			Hourly rate (United					
Routine site visits by CTU staff		Staff hours	Trial Manager	Staff costs per 1 site	Travel costs	Other expenses e.g. Overnight	Number of sites	Frequency of activity	Total costs
	Trial Manager carries out preparation travels to the sites and carries out training and writes up a report. 11 hours of work in total, travel costs: £100, other expenses: overnight costs: £200	11	£ 30.40	£ 334.40	£ 100.00	£ 200.00	10	2	£ 12,688.00

Targeted recruitment of sites/GPs, and flexibility in appointments

Targeted reruitment of sites/GPs		Staff hours	Trial Manager	Total staff costs per 1 site	Number of sites targeted	Total costs = staff cost x number of sites
	Site selection and assosiated investigation into recruitment (1hour of work per site))	1	£ 30.40	£ 30.40	30	£ 912.00
			Hourly rate (United Kingdom)			
Flexibility in appointments - out of hours appointments		Staff hours	Research Nurse	Number of participants needing out of hours appointments		Total costs = staff hours x staff wage x number of appointments
	Length of appointment (per appointment)	1.5	£ 36.00	50		£ 2,700.00

Total cost of interventions

	Total costs of each intervention	
Newsletters		
Manually sending out newsletters	£	1,425.60
Emailing out newsletters	£	549.93
A timeline of participant visits for sites		
Reminder schedule for sites	£	96.28
Reminder schedule for particpants	£	5,249.08
Inclusion of pre-paid envelopes	£	1,158.04
Telephone reminders for trial visits	£	5,152.80
Telephone reminder schedule for questionnaire response	£	489.01
Data collection scheduled with routine care	£	13,500.00
Site initiation training on missing data	£	6,344.00
Investigator meetings face to face	£	12,688.00
Routine site visits by CTU staff	£	12,688.00
Targeted reruitment of sites/GPs	£	912.00
Flexibility in appointments - out of hours appointments	£	2,700.00

MAMI Trial

Newsletter costs (both paper and electronic newsletters)

			Average Hourly Rate (Netherlands)				
		Staff hours	Research Nurse	Staff costs			
Newsletter	Developing newsletter	5	€ 30.00	€ 150.00			
			Research assistant		Postage costs	Number of participants/years	postage costs
	Emailing newsletter	0.24	€ 17.00	€ 4.08	€ 151.78	2	€303.56
	Manually stuffing 60 envelopes and posting	0.96	€ 17.00	€ 16.32	€ 0.96	60	€ 57.60

Costs of developing and electronically posting					
	Staff costs	Mailchimp (electronic emailing)		Frequency of activity	Total cost
	€ 154.08	€303.56		4	€ 919.88
Costs of developing and manually posting					
	Staff costs	Postage costs	staff cost and postage cost	Frequency of activity	Total costs
	€ 166.32	€ 57.60	€ 223.92	4	€ 895.68

Timeline of participant visits – site reminder and participant reminder

			Hourly rate (Netherlands)	
A timeline of participant visits for sites -Site Reminder		**Staff hours**	**Data Manager**	**Staff costs per 1 site**
	Developing reminder schedule software	3	€ 32.00	€ 96.00
	Emailing the reminder schedule software to the sites for the sites to use (10minutes/0.167 hours)	0.167	€ 32.00	€ 5.34
Total costs for site reminder schedule				**€ 101.34**

A timeline of participant visits for sites - Participant reminder		Staff hours	Research Nurse	Staff costs per 1 particpant	Number of participants	Staff cost per 60 participants	Frequency of activity	Total costs = total staff costs x frequenct of acitivty
	Research Nurse directly contacts patient - 5	0.08	€ 30.00	€ 2.40	60	€ 144.00	1	€ 144.00
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	€ 30.00	€ 0.99	60	€ 59.40	1	€ 59.40
Cost of Participant reminder								€ 203.40
Cost of Site reminder								€ 101.34
Total cost of participant reminder								**€ 304.74**

Inclusion of pre-paid envelopes (initial mail out and reminder schedule)

			Average Hourly Rate (Netherlands)				
		Staff hours	Research assistant	Total staff costs	Stamp costs (sending out)	Stamp cost returnin	total stamp costs
Inclusion of pre-paid envelopes	Manually stuffing the 60 envelopes	0.96	€ 17.00	€ 16.32	€ 0.96	€ 0.96	€ 1.92
Reminder schedule	Manually stuffing the 18 envelopes	0.288	€ 17.00	€ 4.90	€ 0.96	€ 0.96	€ 1.92
Total costs for pre-paid and reminder schedule							

Number of participants	total postage costs	frequency of activity	Total cost = staff plus postage x frequency
60	€ 115.20	1	€ 131.52
18	€ 34.56	1	€ 39.46
			€ 170.98

Telephone reminders (for trial visits, for questionnaire reminder schedule and for at home data collection)

			Average Hourly Rate (Netherlands)					
		Staff Hours	Research Nurse	Staff cost per 1 participant	Number of particpants	Staff costs per 60 participants	Frequency of activity	Total costs = total staff costs x frequency of activity
Telephone reminders (for trial visits)	Calling participants (5mins/0.08hrs per	0.08	€ 30.00	€ 2.40	60	€ 144.00	1	€ 144.00
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	€ 30.00	€ 0.99	60	€ 59.40	1	€ 59.40
								€ 203.40
			Research assistant		Number of participants	Staff costs per 18 participants	Frequency of activity	Total cost = total staff costs x frequency of activity
Telephone reminder schedule for questionnaire response	Calling 18 participants as reminder schedule for questionnaire	0.08	€ 17.00	€ 1.36	18	€ 24.48	1	**€ 24.48**
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	€ 17.00	€ 0.56	18	€ 10.10	1	**€ 10.10**
								€ 34.58
		Staff Hours	Research Nurse	Staff cost per 1 participant	Number of particpants	Staff costs per 60 participants	Frequency of activity	Total costs = total staff costs x frequency of activity
Telephone reminders (for at home data collection)	Calling participants (5mins/0.08hrs per	0.08	€ 30.00	€ 2.40	18	€ 43.20	4	€ 172.80
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 attempts per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	€ 30.00	€ 0.99	18	€ 17.82	4	€ 71.28
								€ 244.08

Data collection scheduled with routine care, site initiation training on missing data, investigator meeting face-to-face, routine site visits by CTU staff.

Data collection scheduled with routine care		Staff hours	Research Nurse	Staff costs per 1 participant		Number of particpants	Staff costs per 500 participants	Frequency of activity	Total costs = staff costs x frequncy of acitvity
Data collection scheduled with routine care (2 vistis - outpatient clinic and birth)	Collecting participant data during routine clinic visit - 15minutes/0.25hrs	0.25	€ 30.00	€ 7.50		60	€ 450.00	2	€ 900.00
Site initiation training on missing data									
		Cost per 1 site	Travel costs	Other expenses e.g. overnight expenses	Number of sites	Frequency of activity	Total costs		
	Prep, site visit and report per site @€400 per day. No travel and overnight as it is single centre	€ 400.00	€ -	€ -	1	1	€ 400.00		
Investigator meetings face to face									
		Cost per 1 site	Travel costs	Other expenses e.g. overnight expenses	Number of sites	Frequency of activty (4 visits over 2 years)	Total costs		
	Prep, site visit and report per site @€400 per day. No travel and overnight as it is single centre	€ 400.00	€ -	€ -	1	4	€ 1,600.00		
Routine site visits by CTU staff		Costs per 1 sites	Travel costs	Other expenses e.g. overnight expenses	Number of sites	Frequency of activity (4 visits over 2 years)	Total costs		
	Prep, site visit and report per site @€400 per day. No travel and overnight as it is single centre	€ 400.00	€ -	€ -	1	4	€ 1,600.00		

Targeted recruitment of sites/GPs, and flexibility in appointments

			Average Hourly Rate (Netherlands)			
Targeted reruitment of sites/GPs		**Staff hours**	**Research Nurse**	**Total staff costs per 1 site**	**Number of sites**	**Total costs = staff cost x number of sites**
	Site selection and assosiated investigation into recruitment (1 hour	1	€ 30.00	€ 30.00	1	€ 30.00

			Average Hourly Rate (Netherlands)			
Flexibility in appointments - out of hours appointments		**Staff hours**	**Research Nurse**	**Number of participants needing out of hours appointments**		**Total costs = staff hours x staff wage x number of appointments**
	Length of appointment (per appointment)	1.5	€ 30.00	6		€ 270.00

Total costs of interventions

	Total costs of each intervention	
Newsletters		
Manually sending out newsletters	€	895.68
Emailing out newsletters	€	919.88
A timeline of participant visits for sites		
Reminder schedule for sites	€	101.34
Reminder schedule for participants	€	304.74
Inclusion of pre-paid envelopes	€	170.98
Telephone reminders for trial visits	€	203.40
Telephone reminder schedule for questionnaire response	€	34.58
Telephone reminder for at home data collection	€	244.08
Data collection scheduled with routine care	€	900.00
Site initiation training on missing data	€	400.00
Investigator meetings face to face	€	1,600.00
Routine site visits by CTU staff	€	1,600.00
Targeted reruitment of sites/GPs	€	30.00
Flexibility in appointments - out of hours appointments -	€	270.00

MOON trial

Newsletter costs (both paper and electronic newsletters)

			Hourly Rate (United Kingdom)				
		Staff Hours	Trial manager	Staff costs			
Newsletter	Developing newsletter	5	£ 30.40	£ 152.00			
			Research assistant		Postage Costs	Number of participants/years	Total postage costs
	Emailing newsletter	0.616	£ 28.85	£ 17.77	£ 130.53	1	£ 130.53
	Manually stuffing 154 envelopes and posting	2.464	£ 28.85	£ 71.09	£ 0.66	154	£ 101.64

Costs of developing and electronically posting					
	Staff cost	Mailchimp 1 year sub (electronic emailing)		Frequency of activity	Total cost
	£ 169.77	£ 130.53		2	£ 470.07
Costs of developing and maunally posting					
	Staff costs	Postage costs		Frequency of activity	Total costs
	£ 223.09	£ 101.64		2	£ 649.45

Timeline of participant visits for sites – site reminder and participant reminder

			Hourly rate (United Kingdom)	
A timeline of participant visits for sites -Site Reminder		**Staff hours**	**Data Manager**	**Staff costs per 1 site**
	Developing reminder schedule software	3	£ 30.40	£ 91.20
	Emailing the reminder schedule software to the sites for the sites to use (10minutes/0.167 hours)	0.167	£ 30.40	£ 5.08
Total costs for site reminder schedule				**£ 96.28**

A timeline of participant visits for sites - participant reminder schedule		**Staff hours**	**Trial Manager**	**Staff costs per 1 participant**	**Number of participants**	**Staff cost per 154 particpants**	**Frequency of activity**	**Total costs = staff costs x frequency of activity**
	Trial Manager directly contacts patient - 5 mins/0.08hrs per participant	0.08	£ 30.40	£ 2.43	154	£ 374.53	3	£ 1,123.58
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	£ 30.40	£ 1.00	154	£ 154.49	3	£ 463.48
Cost of participant reminder schedule								£ 1,587.06
Cost of site reminder schedule								£ 96.28
Total cost of participant reminder schedule								**£ 1,683.34**

Inclusion of pre-paid envelopes (initial mail out and reminder schedule)

			Hourly rate (United Kingdom)				
		Staff hours	Research assistant	Staff costs	Stamp costs (sending out)	Stamp cost (return)	total stamp costs
Inclusion of pre-paid envelopes (2 questionnaires are sent out)	Manually stuffing the 154 envelope	2.464	£ 28.85	£ 71.09	£ 0.66	£ 0.66	£ 1.32
Reminder schedule	Manually stuffing the 47 envelopes	0.752	£ 28.85	£ 21.70	£ 0.66	£ 0.66	£ 1.32
Total costs for both pre-paid envelopes and reminder schedule							

Number of participants	Postage costs	Frequency of activity	Total costs = staff costs + postage costs x 2
154	£ 203.28	2	£ 548.73
47	£ 62.04	2	£ 167.47
			£ 716.20

Telephone reminders (for trial visits and for questionnaire reminder schedule)

			Hourly rate (United Kingdom)						
Telephone reminders (for trial visits)		Staff hours	Trial Manager	Staff costs per 1 participant		Number of participants	Staff cost per 154 participants	Frequency of activity	Total costs = total staff costs x frequency of activity
	Calling participants (5mins/0.08hrs per participant	0.08	£ 30.40	£ 2.43		154	£ 374.53	3	£ 1,123.58
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	£ 30.40	£ 1.00		154	£ 154.49	3	£ 463.48
									£ 1,587.06
			Research assistant						
Telephone reminder schedule for questionnaire response	Calling participants (5mins/0.08hrs per participant	0.08	£ 28.85	£ 2.31		47	£ 108.48	2	£ 216.95
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	£ 28.85	£ 0.95		47	£ 44.75	2	£ 89.49
									£ 306.44

Data collection scheduled with routine care, site initiation training on missing data, investigator meetings face-to-face.

			Hourly rate (United Kingdom)					
Data collection scheduled with routine care		Staff hours	Research Nurse	Staff cost per 1 participant	Number of participants	Staff costs per 154 participants	Frequency of activty	Total costs = total staff costs x frequency of activity
	Collecting participant data during a routine clinic visit - 15mintues/0.25hrs	0.25	£ 36.00	£ 9.00	154	£ 1,386.00	3	£ 4,158.00

			Hourly rate (United Kingdom)					
Site initiation training on missing data		Staff hours	Trial Manager	Staff costs per 1 site	Travel costs	Other expenses e.g. Overnight expenses	Number of sites	Frequency of activity	Total costs
	Trial Manager carries out preparation travels to the sites and carries out training and writes up a report. 11 hours of work in total, no travel and overnight as it is single centre	11	£ 30.40	£ 334.40		£ -	1	1	£ 334.40

			Hourly rate (United Kingdom)					
Investigator meetings face to face		Staff hours	Trial Manager	Staff costs per 1 site	Travel costs	Other expenses e.g. Overnight expenses	Number of sites	Frequency of activity	Total costs
	Trial Manager carries out preparation travels to the sites and carries out training and writes up a report. 11 hours of work in total, no travel and overnight as it is single centre	11	£ 30.40	£ 334.40	£ -	£ -	1	2	£ 668.80

Routine site visits by CTU staff, targeted recruitment of sites/GPs, and flexibility in appointments

			Hourly rate (United Kingdom)							
Routine site visits by CTU staff		Staff hours	Trial Manager	Staff costs per 1 site		Travel costs	Other expenses e.g. Overnight expenses	Number of sites	Frequency of activity	Total costs
	Trial Manager carries out preparation travels to the sites and carries out training and writes up a report. 11 hours of work in total, no travel and overnight as it is single centre	11	£ 30.40	£ 334.40		£ -	£ -	1	2	£ 668.80

			Hourly rate (United Kingdom)							
Targeted reruitment of sites/GPs		Staff hours	Trial Manager	Total staff costs per 1 site	Number	Total costs = staff cost x number of sites				
	Site selection and assosiated investigation into recruitment (1hour of work per site)	1	£ 30.40	£ 30.40	1	£ 30.40				

			Hourly rate (United Kingdom)							
Flexibility in appointments - out of hours appointments		Staff hours	Research Nurse	Number of participants needing out of hours appointments		Total costs				
	Length of appointment (per appointment)	1.5	£ 36.00	16		£ 864.00				

Total costs of retention strategies

	Total costs of each intervention	
Newsletters		
Manually sending out newsletters	£	649.45
Emailing out newsletters	£	470.07
A timeline of participant visits for sites		
Reminder schedule for sites	£	96.28
Reminder schedule for participants	£	1,683.34
Inclusion of pre-paid envelopes	£	716.20
Telephone reminders for trial visits	£	1,587.06
Telephone reminder schedule for questionnaire response	£	306.44
Data collection scheduled with routine	£	4,158.00
Site initiation training on missing data	£	334.40
Investigator meetings face to face	£	668.80
Routine site visits by CTU staff	£	668.80
Targeted reruitment of sites/GPs	£	30.40
Flexibility in appointments - out of hours appointments	£	864.00

CINNAMON trial

Newsletter costs (both paper and electronic newsletters)

			Hourly rate (USA)					
		Staff hours	Research Nurse	Staff costs				
Newsletter	Developing newsletter	5	$ 40.00	$ 200.00				
			Research assistant			Postage costs	Number of participants/years	Total postage costs
	Emailing newsletter	1.712	$ 20.00	$ 34.24		$ 179.88	2	$ 359.76
	Manually stuffing 428 envelopes and posting	6.848	$ 20.00	$ 136.96		$ 0.55	428	$ 235.40

Costs of developing and electronically posting					
	Staff costs	Mailchimp 2 year sub (electronic emailing)		Frequency of activity	Total costs = staff costs x 4 plus Mailchimp flat rate
	$ 234.24	$ 359.76		4	$ 1,296.72

Costs of developing and manually posting					
	Staff costs	Postage costs	Staff and postage costs	Frequency of activity	Total costs = Staff and postage x 4
	$ 336.96	$ 235.40	$572.36	4	$ 2,289.44

Timeline of participant visits for sites – site reminder and participant reminder

			Average Hourly rate (USA)	
A timeline of participant visits for sites -Site Reminder		**Staff hours**	**Data Manager**	**Staff costs per 1 site**
	Developing reminder schedule software	3	$ 42.00	$ 126.00
	Emailing the reminder schedule software to the sites for the sites to use (10minutes/0.167 hours)	0.167	$ 42.00	$ 7.01
Total costs for site reminder schedule				**$ 133.01**

A timeline of participant visits for sites		**Staff hours**	**Research Nurse**	**Staff costs per 1 particpant**		**Number of participants**	**Staff cost per 500 participants**	**Frequency of activity (done for each trial visit which is 9)**	**Total costs = total staff costs x frequenct of acitivty**
	Research Nurse directly contacts patient - 5 mins/0.08hrs per participant	0.08	$ 40.00	$ 3.20		428	$ 1,369.60	9	$ 12,326.40
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	$ 40.00	$ 1.32		428	$ 564.96	9	$ 5,084.64
Cost of reminder schedule for participants									$ 17,411.04
Cost of reminder schedule for sites									$ 133.01
Total cost of reminder schedule for sites									**$ 17,544.05**

Inclusion of pre-paid envelopes (initial mail out and reminder schedule)

			Average Hourly Rate (USA)					
		Staff hours	Research assistant	Total staff costs		Stamp costs sending out	Stamp cost return	total stamp cost
Inclusion of pre-paid envelopes	Manually stuffing the 428 envelopes	6.848	$ 20.00	$ 136.96		$ 0.55	$ 0.55	$ 1.10
Reminder schedule	Manually stuffing the 129 envelopes	2.064	$ 20.00	$ 41.28		$ 0.55	$ 0.55	$ 1.10
Total costs for pre-paid and reminder schedule								

Number of participants	Total postage cost	Frequency of activity	Total costs
428	$ 470.80	1	$ 607.76
129	$ 141.90	1	$ 183.18
			$ 790.94

Telephone reminders (for trial visits and for questionnaire reminder schedule)

			Average Hourly Rate (USA)					
		Staff Hours	Research Nurse	Staff cost per 1 participant	Number of particpants	Staff costs per 428 participants	Frequency of activity	Total costs = total staff costs x frequency of activity
Telephone reminders (for trial visits)	Calling participants (5mins/0.08hrs per participant	0.08	$ 40.00	$ 3.20	428	$ 1,369.60	9	$ 12,326.40
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	$ 40.00	$ 1.32	428	$ 564.96	9	$ 5,084.64
								$ 17,411.04

			Research assistant		Number of participants	Staff costs per 129 participants	Frequency of activity	Total cost = total staff costs x frequency of activity
Telephone reminder schedule for questionnaire response	Calling 129 participants as reminder schedule for questionnaire	0.08	$ 20.00	$ 1.60	129	$ 206.40	1	$ 206.40
Time spent trying to contact participant - average of 2 calls - minute per failed attempt - 2 minutes per participant	Failed call attempts per participant (2 minutes/0.033hours for 2 failed calls)	0.033	$ 20.00	$ 0.66	129	$ 85.14	1	$ 85.14
								$ 291.54

Data collection scheduled with routine care, site initiation training on missing data, investigator meetings face-to-face.

			Average Hourly Rate (USA)						
Data collection scheduled with routine care		Staff hours	Research Nurse	Staff costs per 1 participant		Number of particpants	Staff costs per 428 participants	Frequency of activity	Total costs = staff costs x frequncy of acitvity
	Collecting participant data during routine clinic visit - 15	0.25	$ 40.00	$ 10.00		428	$ 4,280.00	9	$ 38,520.00
Site initiation training on missing data									
		Cost per 1 site	Travel costs	Other expenses e.g. overnight expenses	Number of sites	Frequency of activity	Total costs		
	Prep, site visit and report per site @€400 per day + travel + overnight.	$ 400.00	$ 100.00	$ 200.00	5	1	$ 3,500.00		
Investigator meetings face to face									
		Cost per 1 site	Travel costs	Other expenses e.g. overnight expenses	Number of sites	Frequency of activity (4 vists over 2 years)	Total costs		
	Prep, site visit and report per site @€400 per day + travel + overnight.	$ 400.00	$ 100.00	$ 200.00	5	4	$ 14,000.00		

Routine site visits by CTU staff, targeted recruitment of sites/GPs, and flexibility in appointments

Routine site visits by CTU staff		Costs per 1 sites	Travel costs	Other expenses e.g. overnight expenses	Number of sites	Frequency of activity (4 vists over 2 years)	Total costs
	Prep, site visit and report per site @€400 per day + travel + overnight.	$ 400.00	$ 100.00	$ 200.00	5	4	$ 14,000.00
			Average Hourly Rate (USA)				
Targeted reruitment of sites/GPs		Staff hours	Research Nurse	Total staff costs per 1 site	Number of sites (estimate of number of targeted sites)	Total costs = staff cost x number of sites	
	Site selection and assosiated investigation into recruitment (1 hour per site)	1	$ 40.00	$ 40.00	15	$ 600.00	
			Average Hourly Rate (USA)				
Flexibility in appointments - out of hours appointments -		Staff hours	Research Nurse	Number of participants needing out of hours appointments		Total costs = staff hours x staff wage x number of appointments	
	Length of appointment (per appointment)	1.5	$ 40.00	43		$ 2,580.00	

Total costs of retention strategies

	Total costs of each intervention	
Newsletters		
Manually sending out newsletters	$	2,289.44
Emailing out newsletters	$	1,296.72
A timeline of participant visits for sites		
Reminder schedule for sites	$	133.01
Reminder schedule for participants	$	17,544.05
Inclusion of pre-paid envelopes	$	790.94
Telephone reminders for trial visits	$	17,411.04
Telephone reminder schedule for questionnaire response	$	291.54
Data collection scheduled with routine care	$	38,520.00
Site initiation training on missing data	$	3,500.00
Investigator meetings face to face	$	14,000.00
Routine site visits by CTU staff	$	14,000.00
Targeted reruitment of sites/GPs	$	600.00
Flexibility in appointments - out of hours appointments -	$	2,580.00

Appendix 3. Thesis Chapter Five. Supplementary File 2. Scoping Review Protocol

Title: How do trial teams plan for retention during the design stage of the trial? A scoping review protocol.

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Abstract

Background

Retention remains a major challenge for many clinical trials. The SPIRIT guidelines state the following information on retention should be included in the trial protocol "Plans to promote participant retention and complete follow up including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols". This guidance shows the importance of planning retention methods and handling missing data as this can impact how the results of the trial are interpreted. The most recent Cochrane review of strategies to improve retention in clinical trials highlighted that some trials implemented multiple retention strategies and we questioned whether the use of multiple strategies was planned at the design stage and included in the protocol or are strategies implemented when retention becomes an issue within the trial. The purpose of our scoping review is to establish if and how trial teams prepare for retention at the design phase of clinical trials.

Methods and analysis

We will follow the methodological framework and guidelines for scoping reviews outlined by the Joanna Briggs Institute. We will search MEDLINE/PubMed**,** Scopus, EMBASE, CINAHL (EBSCO) and Web of Science. A comprehensive search strategy for PubMed was developed in collaboration with an experienced research librarian. We will include protocols for Phase 2, 3, and 4 RCTs as well as pilot and feasibility

studies. The screening process will involve two reviewers. EM will independently screen all titles and abstracts. FS will screen 10% of the overall search output and where necessary full protocol texts will be screened to determine eligibility. We will randomly sample eligible protocols to ensure the protocols represent a variety of trial and intervention types. Data will be extracted from each protocol and the results will be synthesized. The analysis will be qualitative using a narrative summary and descriptive statistics where appropriate.

Discussion

The scoping review will help trial methodologists better understand if retention strategies are planned for during the design stage of the trial contributing to the PRioRiTy II unanswered question “How should people who run trials plan for retention during their funding application and creation of the trial (protocol development)?”.

Keywords: Scoping review, randomised controlled trial protocols, retention strategies, trial design stage

Background/Rationale

Randomised controlled trials (RCTs) are conducted in accordance with a trial protocol. Having a protocol that is incomplete and non-transparent makes it difficult to critically appraise the trial (217). Protocols are needed for the readers of the corresponding paper to be able to fully appraise and interpret the results of the trial

(128). As per the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) definition, a protocol is “a document that provides sufficient detail to enable understanding of the background, rationale, objectives, study population, interventions, methods, statistical analyses, ethical considerations, dissemination plans, and administration of the trial, replication of key aspects of trial methods and conduct; and appraisal of the trial’s scientific and ethical rigor from ethics approval to dissemination of results” (127;202). Prior to the introduction of SPIRIT, the content and quality of protocols differed greatly (127, 218) but the 33-item SPIRIT checklist for the minimum recommended protocol items improved this. Having a clearly written protocol increases transparency in trial conduct. Protocols are usually published prior to the trial paper publication (219). However, this is not always the case, and some protocol publications will require payment for access. For example, of the cancer clinical trials published in January of 2020 (n=113), only 11.3% had a publicly accessible protocol that was not behind a paywall (128). This further limits transparency and hinders replication in trial methods and conduct, which has been recommended for trial retention strategies in order to improve the evidence base for their effectiveness (3).

Retention remains a major challenge for many clinical trials (220). The SPIRIT guidelines recommend the following information on retention be included in the trial protocol in section 18b “Plans to promote participant retention and complete follow-up including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols” (21;3). These of course are

minimum requirements but the information can impact how missing data is dealt with and interpreted in the analysis of the trial (21).

A recent Cochrane systematic review of strategies to improve retention in clinical trials found that there were none for which the quality of evidence was high that showed improved retention. The review also highlighted that some trials implement multiple retention strategies (3), and thus we questioned whether the use of multiple strategies is planned at the design stage and included in the protocol, or are strategies implemented when retention becomes an issue within the trial. Evidence from a small number of interviews with trial staff is variable (70). Prospective retention planning informs appropriate costing and implementation of retention strategies but also increases transparency in trial conduct.

Objective

The purpose of our scoping review is to establish if and how trial teams prepare for retention at the design phase of clinical trials. This will contribute to the evidence base for the PRioRiTy II (Prioritising Retention in Randomised Trials) unanswered question “How should people who run trials plan for retention during their funding application and creation of the trial (protocol development)?” (4).

Methods

The scoping review will be conducted in accordance with the guidelines and framework outlined by the Joanna Briggs Institute (JBI) (123), the most recent

framework for scoping reviews which builds on prior work (122, 134, 135). The framework consists of the following nine steps:

1. Defining and aligning the objective/s and question/s,

2. Developing and aligning the inclusion criteria with the objective/s and question/s

3. Describing the planned approach to evidence searching, selection, data extraction and presentation of the evidence

4. Searching for the evidence

5. Selecting the evidence

6. Extracting the evidence

7. Analysis of the evidence

8. Presentation of the results

9. Summarising the evidence in relation to the purpose of the review, making conclusions and noting any implications of the findings

The guidance from the Joanna Briggs Institute (123) along with the newly developed reporting guidelines for scoping reviews: the Preferred Reporting Items for a Systematic Review and Meta-Analysis Protocols Extension for Scoping Reviews (PRISMA-ScR)(136) have been consulted in the development of this protocol (Additional File 1).

Data sources and search strategy

A comprehensive search strategy for PubMed was developed in collaboration with an experienced research librarian at University College Cork and is shown below. The following electronic databases will be searched for relevant protocols, MEDLINE/PubMed, Scopus, EMBASE, CINAHL (EBSCO), and Web of Science. The search will be adapted as appropriate for each database using the software Polyglot which translates search strategies across databases. The search and screening process will take place over a six-week period.

Example of PubMed search

This is the full search strategy developed for PubMed. The limits that were applied include; published in the English language between the years of 2014-2019 (inclusive). No other limits will be applied to the search.

("randomised controlled trial"[Title/Abstract]) OR ("randomized controlled trial"[Title/Abstract])) OR ("randomised clinical trial"[Title/Abstract])) OR ("randomized clinical trial"[Title/Abstract])) OR ("randomized controlled trials as topic"[MeSH Terms])) AND ("protocol"[Title/Abstract])) OR ("clinical trial protocols as topic"[MeSH Terms])

Inclusion Criteria

Population: The population include the following: protocols of RCTs that include adults and/or children of any age.

Concepts: The concepts include the following: protocols of RCTs investigating any treatment/intervention type for any disease area. Randomisation can be at the

cluster or individual level. Protocols of RCTs investigating any comparator including placebo and examining any outcome.

Context: The context of this scoping review is open sources of evidence pertaining to any contextual setting.

Types of evidence sources: We will include trial protocols published in the English language. We will include protocols from 2014-2019 (inclusive), giving sufficient time to see the effect of the SPIRIT guidelines, which were published in 2013. We will include protocols for Phase 2, 3, and 4 RCTs as well as pilot and feasibility studies.

Screening and selection process

EM will systematically collate and import titles and abstracts of all electronically sourced search results to EndNote, grouping results separately for each database. Duplicates will be removed, and the remaining results will be exported to Rayyan QCRI software for screening. The screening process will involve two reviewers (EM and FS). EM will independently screen all titles and abstracts. FS will screen a random selection of 10% of the overall search output. If there is less than 80% agreement on the random 10% of the search output that is double screened, we will undertake screening of a further 10% validation sample. We will reiterate this until >80% agreement on the validation sample is reached. If disagreement arises between these two reviewers regarding the eligibility of a protocol a third reviewer KG will be consulted and where necessary full protocol texts to determine eligibility. The protocol screening and selection process will be presented both narratively and

graphically using a PRISMA (Transparent Reporting of Systematic Reviews and Meta-Analyses) flow diagram. Details of excluded sources at full-text review will be outlined and included in the review with reasons for the protocol exclusion.

Sampling

We will select a random sample of 10% of eligible protocols for data extraction, the random sample will be chosen by including blocks of 10 protocols from the list of eligible protocols for inclusion. A randomly chosen 10% will provide a sufficient representation of all eligible protocols.

Data management and data charting (extraction) process

Following screening for eligibility all data on retention plans will be extracted. Data to be extracted is outlined in Table 1. The main outcome of interest is whether SPIRIT item 18b is satisfied (Table 1, variable 7), since this statement has sub-requirements during the data charting process we will divide the statement into three aspects “plans to promote participant retention” and “plans to complete follow-up including list of any outcome data to be collected for participants who discontinue from intervention protocols” and “plans to complete follow-up including list of any outcome data to be collected for participants who deviate from intervention protocols”. Dividing the statement into sub-statements will more accurately reflect whether SPIRIT item 18b is satisfied or not. With regard to retention strategies, we specifically mean an action/activity that is conducted with the purpose of reducing missing data/improving data completeness, we will not

include activities to improve adherence or compliance to an intervention. Where there is ambiguity on the purpose of specific actions, i.e., if they are for participant retention or not, the protocol authors will be contacted. Where contact is not possible/a reply is not received the ambiguous information will be highlighted and included in the data extraction. Prior to the full data charting process, the data extraction form will be piloted using a sample of 10 protocols as the variables to be extracted may need to be refined and improved to best meet the objectives of the scoping review. Data charting will be carried out by one reviewer (EM) and a random sample (10%) of the protocols will be double extracted and checked for consistency by (FS) to ensure consistency and improve the reliability of the data extraction process. If there is less than 80% agreement regarding the data extracted in the 10% random sample of protocols, we will undertake data extraction of a further 10% validation sample. We will reiterate this until >80% agreement on the validation sample is reached. Data charting will be conducted, and information will be entered into a Microsoft Excel file.

Data Items

Table 1. Variables to be extracted

Variables to be extracted
1. Protocol title, author and year, source of funding
2. Trial characteristics (disease area, patient population, duration of the follow-up period, number of follow-up assessments, intervention and comparator)
3. Primary outcome (the primary outcome, whether it is a patient reported vs non-patient reported outcome)
4. Planned sample size

5. Mention of using the SPIRIT guidelines in the development of the protocol (“yes” or “no”)
6. Description of retention strategies outlined in the protocol
7. Does the description of the retention strategy include all the information recommended by the SPIRIT guidelines section 18b (“yes” or “no”) “Plans to promote participant retention and complete follow up including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols” (21;3)
8. Mode of follow up e.g., questionnaire, clinic visit, telephone call etc.
9. Routine data collection (yes or no)
10. Mention of Patient and Public Involvement (PPI) in relation to retention
11. Mention of cost associated with retention strategy

Data synthesis

We will synthesise the data in a narrative synthesis with descriptive statistics where appropriate. The descriptive statistics that will be generated will include the frequencies and percentages of the trial characteristics such as the percentage of trials conducted in different disease areas, percentage of trials conducted among vulnerable populations, percentage of trials that are publicly or privately funded, and the percentage of drug trials, surgical trials, non-drug/behavioural intervention, and medical device trials, modes of follow up methods used by trials, number of trials with patient reported primary outcomes vs non-patient reported outcomes . We will also generate the percentage of trial protocols that have satisfied the SPIRIT item 18B statement”.

Since we will include pilot and feasibility trial protocols, we plan to conduct a sub-analysis of this group of studies as one of the purposes of pilot and feasibility trials may be to develop and test retention strategies.

The content will be analysed to determine if the protocol complies with the SPIRIT guidelines for retention strategies section 18b- “Plans to promote participant retention and complete follow up including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols” (21;3). We will divide the statement into three aspects “plans to promote participant retention” and “plans to complete follow-up including list of any outcome data to be collected for participants who discontinue from intervention protocols” and “plans to complete follow-up including list of any outcome data to be collected for participants who deviate from intervention protocols”. This will be recorded as either “yes” or “no” for each separate aspect.”. If the protocols include information regarding planned retention strategies this information will be analysed in the narrative synthesis. The narrative synthesis approach will be based on the Guidance on the Conduct of Narrative Synthesis in Systematic Reviews (138).

Presentation of findings

We will present the search results in a PRISMA flow diagram illustrating the total number of protocols generated by the search strategy, and the number of protocols excluded following the application of the inclusion/exclusion criteria and ultimately the number of protocols included in the scoping review. Summary tables will depict the study characteristics described in the included protocols. Additional tables, figures and narrative descriptions will illustrate the data addressing our research question. The findings of the scoping review will be disseminated via publication in a peer-reviewed journal.

Discussion

Conducting a scoping review of randomised controlled trial protocols to investigate if retention strategies are planned by trial teams during the design stage of the trial will contribute to the PRioRiTy II unanswered question “How should people who run trial plan for retention during their funding application and creation of the trial (protocol development)?” (4). The strength of this review is the intention to include a variety of trial types as described in the methods section. The review will highlight the gaps that exist in the planning and communicating of retention strategies in clinical trial protocols, which may have the potential to increase transparency in trial conduct and make trials more efficient as it will highlight to researchers the lack of consideration and/or communication of trial retention strategies during the initial planning and design stages of the trial. Foreplaning could increase retention strategy success as trial teams will be able to spend greater time researching the most effective strategies in terms of retaining participants and carefully consider the resources required as retention strategies can be very expensive to implement often with little reward in terms of retaining participants (3, 68, 221). The findings of this review have the potential to inform trialists to plan retention strategies during the design stage of the trial rather than when retention issues appear. The review will also help identify questions for future research projects and findings from this review can be explored in more depth in future research investigating retention strategies in clinical trials.

Abbreviations

Randomised controlled trials (RCTs)

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

Prioritising Retention in Randomised Controlled Trials (PRioRity)

Preferred Reporting Items for a Systematic Review and Meta-Analysis Protocols Extension for Scoping Reviews (PRISMA-ScR)

Transparent Reporting of Systematic Reviews and Meta-Analyses (PRISMA)

Declarations

Ethics approval and consent to participate

As this will be a scoping review of previously published protocols no ethical approval or consent to participate is required.

Consent for publication

Not applicable as this protocol does not contain any individual persons' data.

Availability of data and materials

Not applicable as this is a protocol for a scoping review.

Competing interests

All authors confirm that they have no competing interests.

Funding

This research forms part of a doctoral research project supported by the Health Research Board Trial Methodology Research Network (HRB-TMRN) PhD scholarship awarded to EM. The funder had no role in the design, data collection and analysis or preparation of the protocol.

Authors' contributions

All authors contributed to developing the review question and the review design. EM designed and drafted the protocol and is the guarantor of this protocol. FS and KG reviewed the protocol. All authors read and approved the final version of the protocol.

Acknowledgements

Not applicable

Patient and Public Involvement

No patient or public involvement.

Amendments

The protocol will be closely followed during the scoping review, due to the iterative nature of scoping reviews any amendments that are made to the published protocol will be reported in the final publication.

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Appendix 4. Thesis Chapter Five. Supplementary File 1. PRISMA-ScR Checklist

(page numbers adjusted to match the pages within this thesis)

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	114
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	115-116
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	117-119
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	119
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	120
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	121
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	120
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	121

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	120-122
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	121-125
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	122-123 and Supplementary File 2 Appendix 3
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	Not applicable
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	124-125
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	PRISMA Flow Diagram – Appendix 5
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	126-130
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	132-150
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	132-150
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	150-158
Limitations	20	Discuss the limitations of the scoping review process.	158-159

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	160
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	162

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

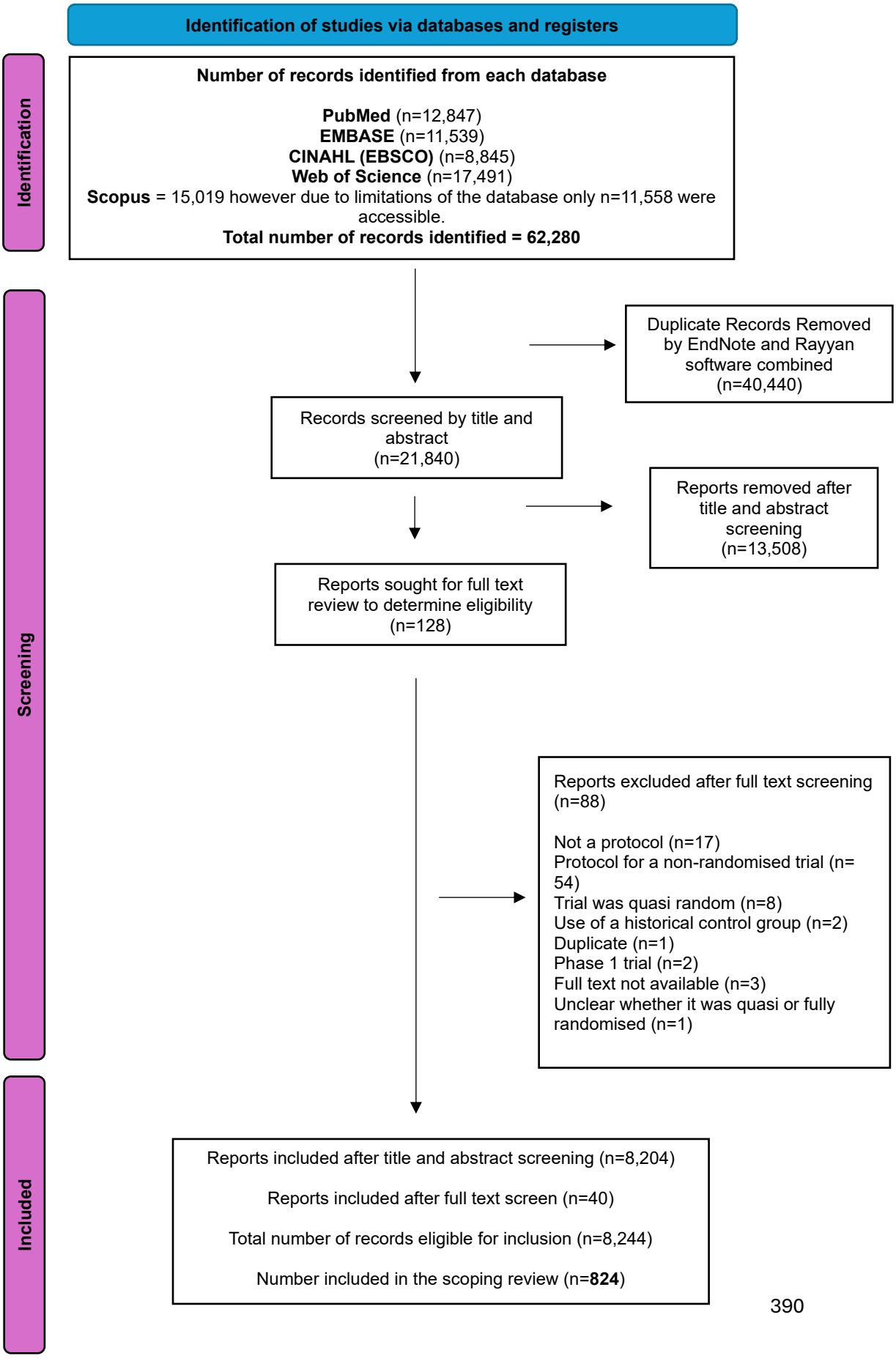
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Appendix 5. Thesis Chapter Five. Figure A5.1. The PRISMA Flow Diagram.

Figure A5.1. PRISMA Flow Diagram



Appendix 6. Thesis Chapter Five. Supplementary File 1. SPIRIT Information and a list of all combinations of retention strategies.

Table A5.1 provides SPIRIT information breakdown for RCT protocols.

Table A5.1: SPIRIT 2013 Statement Results for RCT protocols (n=722 protocols)	
Reported use of the SPIRIT guidelines	**Number of RCT protocols (n, %)**
Yes	253 (35%)
No	469 (65%)
Reported using the SPIRIT guidelines and reported all aspects of item 18b (18b(i) and 18b(ii) and/or 18b(iii)) – "Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols" (21;3)	
Yes	**24 protocols out of the 253 that reported using SPIRIT (9.5%)**
No	229 (90.5%)
Reported using the SPIRIT guidelines (n=253) and reported item 18b(i) "plan to promote participant retention"	**Number of protocols (n, %)**
Yes	**105 protocols out of the 253 that reported using SPIRIT (41.5%)**
No	148 protocols (58.5%)
Reported using the SPIRIT guidelines (n=253) and reported item 18b(ii) and/or 18b(iii) plans to "complete follow up including list of any outcome data to be collected for participants who **discontinue or deviate from protocol interventions**	
Yes	**40 protocols out of the 253 that reported using the SPIRIT (15.8%)**
No	213 protocols (84.2%)

RCT protocol SPIRIT item 18b figures, regardless of reporting SPIRIT guidelines in the protocol i.e., information mapped to SPIRIT item 18b.	
	Number of protocols (n, %)
Reported all aspects of item 18b (18b(i) and 18b(ii) and/or 18b(iii)) – "Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols" (21;3)	
Yes	**53 protocols out of the total (n=722) (7.3%)**
No	669 protocols (92.7%)
Reported item 18b(i) "Plans to promote participant retention" (out of the total 722 protocols)	
Yes	**266 (36.8%)**
No	456 (63.2%)
Reported item 18b(ii) – Plans to complete follow up including list of any outcome data to be collected for participants who **discontinue from intervention protocols**	
Yes	**85 (11.8%)**
No	637 (88.2%)
Reported item 18b(iii) – Plans to complete follow up including list of any outcome data to be collected for participants who **deviate from intervention protocols**	
Yes	**8 (1.1%)**
No	714 (98.9%)
Reported item 18b(ii) and 18b(iii) – Plans to complete follow up including list of any outcome data for participants who **discontinue and deviate from intervention protocols**	
Yes	**6 (0.8%)**
No	716 (99.2%)

Reported item 18b(ii) and/or 18b(iii) Plans to complete follow up including list of any outcome data to be collected for participants who **discontinue and/or deviate from intervention protocols**	
Yes	**99 protocols (13.7%)**
No	623 protocols (86.3%)
Mention of PPI (Patient and Public Involvement) in relation to retention	**Number of protocols (n, %)**
For protocols with a retention strategy (n=266)	
Yes	2 (0.8%)
Possible PPI involvement[1]	9 (3.4%)
No	255 (95.9%)
Mention of cost associated with a retention strategy	**Number of protocols (n, %)**
For protocols with a retention strategy (n=266)	
Yes	80[2] (30.1%)
No	186 (69.9%)

*Excluding data from Pilot and Feasibility studies. [1]Mention of PPI (patient and public involvement), where there was a plan to promote participant retention and PPI was mentioned but it was unclear if PPI members were involved in the designing and planning of the retention strategy specifically that was included as a "possible PPI involvement". [2] 80 protocols mentioned a cost associated with the retention strategy however this was all related to the cost of the monetary incentive/compensation that was going to be used to promote participant retention. Not all monetary incentives mentioned cost.

Table A5.2 provides SPIRIT information for Pilot and Feasibility trial protocols.

Table A5.2: SPIRIT 2013 Statement Results for Pilot and Feasibility trial protocols (n=102)	
Reported use of the SPIRIT guidelines	**Number of protocols (n, %)**
Yes	35 (34.3%)
No	67 (65.7%)
Reported using the SPIRIT guidelines and reported all aspects of item 18b (18b(i) and 18b(ii) and/or 18b(iii)) – "Plan to promote participant retention and	

complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols" (21;3)	
Yes	**4 protocols out of the 35 that reported using SPIRIT (11.4%)**
No	31 (88.6%)
Reported using the SPIRIT guidelines (n=35) and reported item 18b(i) "plan to promote participant retention"	**Number of protocols (n, %)**
Yes	**15 protocols out of the 35 that reported using SPIRIT (42.9%)**
No	20 protocols (57.1%)
Reported using the SPIRIT guidelines (n=35) and reported item 18b(ii) and/or 18b(iii) plans to "complete follow up including list of any outcome data to be collected for participants who **discontinue or deviate from protocol interventions**	
Yes	**7 protocols out of the 35 that reported using the SPIRIT (20%)**
No	28 protocols (80%)
Pilot and Feasibility trial protocol figures, regardless of reporting SPIRIT guidelines in the protocol i.e., information mapped to SPIRIT item 18b.	
	Number of protocols (n, %)
Reported all aspects of item 18b (18b(i) and 18b(ii) and/or 18b(iii)) – "Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols" (21;3)	
Yes	**7 protocols out of the total (6.9%)**
No	95 protocols (93.1%)
Reported item 18b(i) "Plans to promote participant retention"	
Yes	**41 (40.2%)**
No	61 (59.8%)

Reported item 18b(ii) – Plans to complete follow up including list of any outcome data to be collected for participants who **discontinue from intervention protocols**	
Yes	**13 (12.7%)**
No	89 (87.3%)
Reported item 18b(iii) – Plans to complete follow up including list of any outcome data to be collected for participants who **deviate from intervention protocols**	
Yes	**1 (1%)**
No	101 (99%)
Reported item 18b(ii) and 18b(iii) – Plans to complete follow up including list of any outcome data for participants who **discontinue and deviate from intervention protocols**	
Yes	**1 (1%)**
No	101 (99%)
Reported item 18b(ii) and/or 18b(iii) Plans to complete follow up including list of any outcome data to be collected for participants who **discontinue and/or deviate from intervention protocols**	**Number of protocols (n, %)**
Yes	15 protocols (14.7%)
No	87 protocols (85.3%)
Mention of PPI (Patient and Public Involvement) in relation to retention	**Number of protocols (n, %)**
For protocols with a retention strategy (n=41)	
Yes	0
Possible PPI involvement[1]	7 (17.1%)
No	34 (82.9%)
Mention of cost associated with a retention strategy	**Number of protocols (n, %)**
For protocols with a retention strategy (n=41)	
Yes	16[2] (39%)

No	25 (61%)

[1]Mention of PPI (patient and public involvement), where there was a plan to promote participant retention and PPI was mentioned but it was unclear if PPI members were involved in the designing and planning of the retention strategy specifically that was included as a "possible PPI involvement". [2] 16 protocols mentioned a cost associated with the retention strategy however this was all related to the cost of the monetary incentive/compensation that was going to be used to promote participant retention. Not all monetary incentives mentioned cost.

List of 'combined strategies' outlined in the trial protocols.

We grouped actions/activities into ORRCA domains based on guidance from ORRCA and from the Cochrane review of strategies to improve retention in clinical trials (3).

Table A5.3 provides all 'combined strategies' (n=128) included in RCT protocols (n=722)

Table A5.3: All combinations of strategies (n=128) outlined in RCT protocols			
Most common combination of retention strategies	**Number of protocols**	**Most common combo – updated conditional vs unconditional incentives**	**Number of protocols**
• Non-monetary incentive • Randomisation method • Supporting participation • Reminders • Monetary incentives	**1**	• Non-monetary incentive – Unconditional incentive • Randomisation method • Supporting participation • Reminders • Monetary incentives - conditional	**1**
• Monetary incentive • Reminder	**6**	• Monetary incentive – Conditional incentive • Reminder	**4**
		• Monetary incentive – unclear if conditional or not • Reminder	**2**
• Data collection location and method • Reminder	**6**		
• Reminders • Maintaining engagement	**3**		
• Prompt	**5**	• Prompt	**5**

• Monetary incentive		• Monetary incentive – conditional incentive	
• Monetary incentives • Supporting participation	**4**	• Monetary incentives – conditional incentive • Supporting participation	**3**
		• Monetary incentive – unclear • Supporting participation	**1**
• Prompts • Supporting participation • Monetary incentive	**1**	• Prompts • Supporting participation • Monetary incentive – conditional incentive	**1**
• Monetary incentives • Maintaining participant engagement	**1**	• Monetary incentives – conditional • Maintaining participant engagement	**1**
• Non-monetary incentive • Monetary incentive	**3**	• Non-monetary incentive – conditional • Monetary incentive – conditional	**2**
		• Non-monetary incentive - unclear • Monetary incentive – conditional	**1**
• Contact information • Monetary incentives	**2**	• Contact information • Monetary incentives – conditional	**2**
• Contact information • Maintaining engagement • Monetary incentive	**1**	• Contact information • Maintaining engagement • Monetary incentive – conditional incentive	**1**
• Supporting participation • Maintaining engagement	**4**		
• Monetary incentive • Data collection location and method • Reminder	**5**	• Monetary incentive – conditional • Data collection location and method • Reminder	**4**
		• Monetary incentive – unconditional • Data collection location and method	**1**

		• Reminder	
• Supporting participation • Maintaining engagement • Resources and infrastructure	**1**		
• Prompt • Reminder • Monetary incentive	**4**	• Prompt • Reminder • Monetary incentive – conditional	**4**
• Prompt • Reminder • Supporting participation	**1**		
• Prompt • Reminder • Data collection location and method • Monetary incentive	**1**	• Prompt • Reminder • Data collection location and method • Monetary incentive – conditional	**1**
• Data collection location and method • Contact information • Supporting participation	**1**		
• Data collection location and method • Maintaining engagement • Reminder	**2**		
• Prompt • Maintaining participant engagement	**1**		
• Data collection scheduled with routine care • Data collection location and method	**2**		
• Supporting participation • Contact information • Prompt • Monetary incentives	**1**	• Supporting participation • Contact information • Prompt • Monetary incentives – conditional	
• Trial design • Monetary incentive • Data collection location and method	**1**	• Trial design • Monetary incentive – conditional • Data collection location and method	**1**

• Data collection location and method • Reminder • Trial design • Maintaining participant engagement	**1**		
• Prompt • Supporting participation • Data collection location and method • Monetary incentives • Non-monetary incentive	**1**	• Prompt • Supporting participation • Data collection location and method • Monetary incentives – unconditional • Non-monetary incentive – conditional	**1**
• Monetary incentives • Data collection location and method	**3**	• Monetary incentive – conditional • Data collection location and method	**3**
• Prompts • Reminder • Data collection with routine care • Data collection location and method	**1**		
• Cultural consideration • Supporting participation • Reminders	**1**		
• Data collection location and method • Supporting participation	**1**		
• Supporting participation • Data collection location and method • Prompt	**1**		
• Supporting participation • Maintaining participant engagement • Monetary incentives	**1**	• Supporting participation • Maintaining participant engagement • Monetary incentives – conditional	**1**
• Contact information • Supporting participation • Incentives – conditional but unclear if monetary or non-monetary	**1**		
• Reminder	**1**	• Reminder	**1**

• Monetary incentive • Non-monetary incentive Data collection location and method		• Monetary incentive – conditional • Non-monetary incentive – unconditional • Data collection location and method	
• Monetary incentives • Non-monetary incentive • Prompts • Maintaining participant engagement	**1**	• Monetary incentives – conditional • Non-monetary incentive – unconditional • Prompts • Maintaining participant engagement	**1**
• Maintaining participant engagement • Supporting participation • Non-monetary incentives • Data collection location and method	**1**	• Maintaining participant engagement • Supporting participation • Non-monetary incentives – conditional • Data collection location and method	**1**
• Acceptability of the protocol • Randomisation method • Questionnaire design • Reminder	**1**		
• Maintaining participant engagement • Data collection location and method	**1**		
• Prompt • Supporting participation • Relationship with clinical staff • Contact information	**1**		
• Reminder • Non-monetary incentive	**2**	• Reminder • Non-monetary incentive – unconditional	**1**
		• Reminder • Non-monetary incentive –conditional	**1**
• Data collection frequency and timing	**1**	• Data collection frequency and timing	**1**

• Contact information • Questionnaire design • Reminder • Prompt • Relationship with clinical staff • Non-monetary incentive • Staff training • Supporting participation		• Contact information • Questionnaire design • Reminder • Prompt • Relationship with clinical staff • Non-monetary incentive – unclear if conditional or not • Staff training • Supporting participation	
• Prompt • Reminder	**4**		
• Prompt • Maintaining participant engagement • Non-monetary incentive	**1**	• Prompt • Maintaining participant engagement • Non-monetary incentive – unconditional	**1**
• Prompt • Reminder • Monetary incentive • Maintaining participant engagement	**1**	• Prompt • Reminder • Monetary incentive – conditional • Maintaining participant engagement	**1**
• Reminder • Maintaining participant engagement • Supporting participation	**1**		
• Prompt • Reminder • Data collection location and method	**2**		
• Maintaining participant engagement • Monetary incentive • Reminder	**1**	• Maintaining participant engagement • Monetary incentive – conditional • Reminder	**1**
• Maintaining participant engagement • Non-monetary incentive • Monetary incentive • Reminder	**1**	• Maintaining participant engagement • Non-monetary incentive – unconditional • Monetary incentive – unconditional	**1**

		• Reminder	
• Monetary incentive • Reminder • Supporting participation	**2**	• Monetary incentive – conditional • Reminder • Supporting participation	**2**
• Reminder • Data collection location and method • Data collection frequency and timing • Supporting participation	**1**		
• Monetary incentive • Contact information • Prompt • Supporting participation	**1**	• Monetary incentive – conditional • Contact information • Prompt • Supporting participation	**1**
• Routine data • Maintaining participant engagement • Reminder	**1**		
• Maintaining participant engagement • Prompt • Supporting participation • Monetary inventive • Non-monetary incentive	**1**	• Maintaining participant engagement • Prompt • Supporting participation • Monetary inventive – conditional • Non-monetary incentive – unconditional	**1**
• Monetary incentive • Prompt • Reminder • Data collection location and method	**1**	• Monetary incentive – conditional • Prompt • Reminder • Data collection location and method	**1**
• Maintaining participant engagement • Non-monetary incentive • Monetary incentives	**1**	• Maintaining participant engagement • Non-monetary incentive – unconditional • Monetary incentives – conditional	**1**

• Maintaining participant engagement • Reminder • Monetary incentive • Non-monetary incentive	**1**	• Maintaining participant engagement • Reminder • Monetary incentive – conditional • Non-monetary incentive – conditional	
• Prompt • Maintaining participant engagement • Monetary incentive	**3**	• Prompt • Maintaining participant engagement • Monetary incentive – conditional	**2**
		• Prompt • Maintaining engagement • Monetary incentive – conditional • Monetary incentives – unconditional	**1**
• Prompt – sites and site staff • Prompt - participants • Maintaining participant engagement • Monetary incentive • Data collection location and method	**1**	• Prompt – sites and site staff • Prompt - participants • Maintaining participant engagement • Monetary incentive – conditional • Data collection location and method	**1**
• Contact information • Monetary incentives • Prompt • Reminder	**1**	• Contact information • Monetary incentives – conditional • Prompt • Reminder	**1**
• Monitoring approach • Maintaining participant engagement	**1**		
• Contact information • Prompt • Reminder • Data collection location and method • Non-monetary incentive • Supporting participation	**1**	• Contact information • Prompt • Reminder • Data collection location and method • Non-monetary incentive – unconditional • Supporting participation	**1**

• Maintaining engagement – site and staff • Monetary incentives • Maintaining participant engagement • Data collection location and method	**1**	• Maintaining engagement – site and staff • Monetary incentives – unconditional • Maintaining participant engagement • Data collection location and method	**1**
• Monetary incentive • Randomisation method • Acceptability of protocol • Data collection location and method • Supporting participation	**1**	• Monetary incentive – conditional • Randomisation method • Acceptability of protocol • Data collection location and method • Supporting participation	**1**
• Data collection location and method • Contact information	**1**		
• Reminder • Supporting participation	**2**		
• Monetary incentives – conditional • Non-monetary incentives – conditional • Contact information • Reminder	**1**	• Monetary incentives – conditional • Non-monetary incentives – conditional • Contact information • Reminder	**1**
• Training – sites and site staff category • Contact information	**1**		
• Choice of study outcomes • Maintaining participant engagement • Reminder	**1**		
• Prompt • Reminder • Maintaining participant engagement	**1**		
• Data collection timing and frequency • Reminder	**1**		

• Contact information			
• Prompt • Non-monetary incentive	**1**	• Prompt • Non-monetary incentive – unconditional	**1**
• Prompt • Data collection location and method	**2**		
• Contact information • Reminder	**1**		
• Prompt • Maintaining participant engagement • Data collection location and method	**1**		
• Monetary incentive • Reminder • Contact information • Supporting participation • Data collection frequency and timing	**1**	• Monetary incentive – conditional • Reminder • Contact information • Supporting participation Data collection frequency and timing	**1**
• Supporting participation • Trial staff • Non-monetary incentive • Trial setting	**1**	• Supporting participation • Trial staff • Non-monetary incentive – unconditional • Trial setting	**1**
• Reminder • Monetary incentive • Non-monetary incentive	**1**	• Reminder • Monetary incentive – conditional • Non-monetary incentive – unconditional	**1**
• Monetary incentive • Supporting participation • Data collection location and method	**1**	• Monetary incentive – conditional incentive • Supporting participation • Data collection location and method	**1**
• Reminder • Data collection location and method • Supporting participation	**1**		
• Prompt	**1**		

• Supporting participation			
• Data collection scheduled with routine care • Maintaining participant engagement	**1**		
• Trial site factors • Monitoring visits – site and site staff	**1**		
• Relationship with clinical staff • Maintaining participant engagement	**1**		

Table A5.4 provides all 'combined strategies' (n=19) included in pilot and feasibility trial protocols

Table A5.4: Combination of retention strategies (n=19) in Pilot and Feasibility trial protocols	19 protocols (46.3%)
All combinations;	
Monetary incentives – conditional Prompt	2
Monetary incentives – conditional incentive Supporting participation Data collection location and method	2
Data collection location and method Reminder	2
Monetary incentives –Conditional incentive Prompts Reminders Acceptability of the protocol	1
Prompt Data collection location and method Supporting participation Questionnaire design Non-monetary incentive – conditional	1
Data collection location and method Reminder Maintaining engagement	1
Monetary incentive – unconditional Data collection location and method	1

Reminder	
Monetary incentives – conditional incentive Contact information	1
Contact information Supporting participation Monetary incentives – conditional	1
Prompt Maintaining participant engagement	1
Reminder Data collection scheduled with routine care	1
Reminder Non-monetary incentive – unconditional	1
Monetary incentive – conditional incentive Supporting participation	1
Monetary incentive – conditional Monetary incentive – unconditional Acceptability of the protocol	1
Relationship with clinical staff Prompt	1
Prompt Monetary incentive – conditional Supporting participation	1

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2. Gillies K, Kearney A, Keenan C, Treweek S, Hudson J, Brueton VC, et al. Strategies to improve retention in randomised trials. Cochrane Database of Systematic Reviews. 2021(3).

Appendix 7. Chapter Six. Supplementary File 1. Additional information and list of all combined strategies

Examples of codes mapped to the ORRCA retention domains

Codes that were used based on the existing literature of retention strategies identified by the Cochrane Review on strategies to improve retention in randomised trials (3) and retention strategies that were identified and routinely used by UK Clinical Trial Units (CTUs) (68). These codes were then mapped to the ORRCA (Online Resources for Research in Clinical triAls) retention domains (139). Where multiple codes were identified within a single participant information leaflet a new code was developed; 'combined strategies'. Within this new code the individual codes were also identified.

We mapped strategies based on the groupings outlined by ORRCA, examples shown in table A6.1.

Table A6.1: Codes mapped to ORRCA

Retention Domains **ORRCA retention domains**	**Retention strategies we placed into each group**
A. Data collection	
A3. Data collection location and method	If participants are provided with pre-paid return envelopes If participants are offered multiple/alternative options of data collection
A5. Data collection during routine care	If data collection was during a routine clinic visit
B. Participants	

B1. Reminders **Prompts**	If participants are sent any type of reminder (phone call, text, email, postal) for when they miss a data collection point. If participants are sent any type of prompt (phone call, text, email, postal) for upcoming data collection points
B2. Monetary incentives – direct cash provided to participants/gift vouchers, prizes that are monetary **Conditional Incentives** **Unconditional incentives**	If participants are offered direct cash payments for data collection points, gift vouchers, prizes that are monetary, entry to raffles for monetary prizes. Conditional – if they have to complete a task to obtain the incentive. Unconditional – they receive the incentive regardless of completing the activity
B3. Non-monetary incentives –entry to raffles for prizes that are non-monetary, completion of trial certificates, offering the controls the intervention at the end of the trial **Conditional incentives** **Unconditional Incentives**	If participants are offered any type of non-monetary incentive, completion of trial certificates, offering the controls the intervention at the end of the trial. Conditional – if they have to complete a task to obtain the incentive. Unconditional – they receive the incentive regardless of completing the activity
B4. Maintaining participant engagement	If participants are sent newsletters during the trial to keep them updated on trial activity, if participants are sent
B7. Supporting participation	If participants travel fees are remunerated, parking, day-care for their children is covered by the trial
B8. Contact information	If the trial collects multiple forms of contact for the participant, alternative contact person for the participant
Combined strategies	If is where any of the above strategies are used in combination with each

	other within the trial, we coded them as "combined methods" – the individuals strategies were also identified.

Adult PIL analysis

List of all combinations of retention strategies

Fifty-seven percent of (n=43/75) participant information leaflets (PILs) communicated plans to use 'combined strategies' to promote participant retention.

Table A6.2 shows all combinations of strategies planned to promote retention.

Table A6.2: All combinations of plans to use strategies to promote participant retention

'Combined strategies'	**Number of PILs (total n=43)**
Data collection location and method Data collection scheduled with routine care	6
Supporting participation Data collection location and method	6
Reminder Data collection location and method	5
Monetary incentive – conditional Data collection location and method	3
Reminder Supporting participation Data collection location and method	3
Reminder Data collection location and method Data collection scheduled with routine care	2
Reminder Monetary incentive - conditional Data collection location and method	2
Supporting participation Data collection scheduled with routine care	2
Reminder	2

Supporting participation Data collection location and method Data collection scheduled with routine care	
Prompt Reminder Supporting participation Data collection location and method Data collection scheduled with routine care	1
Contact information Monetary incentive - conditional	1
Reminder Contact information Data collection location and method Data collection scheduled with routine care	1
Supporting participation Monetary incentive – conditional	1
Monetary incentive – unconditional Data collection location and method	1
Monetary/Non-monetary incentive – conditional Data collection location and method	1
Reminder Data collection location and method Monetary incentive – conditional and unconditional Data collection scheduled with routine care Maintaining staff engagement	1
Reminder Data collection location and method Monetary/Non-monetary incentives – conditional	1
Reminder Contact information	1
Monetary incentives – conditional Supporting participation Data collection location and method	1
Supporting participation	1

Data collection location and method Data collection scheduled with routine care	
Supporting participation Monetary incentives conditional Data collection location and method	1

The reporting of SPIRIT guidelines and SPIRIT item 18b in the corresponding trial protocols

We report the results regarding the communication of retention strategies in terms of SPIRIT items 18b(i) plans to promote participant retention, 18b(ii) plans to complete follow-up including list of any outcome data to be collected for participants who *discontinue* from intervention protocols, and item 18b(iii) plans to complete follow-up including list of any outcome data to be collected for participants who *deviate* from intervention protocols (21, 127).

Of the 90 corresponding trial protocols, 35.6% (n=32/90) of protocols reported using the SPIRIT 2013 guidelines when developing the protocol. Of the protocols that reported using the SPIRIT 2013 guidelines 81.3% (n=26/32) reported item 18b(i) “plans to promote participant retention”. Reporting of “plans to complete follow up including list of any outcome data to be collected for participants who *discontinue* (item 18b(ii)) or *deviate* (item 18b(iii)) from intervention protocols” (21:3) were reported in 25% (n=8/32) and 6.3% (n=2/32) of protocols respectively.

Regardless of using the SPIRIT guidelines, protocols still reported retention strategies. Of the 90 trial protocols in total, 74.4% (n=67/90) reported plans to use strategies to promote participants retention.

Table A6.3 provides a full breakdown of information regarding the protocols included in the analysis and whether they reported SPIRIT item 18b.

Table A6.3: Corresponding protocol information on plans to use retention strategies according to SPIRIT (127)	
Publication location	**Number of protocols (% out of 90 protocols)**
Protocols published in a peer reviewed journal	73/90 trial protocols (81.1%)
Protocols published outside a peer reviewed journal e.g. trial website	17/90 trial protocols (18.9%)
Number of corresponding protocols that reported using the SPIRIT 2013 guidelines	
Yes	32/90 trial protocols (35.6%)
No	58/90 trial protocols (64.4%)
Reported using SPIRIT and reported item 18b(i) "plans to promote participant retention"	

Yes	26/32 protocols (81.3%)	These 26 protocols have 27 corresponding PILs of which 22 PILs also report 18b(i) (81.5%)
No	6/32 protocols (18.8%)	
Reported using SPIRIT and reported item 18b(ii)		
Yes	8/32 protocols (25%)	These 8 protocols have 9 corresponding PILs of which 2 report item 18b(ii) (22.2%)
No	24/32 protocols (75%)	
Reported using SPIRIT and reported item 18b(iii)		
Yes	2/32 protocols (6.3%)	These 2 protocols have 3 corresponding PILs of which 0 report item 18b(iii) (0%)
No	30/32 protocols (93.8%)	
Corresponding protocols that reported 18b(i) "plans to promote participant retention" regardless of reporting the SPIRIT guidelines		
Yes	67/90 protocols (74.4%)	These 67 protocols correspond to 69 PILs of which 59 PILs reported 18b(i) (85.5%)
No	23/90 protocols (25.6%)	
Protocols that reported item 18b(ii) regardless of		

reporting the SPIRIT guidelines		
Yes	28/90 protocols (31.1%)	These 28 protocols correspond to 30 PILs of which 15 PILs reported 18b(ii) (50%)
No	62/90 protocols (68.9%)	
Protocols that reported item 18b(iii) regardless of reporting the SPIRIT guidelines		
Yes	4/90 protocols (4.4%)	These 4 protocols correspond to 5 PILs of which 0 reported 18b(iii) (0%)
No	86/90 protocols (95.5%)	
Protocols that report PPI involvement		
Yes	49/90 protocols (54.4%)	These 49 protocols have 50 corresponding PILs of which 5 report PPI (10%)
No	41/90 protocols (45.6%)	

Comparison of PIL content versus protocol content in terms of communicating plans to use strategies to promote participant retention

Overall, 81.5% (n=75/92) of PILs report “plans to promote participant retention”, these 75 PILs correspond to 74 protocols (two PILs correspond to one protocol). Of these 75 PILs and 74 corresponding protocols, there are 59 PILs corresponding to 58 protocols where both the PIL and the protocol communicate plans to use strategies

to promote participant retention. Table A6.4 shows all the plans to use strategies to promote retention in the protocols and their corresponding PILs.

Table A6.4: Communicate the same information regarding plans to use a strategy to promote participant retention	
PIL content	**Protocol content**
These follow up appointments will coincide with your usual regular clinic appointments	Patients will be assessed at 3 monthly intervals from baseline to 3 years in the patient's routine outpatient clinic visit as per the trial schedule of assessments
If you agree to take part in the trial, your hospital visits will be at the times when you would normally have hospital visits for your burn injury - There will be no additional hospital visits to make for the trial and all hospital visits will be at times when you would normally have appointments for your burn injury, as such, there will be no provision for travel expenses)	The fit and wear of the garments was checked throughout the trial at the routine clinic visits and garments were replaced as required. All participants were required to attend routine follow-up scheduled appointments
As part of your standard treatment for ITP, you will have regular blood tests and doctor or nurse reviews to check how you are getting on. This will be the same whether you chose to take part in this trial or not. There will be no extra doctor visits for the research trial and your usual visits will be used to collect information on how you are	Laboratory and clinical data will be collected from routine appointments
These visits can take place by telephone in order to minimise the number of visits needed to hospital, but you may be asked to attend in person. - You will also be asked to complete questionnaires about your health at the 6,12 and 24 month visits. As above, these may be done by telephone	This is standard follow up of these patients. In cases where it is felt to be a risk to bring patients to hospital for follow-up visits, you may conduct these visits by telephone;

We will send you up to two reminders and will aim to contact you by post, email and/or telephone, taking into account which communication method is best for yourself	At six weeks after surgery, participants will complete a questionnaire to measure Pain Numerical Rating Scales (NRS), time to return to normal activities and acceptability, EQ5D and SF12. At six months after surgery and at 15 months following randomisation, participants will complete the SF12, MMAS, EQ5D, satisfaction with treatment and questions about healthcare utilisation. Participants will receive up to two reminders by post, email or phone, taking into account any preferences they may have for mode of communication
We will also ask you to fill in some questionnaires about your experience either by phone or by post - We will either see you at one of your routine clinic appointments or telephone you to see how you are.	Study visits could be face to face or by phone or other means of communication, for example, via letter or email
If for any reason we were unable to follow up with you in clinic we may contact you by telephone to as about your wellbeing since you joined the study - We will do the study follow up within your normal NHS care	The 6, 12, 24, 36, 48 and 60-month follow-up is in person or over the telephone, according to local practice. If contact cannot be made with the participant then medical notes can be used
Any additional appointments at the hospital that you need to attend because of the study, for example– attending for extra out-patient appointments, you will be able to claim travelling expenses from the research team. -We will try to collect the study information when you come to your psoriatic arthritis clinic visits	Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate
the stitch is normally removed around 38 weeks of pregnancy or when labour starts	Plans to promote participant retention and complete follow-up: The trials team ensures that all outstanding data is queried monthly with all sites. Where babies are not delivered at the site in

	which the cerclage was performed, follow-up is facilitated through a continuing care site setup processes. - The trial is pragmatic in nature and requires no additional visits or assessments.
We may send you up to two reminders and will aim to contact you by post, email, telephone and/or text message, taking into account which communication method is best for yourself - On return of your 12 week questionnaire and again after the return of your final questionnaire (sent 12 months after you join the study) we will send you a love2shop high street voucher to thank you for completing the questionnaires. Please let us know if you do not wish to receive these vouchers -	Reminders may be used; for the earlier time points this may be a text message or email on the day that the questionnaire is due and, for the later time points (e.g. 12 weeks and 12 months), this reminder will be sent approximately 2 weeks and 4 weeks after the questionnaire is due. We will offer and use all methods of delivery and col lection of questionnaires and reminders including use of research teams for time points associated with hospitalisation, postal mail, email, web-based, telephone and SMS text, taking into account each participant's stated preferred means of receiving and completing the measures. Participants will be sent a voucher (of modest value) as a token of appreciation for completion and return of the questionnaire - We intend to maintain interest in the trial by publication of *[trial name]* newsletters at intervals for staff and collaborators [two PILs share this one protocol]
We may send you up to two reminders and will aim to contact you by post, email, telephone and/or text message, taking into account which communication method is best for yourself - On return of your 12 week questionnaire and again after the return of your final questionnaire (sent 12 months after you join the study) we will send you a token of appreciation for your time spent on completing the questionnaires. Please let us know if you do not wish to receive these vouchers	
Partially communicate the same information regarding plans to use a strategy promote participant retention	
PIL content	**Protocol content**
Please tell use if you would prefer to be contacted by phone, email or post -This study will fit into your usual care.	The participant will be asked to complete the questionnaires during the clinic visit (prior to other clinical assessments) or at home where

	required - **For forms completed at home, the patient will be provided with a pre-paid, self-addressed envelope which will be used to send the completed questionnaires to the [trial name] trial office.** Alternatively women may return completed forms to the [trial name] email account or, for the CSQ 8, **women may complete this electronically via SmartSurvey**. - **To reduce loss to follow-up, the local research team will record the NHS numbers of participants, to trace the participants via local GP practices and non-participating NHS trusts where necessary** - the trial is designed to fit in with routine hospital practice as far as possible, imposing minimal additional workload by keeping extra clinic-based tests and evaluations to a minimum.
We will collect most of our study information about your pregnancy and your baby from your hospital notes but we may need to contact you to check some details. Please tell us if you would prefer to be contacted by phone or email - This study will fit into your usual antenatal care, so that you will not have to make any extra hospital visit	Loss to Follow-Up **To reduce loss to follow-up, the local research team will record the NHS numbers of participants, to trace the participants via local GP practices** - The trial pathway fits within the current standard care pathway for women presenting with early pregnancy bleeding
We will post the paper questionnaire out to you about 1 week before your appointment so you can complete it at home and bring it with you to clinic .**Occasionally, we may contact you over the phone** - **For the intervention group only - You will receive reminders when your ePROM report is due. The reminders will be sent by text or email, depending on your preference**. - ALL participants **- We will reimburse**	This questionnaire may be posted out to participants prior to their scheduled clinic/research visit, but research staff will be on hand in clinic to assist with completion where required. - Since these measures are routinely collected for clinical monitoring, the results closest to the calculated visit due date will be used for trial data, rather than repeating tests which have already

your travel expenses (including car parking fees) for all study clinic visits - Whichever group you are assigned to, you will be closely monitored for the study by the kidney research team at the Queen Elizabeth Hospital every 3 months for 1 year. We would try to do this while you are already in clinic for your routine CKD appointment	been performed - very attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal
As a thank you for taking part in the study and for completing the questionnaires, we will reimburse you for your time on this study after you have completed the 6 month questionnaire	**To try to maximise follow-up rates, data will be triangulated with routinely collected data on initiation and feeding status at 6–8 weeks and women will be offered a £25 'thank you' voucher if they complete all the follow-ups**
We will ask you for your name, email address and alternative telephone numbers so that we can contact you to find a suitable time to conduct these questionnaires. In the event that we are unable to contact you, for example your contact details change, we may request further information about you from your Local Authority so that we can reach you - For your time and contribution to the study we would like to provide you with a **voucher worth £20** for each questionnaire you take part in as a thank you for taking part	We will make every effort to ensure retention. At enrolment, participants will be asked to provide alternative telephone numbers, email addresses and any other forms of communication that may be helpful to contact them. Researchers will endeavour to build a positive rapport with each participant for subsequent follow-up. Participants will also be emailed/posted vouchers as a reimbursement for their time after each questionnaire. **Finally, a third-party text messaging platform (Esendex) will be used to send text messages to participants to keep in touch, or remind them of their follow-up contact**
To remind you to complete the questionnaires, we will be collecting your contact details including your name, email address, telephone and mobile numbers, and address so that we can send you a link to the questionnaire either by email or text	Lost to Follow Up: Sites will contact patients for each visit in accordance with the procedure outlined in section 13.2. If patients are not able to be contacted after three missed regular (fortnightly or monthly) GOSE assessment, a letter will be sent out to

message. We may also send out a letter asking about your recovery if we can't get a hold of you or your study partner. We may also call you to ask you to complete it over the phone - We will also be asking someone close to you to act as a study partner. We will collect their contact details including their name, email address and telephone number and with your permission we will contact them in the event that we are not able to contact you after you have been discharged from hospital. We may also ask them to complete the GOSE questionnaire, on your behalf if you are unable to. - The study will not require additional hospital visits over and above the standard of care.	the participant asking them to get in contact with the trial team. Participants will not be contacted again until the 3-month, 12 month, or annual follow up occurs. Sites will record all details regarding attempts to contact the participant on the appropriate CRF. To minimise missing data, participants will be able to complete the primary outcome online or over the phone. In addition, contact details for participant's study partner will be collected and they will be able to complete the primary outcome on behalf of the participant (Patients will have the option of completing the GOSE online, or via the telephone - **Automated alerts will be set up to help patients complete the GOSE in the right time window**, and to inform the study team if this appears not to be happening. -**Once patients are discharged from hospital, they and their study partner will receive a reminder on the day before the GOSE follow up window starts and a reminder on the first day of the follow up window, that the GOSE should be completed** - If the GOSE is not completed on the correct day, the trial team will receive a notification and they will attempt to contact the participant by phone for 4 days (for fortnightly assessments) or 6 days (for monthly assessments), or until the assessment is completed
We will provide you with a £10 high street voucher each time you complete the package of questionnaires as a thank you. If two	Retention strategy To maintain engagement, encourage retention and to thank family caregivers for their time, primary carers will be provided with a £10 high street voucher

parents from each family take part in the study, the second parent will be given a £15 high street voucher as a thank you for each time the questionnaire package is completed - You will have the choice to complete these questionnaires yourself by post, or with a researcher during a visit to your home or over the telephone	when contacted to complete follow-up data collection, as has previously been shown to be effective [21]. **Contact details will be collected during recruitment, and participants will be reminded by email and text message when a data collection follow-up is due and to complete questionnaires when posted. Participants will also receive a study newsletter at approximately 9–10 months post randomisation to maintain participant engagement.** Participants will be offered three methods of data collection: via telephone, postal or face-to-face at a convenient location. **For non-responding participants, a minimum data set (consisting of 3 prioritised outcome measures (Warwick Edinburgh Well-Being Scale, EQ-5D and Parenting Sense of Competence Scale) aligning with the intervention logic model and taking into consideration participant burden) will be offered to reduce participant burden and maximise follow-up rates.**
The study team will telephone you to remind you to return your questionnaires.	In order to facilitate the process of patient recruitment and data collection into busy routine clinics, data collection can be conducted by any suitably trained clinician (nurse, health care assistant or GP) - Participants will be telephoned by the trial team 1 week after the due date to remind them to return the questionnaire by post **or to offer to complete these instruments over the telephone at that point. If the questionnaire is not received within 1 week of the first telephone reminder,**

	the trial team will telephone the participant again
However, we will provide you with a £10 high street voucher each time you complete the 3 and 12 month follow-up questionnaires as a thank you everyone taking part will be contacted approximately 4 months and 12 months after your initial home visit / recruitment group session by the research team to complete questionnaires, either by post or on the internet	To maintain engagement, encourage retention and thank foster carers, trial participants will receive a £10 high street voucher on completion of the 3 month and 12 month questionnaires. Contact details will be collected during recruitment and will be verified by provider agencies as the trial continues. **Participants will be reminded via text and email when a questionnaire will be posted to them and will also receive a newsletter updating them on study progress at 9 months post-recruitment. Participants who do not respond to postal follow-up will be contacted with the offer to complete their follow-up questionnaires via telephone if they wish.**
You will receive a gift voucher at the follow-up consultations to say thank you for taking part, and any travel expenses will be reimbursed	**Follow-up assessments will be carried out either by telephone or in person at approximately 2 and 6 months**. The schedule of enrolment, interventions and assessments is shown in line with the SPIRIT 2013 recommendations in Fig. 2 [24]. Participants completing follow-up assessments will be given incentive vouchers to encourage them to engage with follow up.
You will not be paid any expenses for your involvement in this study**, however a five pound gift voucher will be sent to you with your 18 month questionnaire** - these can be completed and returned by post or completed on your computer or smart phone (you can pick your preferred option)	Plans to promote participant retention and complete follow-up {18b} Active measures to minimise loss to follow-up of women include: 1. Recording at the outset women's email addresses and mobile phone numbers, their preferred method of contact (for follow-up contact) and

	their preferred method of completion of questionnaires. Questionnaires can be completed online (via an email link) or in paper format and returned by post. 2. **Participants who do not return their questionnaires within 3 weeks will be sent up to three reminders using a variety of methods (post/email/ text message dependent on participants preferred method). The third reminder will be by telephone where the researchers will aim to gather, at a minimum, the primary outcome data during the call**. 3. Response rates to the self-reported questionnaires will be monitored to ensure they remain above 80% (the level assumed in the sample size calculation). If response rates are seen to drop, the team will discuss appropriate actions with the project management group. Relevant action may include phone calls at different times of day or asking women to only complete the primary outcome measure.
You will be asked to send the questionnaires back to the study office, in the prepaid envelope provided. - When we receive your completed 15 month questionnaire, we will send you a token of appreciation for your help. If you don't want to receive this gift, please let us know on the consent form. - You may be sent this questionnaire by post (or email if you prefer) to complete at in the convenience of your home -	Plans to promote participant retention and complete follow-up {18b} **We offer and use all methods of delivery and collection of questionnaires and reminders including use of research teams for time points associated with hospitalisation, post, e-mail, web-based and SMS text, taking into account each participant's stated preferred means of receiving and completing the measures** (recorded on the participant contact preference

	form). **We will send up to three reminders to participants by post, email, phone or text message, taking into account any preferences they may have for mode of communication.** **We will send a small token of appreciation (gift Voucher (s) of modest value up to £15**) to participants on receiving their completed follow-up questionnaires, unless they opt out on the study consent form.
Everyone in the study will also be sent questionnaires by post at approximately 3, 6, 12, 18, 24, 30 and 36 months **after you join the study up to two reminders may also be sent if we don't hear back from you....A self-addressed envelope will be provided for your convenience** – As part of this study, we will perform assessments at the same time of these check-ups	Data will be collected from the following routine visits; 3, 6, 9, 12, 18, 24 and 36 months post initial TURBT (or second TURBT if required).
We will provide a FREEPOST envelope for return of the annual questionnaires to the *[trial name]* Study Office, a reminder letter may also be sent if we don't hear back from you. It is estimated that each questionnaire will take approximately 15 minutes to complete but you can take as long as you need. We realise completing the questionnaire will take a little time and to recognise this we will provide all participants a £25 gift voucher at the start of the trial and another £25 voucher at the end to thank you your support - We in tend to maintain interest in the trial by publication of newsletters at intervals for staff and collaborators. - At the first visit your dentist will examine your teeth and	All participants will be given a £25 gift voucher at the start of the trial and another £25 voucher at the end in acknowledgment of the time that participation in the trial will entail and to thank them for their support.

gums to record information about your dental health. Every effort will be made to include this as part of your routine dental check up	
If you agree, we will send you a text message reminder 48 hours before surgery to undertake these tests. - At 4 weeks after the operation you will complete the last section of your paper diary and send the completed diary by pre-paid post to the Study Office in Aberdeen - The local research team will provide you with a baseline questionnaire which can be completed in the hospital or in the convenience of your home and returned in the pre-paid enveloped provided. - On return of your 3 month and yearly questionnaires we will send you a token of appreciation for your time spent on completing the questionnaires. Please let us know, on the consent form, if you don't wish to receive such a token.	**Questionnaires and up to two reminders will be sent to participants by post**. **Non-responders to the 12-month post randomisation questionnaire will be contacted by phone for a short interview to capture the primary outcome** - **participants will be sent a voucher (of modest value) as a token of appreciation for completion and return of the 3-month and follow-up questionnaires** - participants will be sent the follow-up questionnaires directly from the Study Office in Aberdeen and asked to return the completed questionnaires in prepaid envelopes - We intend to maintain interest in the study by publication of *[trial name]* newsletters at intervals for staff and collaborators
Every week for the 12 months of the trial we will send a reminder via the app, asking if you have had a fever or respiratory symptoms since the last time you responded - The blood collections at 6 months and 9 months may be done by self- administered finger prick blood spots with kits provided to you by the study team. This means you could collect the sample at home yourself instead of at a site study visit. If this is your preferred way of providing your sample we will also ask you for your home address so that we can mail the in-home collection kits to you -	Participants will be asked weekly if they have been unwell since the last contact using a smartphone application designed for the trial (Trial Symptom Tracker, WeGuide) **and/or by contacting the participant by telephone, text message or email**

Two questionnaires will be sent through the post. They will ask you your views about your health and quality of life. **Please send them back in a pre-paid envelop** - **They can be done in one day or divided over a few short visits If you have left hospital we can travel to see you in a convenient place for you.** The test will be - arranged on a day(s) which suits you - We will reimburse mileage or public transport costs for any research visits	Trial participants are not paid to participate in the trial but are paid travel expenses for the follow-up visits. - As there is a low number of participants to be recruited, the trials unit are able to liaise regularly with each site following randomisation to ensure all follow-up data are collected
Travel expenses will be provided for attending additional visits to increase the dose of telmisartan - We will try to arrange the study visits at the same time as your clinic visits	Follow-up visits will be designed to fit with routine hospital visits where possible. The study will also allow a 2 week window on either side of the scheduled follow-up visit date to ensure flexibility. **Individual patients will be sent reminders about follow-up visits by the research nurses provided they have agreed to receive them**. If any of the trial patients are lost to follow-up, contact will be attempted through the research nurse and lead investigator at each centre
We will ask you to give us multiple forms of contact (e.g. email, mobile / landline, and postal address) so that we can contact you for follow-up assessments and check you are the same person - Only for the intervention group - We will send reminders to visit the website over the following 24 weeks (you can opt out of this if you wish	**Twelve and 24 weeks after randomisation, all participants are sent an email reminder to complete the follow-up measures**. At 24 weeks, the email content will vary depending on whether participants have been randomised to either £10 or £20 reward and to the reward being conditional (ie, dependent on completion of follow-up questionnaires) or unconditional (ie, offered with the initial request for follow-up data). To maximise follow-up at the primary outcome point we will:

	1. only randomise participants once baseline assessment measures are completed 2. include detailed explanations in our recruitment materials to explain to participants why data completion at follow-up is so important 3. require email, telephone and postal contact details at registration so we have multiple methods of contact for follow-up **4. send participants up to three automated email reminders at 5-day intervals, followed by text, telephone and/or postal requests** **5. incentivise completion of follow-up measures by paying participants shopping voucher(s) at each time point.** To increase overall acceptability and participation rates, we will inform RD participants that they will be able to access toolkit modules after the final follow-up.
You will do it during a face-to-face appointment with our researcher. This appointment will last about one hour and happen at a time and place that is convenient for you - We do not expect you will have any expenses from taking part in our study. **If needed, we can pay for a taxi to take you and your family member or friend to and from the course.** We will also provide refreshments for you. All participants will receive a £10 shopping voucher for each of the questionnaires they do by post or in person. This is to thank them for their time and effort. Therefore, each person who takes part in our study can get up to £30	A number of evidence-based strategies were used to maximise retention of participants in the trial. This included patient and SO participants receiving a £10 shopping voucher after each follow-up assessment that they completed and delayed access to SAFE for the TAU arm. **Unless a participant formally withdrew consent to participate in the trial, HES data on them were requested and up to three attempts were made to contact patients or SO participants each time a follow-up assessment was due. The research worker also contacted participants by telephone**

	approximately 2 weeks after the 6-month questionnaires were posted. When a patient participant did not complete a follow-up assessment, an attempt to monitor SAEs was made by sending their GP a letter asking them to inform us if the patient was no longer alive and the circumstances of death
We will offer you £5 as compensation for your time at each follow up: for the 1 month questionnaire and the 12 month questionnaire. You will be compensated for your time for returning your 12 month sample.	At 4 weeks and at 1year, postal questionnaires will be sent to all participants to collect self-reported data. **Non responders will be contacted by any method the participant agrees to at enrolment (post, email, text message, telephone call).** Participants can directly enter self-reported outcome data via a web-based data entry form. Paper based self-reported outcome data or self-reported data collected by telephone will be directly entered into the web-based data entry form by a trial assistant blinded to treatment allocation. Participants will be sent a £5 unconditional incentive with each postal request, that is, when sending the 4 weeks questionnaire and 1year test and questionnaire. **Participants who return the test sample will be sent £20.**
So we know how you are getting on we will also send you a questionnaire, this questionnaire will take approximately 30 minutes to complete. There will be an option to complete this questionnaire online.	- each woman will be sent a postal or online questionnaire (as preferred by each woman) for col lection of data on secondary outcomes. **Text reminders for completion will be sent as appropriate, with the option for telephone completion in the event of a delayed response to ensure a high response rate.**

You will not be compensated for your involvement in this study but **reasonable travel expenses to the hospital for any appointments that are outside of routine care can be reimbursed.** The local research team will provide further details about this - Whichever treatment you receive, you will be asked to complete an email or paper follow up questionnaire at six months; twelve months and eighteen months after warhysiotherapy or surgery - All patients participating in this study will attend follow up visits and be monitored at their local hospital as they would normally	Follow up for study purposes will be by patient self-reported questionnaire completed using a web-based data collection system. The option of being able to fill out the follow-up questionnaires in a hard copy and returning via post will also be available. Non-response will be minimised through use of multiple reminders such as web-based messages, phone calls and texts
We ask that you complete and return this to the Research team in the stamped addressed envelope provided. We will remind you with a letter and via telephone if you do not return your questionnaires. - **Travel expenses for your research appointments will be refunded by the Research team. We are not able to pay travel expenses for your physiotherapy treatment** -	All participants are invited to attend a face-to face clinic appointment at 6 and 12 months. This is arranged by the researcher at each site. However, if a participant is unable to attend the clinic appointment, they are mailed a questionnaire that contains the primary outcome, all self-reported items and a participant completed version of the Client Service Receipt Inventory, but excludes the physical assessment. If the questionnaire is not returned within 2weeks, then a second copy of the questionnaire is sent by the *[trial name]* Trial Office as a reminder. If this is not returned within a further 2weeks, then the *[trial name]* Trial Office carries out a reminder phone call. **After another 2 weeks, if the questionnaire has not been returned, then the *[trial name]* Trial Office will attempt to contact the participant by telephone and collect core outcomes consisting of the primary outcome (ODI), pain**

	troublesomeness rating, whether they are on a waiting list for spinal surgery, EQ-5D-5L, self-rated walking ability, falls and falls-related fractures, self-reported exercise adherence, and a brief version of the Client Service Receipt Inventor
Reasonable travel expenses to study-specific appointments can be reimbursed. - you can choose to complete these online or by post. The research team in your hospital will have access to your answers. We may get in contact by post, email or phone to remind you to complete the questionnaires	These will be posted or emailed by the Clinical Trials Unit and can be completed by post or online. **If participants do not respond within 2 weeks of sending the questionnaire, a reminder will be sent. Following this, if still no response, the central trial team may telephone the participant to collect the required data.** - Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate. **Participants attending focus groups will receive a £20 shopping voucher to thank them for their time and participation, in addition to travel reimbursement as above**.
If for any reason you miss your clinic appointments or do not respond to our postal questionnaires we will contact you by phone on a maximum of 2 occasions. We can then post the questionnaires for you to complete and return in the stamp addressed envelope provided. You will not have to make any extra visits to your doctor or the hospital over and above those needed for your normal care - -**All postage will be pre-paid** - you will not be asked to attend any appointments which you would not have to for your regular clinical appointments as we will	Data will be collected alongside routine clinical appointments at each site - Data will be collected from participants at 6 and 12months (if applicable) from date of surgery with a target of ±1month, at their routine NHS check-up appointments. If participants do not attend their follow-up appointment, they will be contacted by telephone, and, if appropriate, sent the questionnaires to complete. The study team will attempt to telephone these participants on up to two occasions. If these methods fail, we will categorise the participant as a

aim to schedule these alongside your clinical appointments.	'nonresponder' for that time-point only - Follow-up data collection via telephone, and postal questionnaire data collection options have been added to minimise the need for participant hospital attendance. The study team will attempt to contact these participants on up to two occasions to remind them to complete the questionnaires. If these methods fail, we will categorise the participant as a 'non-responder' for that time point only. Qualitative data will now be collected using telephone interviews for all group
We can reimburse some travel costs if these are additional to your routine medical care travel. - and you will be asked to complete them on-line (a paper version is also available).You will be sent e-mails and text reminders to complete these, or reminders in the post if you have chosen to complete paper versions. -A member of the *[trial name]* team may contact you by telephone (up to a maximum of 5 times over the 6 months that you are in the trial) if you have not completed these questionnaires and to see if you require any assistance. - **We would normally expect all trial visits to coincide with routine standard care. If you do incur any additional parking expenses for travel, please talk to the research team about completing a claim form**	Loss to follow-up: If a participant moves from the area, every effort should be made to follow the participant up at another participating trial site and for this new site to take over the responsibility for the participant. If a participant is lost to follow-up at a site, every effort should be made to contact the participant's GP to obtain information on their current status. - Those participants who state at recruitment that they cannot or do not wish to complete these questionnaires online will be sent the paper version by the *[trial name]* trial office and requested to complete the questionnaires and to return them in a prepaid envelope. - participants will be requested to complete PROM questionnaires and resource-use diaries electronically using LimeSurvey every week and every 3 months, respectively. A paper version will also be available for participants to complete, which can be returned using prepaid

	envelopes. Text messaging and email reminders to participants (who have consented to provide their telephone numbers and email addresses) who have not returned the completed PROM questionnaires and resource-use diaries will be used to maximise the completeness of the data. The *[trial name]* trial office may also call participants if there are a number of outstanding PROM questionnaires and resource-use entries not completed by the participant
Do not communicate the same information regarding plans use a strategy to promote participant retention	
PIL content	**Protocol content**
Patients will be reimbursed for any additional travel costs incurred from trial related visits to the hospital (outside of standard medical care). To claim, please contact your local researcher - additionally those in the control group have choice of phone data collection for follow up if they do not need to attend the clinic for another reason	The questionnaires can be filled in online. For this a personal email with the invitation and access code will be sent to the patients by mail. Patients not willing or unable to complete the online questionnaires will receive identical paper questionnaires at their home address, accompanied by a free return envelope.
Most of the treatment you will receive will be the same whether you were in the study or not but you will also be asked to complete a questionnaire about your quality of life before you have your treatment, and 1, 6, 12, 24, and 36 months after wards	Appropriate strategies to promote participant retention will be considered and implemented by the Trial Management Group (TMG) as required.
Filling out the diary will take about five minutes at the end of each day. This can either be on paper form or over the internet. We will send you a brief text message or phone you every week to remind you complete this. - Reasonable travel	Every attempt will be used to collect full follow-up data on all women. In particular, participants will continue to be followed up even after protocol treatment violation. It is thus anticipated that missing data will be minimal

expenses will be reimbursed for all research visits	
You will be asked to complete these, and then post them back to BCTU in the freepost envelope they will send you	participants will be sent a newsletter thanking them for their support and informing them of the trial results
Although you will not be paid to take part in the study, we will cover your expenses to attend study visits	All patients in the RCT and cohort study will be contacted every 6 months by phone to enhance follow-up rates and to collect data about any new relevant developments and ensure continuation of consent and patient safety.
We are unable to pay you for participating but we will reimburse your travel expenses to and from the hospital for all visits	In the event of participants being unable to attend for scheduled visits because of other intercurrent issues, they are asked to attend at the closest possible date, whenever possible within 2 weeks of the due date. Where a participant cannot attend their week 40 study visit and investigations, they are asked either to undertake this visit up to 3 weeks before the due date or, alternatively, to continue the study medication until the scheduled investigations can be undertaken (whenever possible within 4 weeks of the planned date)
The Sponsors of this study (Imperial College London) will pay your hospital to cover the costs of your participation in this study. Yes - You are able to claim the travel costs (e.g. bus / train / tube fare or parking costs and petrol) of your hospital visit for your scan at 2 to 3 weeks following your surgery	Telephone or online review (according to patient preference) will be performed 1 week after surgery or at discharge, and at 90 days - Routinely scanning patients only once reduces cost, and limits the time and inconvenience to the enrolled study subjects (ethical consideration, improve recruitment, and reducing drop-outs and loss to follow-up)
Whenever you visit the hospital for a visit that would not be part of your normal routine care (This will happen during your maintenance treatment)	All efforts should be made to contact the patient's GP to assess their condition, if a patient fails to attend a clinic or cannot be followed up at site.

you will be able to claim £5 towards your travel expenses - Most of your visits and assessments will be as you would have in routine care if you weren't taking part in a trial (However some visits and assessments are additional)	
We will offer you a total of £20 in vouchers as a thank you for taking part. We will offer £10 for completing the first set of questionnaires and another £10 when you complete the third set of questionnaires at 12 months - Initial postal questionnaire sent with a pre-paid return envelope	all participants will be provided with study progress updates at 3 and 9 months via a newsletter to maintain engagement with the trial and encourage response rates of follow-up questionnaires. The newsletter does not provide any detail on the *[trial name]* intervention - All participants complete self-reported outcome measures in the form of questionnaires (IPSS, ICIQ-UI-SF,EQ-5D-5 L and B-IPQ) at baseline (postal), 6 and 12 months (postal, online or phone) post enrolment. Participants are sent one reminder to return their baseline materials, and up to three reminders to return their 6- and 12-month questionnaires.
The sponsors of this study will pay [enter name of hospital department]to cover the costs of your participation in this study - - You will have one additional hospital visit at 6 weeks for assessment of your ulcer. Other than the 6-week leg ulcer clinic visit, the number of appointments is the same as treatment for your ulcer outside the study	Similarly, efforts will be made to obtain complete follow-up for all randomised participants (irrespective of whether or not they underwent allocated treatment). For those participants unable or unwilling to attend follow-up appointments, home-visits or follow-up by community nurses may be considered
We would be very grateful if you would complete them and post them back in the provided prepaid envelope. *[not communicated in the other corresponding PIL]*	Patients will be followed up as per routine clinical practice and typically at 3, 6 and 12 months and annually thereafter. Patients may be seen at other times as clinically indicated.

Study visits will take place every three months and should normally be scheduled to take place at the same time as your normal hospital visit	Scheduled study visits are designed to fit with routine hospital visits where possible. - If any of the trial participants are lost to follow up contact will initially be attempted through the PI or delegated research staff at each centre. If the lead investigator at the trial centre is not the participants usual clinician responsible for their specialist care then follow up will also be attempted through this latter clinician. Where these attempts are unsuccessful, the participants GP will be asked to contact the patient or the participants' family to provide follow up information to the recruiting centre. This information will be included on the Patient Information Sheet. Wherever possible, information on the reason for loss to follow up will be recorded.
Completing 6 short questionnaires on your muscle symptoms every 2 months. There are a few ways in which you can choose to complete the questionnaires; via the web, verbally over the phone, mobile phone app or conventional paper form -	In the seventh week of each 2-month treatment period, participants will receive reminders to alert them that follow-up data collection is approaching. Symptom scores on the VAS will be collected daily in the eighth week of each treatment period. Participants can choose to receive daily reminders on each day their data is due to be collected. Non-responders will automatically receive a reminder from the trial team after 24hours of the due date
The study can pay you back for all reasonable costs for travelling to your study appointments (e.g. car parking and petrol or other transport costs). Please make sure to ask at the clinic	For participants who become unwilling or unable to attend study clinic visits, local research staff telephone the participant (or interview their local doctor or relative). All efforts are made to continue to follow up such participants, with those being followed

	remotely encouraged to continue to provide central blood samples
we will reimburse reasonable expenses for travelling to your *[trial name]* appointments. Please make sure you ask about this at the clinic. Taxi travel can also be provided if needed	Patients will be asked, if willing, to provide details of a friend or relative living at a different address who may be contacted in the event of loss of contact. They will also be asked their preference for receiving questionnaires (by email or telephone) and email addresses will be recorded. - Trial-specific questionnaires will be administered either electronically (for completion on participants' own computer) or by telephone (according to the preference of the participant) while EQ-5D and VFQ-25 questionnaires will be administered electronically, by phone or on paper at set intervals as detailed in section 4.7. The *[trial name]* trial website will provide information regarding the progress of the trial and newsletters will be sent to participants updating them about the progress of the trial - Failure by participants to complete electronic questionnaires will result in emailed reminders being sent, followed by LCC research nurses undertaking telephone follow-up if there is still no response.
We are not able to pay travel expenses for you to attend your follow-up sessions, however any research questions asked will be as part of your routine out-patient follow-up appointments, via email, or over the telephone	Data will be collected from participants and proxies via questionnaires and CRFs that will be returned to the central trial office in Oxford, via post using a pre addressed freepost envelope, NHS email as appropriate or directly into an online secure database
if you were required to attend any additional visits, travel costs for these would be reimbursed. All postage and telephone costs will be pre-paid	Questionnaires will be sent to participants by post from the trial office and returned using a pre-addressed, prepaid envelope. If participants have

	not responded within 14 days of posting, the trial team will attempt to telephone the participant on up to two occasions to remind them to complete the questionnaires. If required, a second postage of the questionnaires will be provided if requested by the participant during these follow-up telephone calls. If participants wish not to complete the questionnaires, they will be provided with the opportunity to complete the UCLA Activity Scale and EQ-5D-5L questionnaires over the telephone. If these methods fail, the participant would be categorised as a non-responder for that time point only. In an effort to find evidence-based techniques to improve retention and recruitment to RCTs, a study within a trial (SWAT) will be undertaken. This will examine whether there is a difference in questionnaire response rate by printing the UCLA Activity Scale on pink rather than white coloured paper at the 6month time point. Results of this SWAT will be reported separately to the 'host' trial.
Visits would be held at your school/college unless you leave school during the study, in which case we will arrange follow up visits in the community	Meningitis Now provided funding for a prize draw to facilitate participant retention.
You will not be paid for taking part in this trial. However, we will reimburse you for any travel expenses you incur for visits resulting from your participation in the trial, as by participating in the trial, you will be asked to attend more clinics at your GP surgery. If independent travel is difficult for you and might preclude your	Where questionnaires are not validated for use on a tablet computer, or where individuals are not comfort able using one, paper copies will be made available for completion

participation in the trial, you can contact the trial team directly who will discuss alternative arrangements for travel with you	
Your *[trial name]* appointments will be planned at the same time as your usual appointments. If this is not possible, we can carry out these over the phone or pay back any additional travel expenses	participants will be contacted at around 8 weeks postdelivery and asked either in person/over the phone/by post/or via email to complete patient questionnaires and arrange for collection of the loaned BP monitor if not returned
You will receive £40 in shopping vouchers for completing the study	At 3 and 9 months post-baseline all participants are posted a questionnaire booklet and a freepost envelope to return the completed booklet to the CTU. A £20 shopping voucher is mailed to participants on CTU receipt of the completed booklets at both 3 and 9 months. To increase response rates, motivational postcards are mailed to participants before the follow-up questionnaires are sent out. Up to two reminder letters are issued (and a further three telephone calls as required) to remind participants to return the questionnaire booklets, and the option of the participant telephoning a member of the research team to aid completion of the booklets is offered. Participants are given the option to just complete the key questions about smoking behaviour if the questionnaire booklet is not returned to the CTU within 2 weeks and to submit these responses by email, phone or text if preferred to maximise follow-up data on key outcomes. - , and a freepost return envelope to be sent to the CTU. To maximise data

	completeness, participants scheduled to receive an accelerometer were sent a standardised letter from the CTU, 2weeks before receiving the accelerometer, advising them that they would shortly be receiving the device, and asking them to inform the CTU if they were unable to wear it. A letter was sent to participants who did not object to wearing the device, 3 days into the 10-day recording period prompting participants to start wearing the device if they had not already done so. Up to two reminder letters and a follow-up phone call were made to participants if they did not return the accelerometer.

Mention of Patient and Public Involvement in the PILs

In terms of Patient and Public Involvement (PPI), 7.6% (n=7/92) of the PILs communicated that there was PPI involvement in the trial.

Table A6.5: Mention of PPI involvement in the trial in the PIL	
	Number of PILs (% out of 92 PILs)
Yes	**7 (7.6%)** **Examples from PILs** "A group of patients and members of the public helped to develop this research topic and the research questions that should be asked. The group helped to design the study and develop this leaflet. They will continue to be involved throughout the study". "A Patient and Public Involvement (PPI) group have contributed to the design of the trial and will continue

	to be involved throughout the study, overseeing the study progress". "Our study team includes *[disease specific charity]*, a charity that supports patients and families". "People with *[disease]* and their carers are part of the study team" **Note:** These 7 PILs correspond to 7 protocols of which 5 report PPI involvement (71.4%)
No	85 (92.4%)

Abbreviations

Clinical Trial Units (CTUs)

Online Resources for Research in Clinical triAls (ORRCA)

Participant Information Leaflets (PILs)

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

Patient and Public Involvement (PPI)

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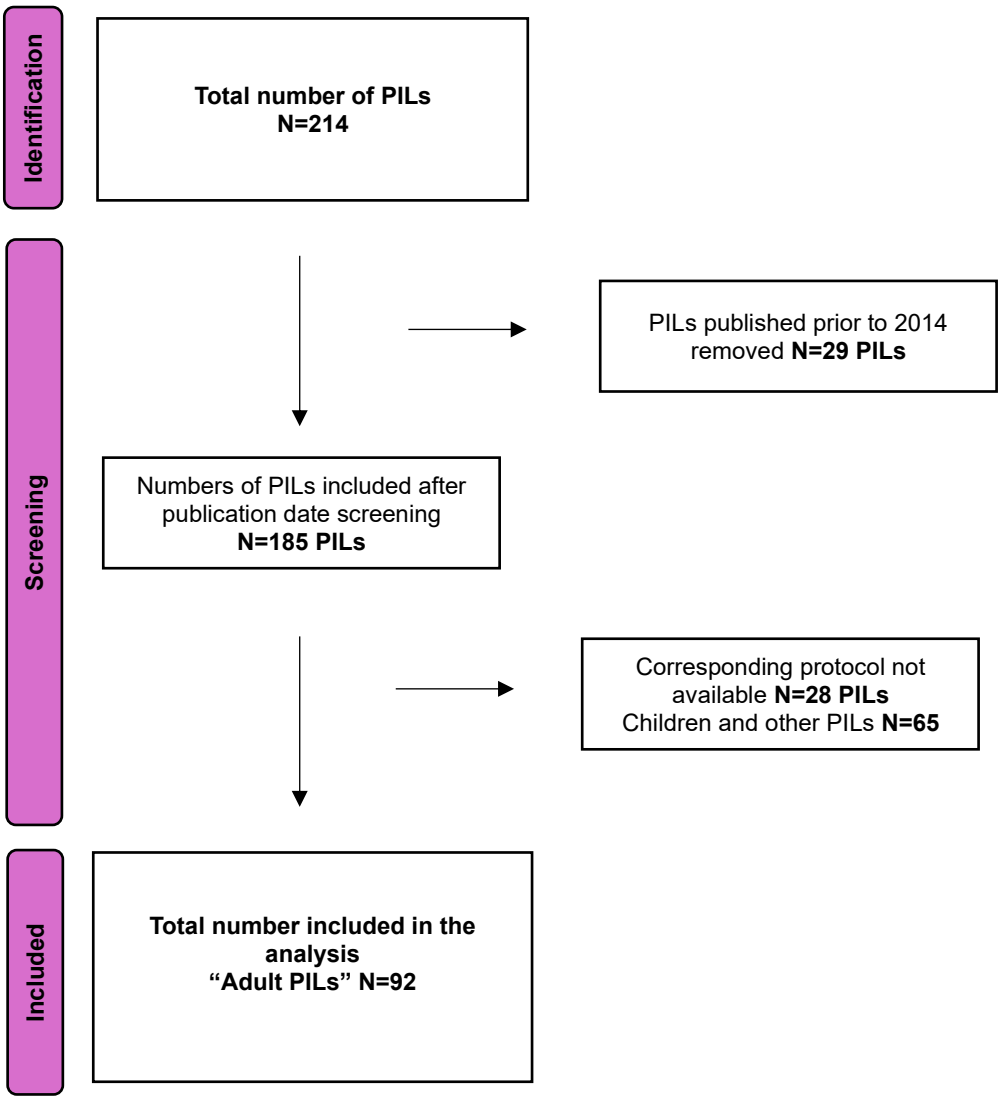
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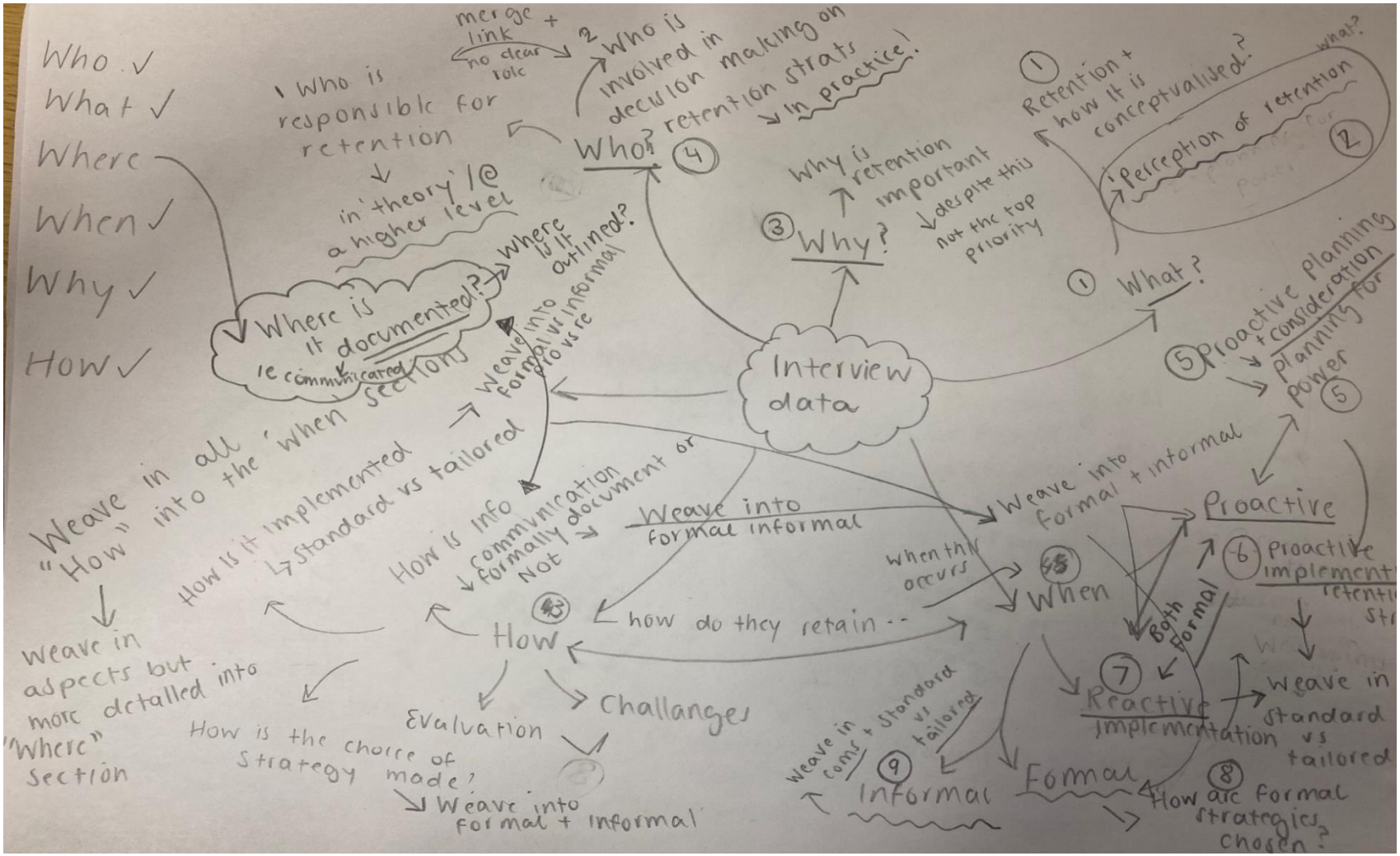
Appendix 8. Thesis Chapter Six. Figure A6.1. The PRISMA Flow Diagram.

Figure A6.1. PRISMA Flow Diagram. Flow Diagram showing the number of participant information leaflets at each stage of the screening process.

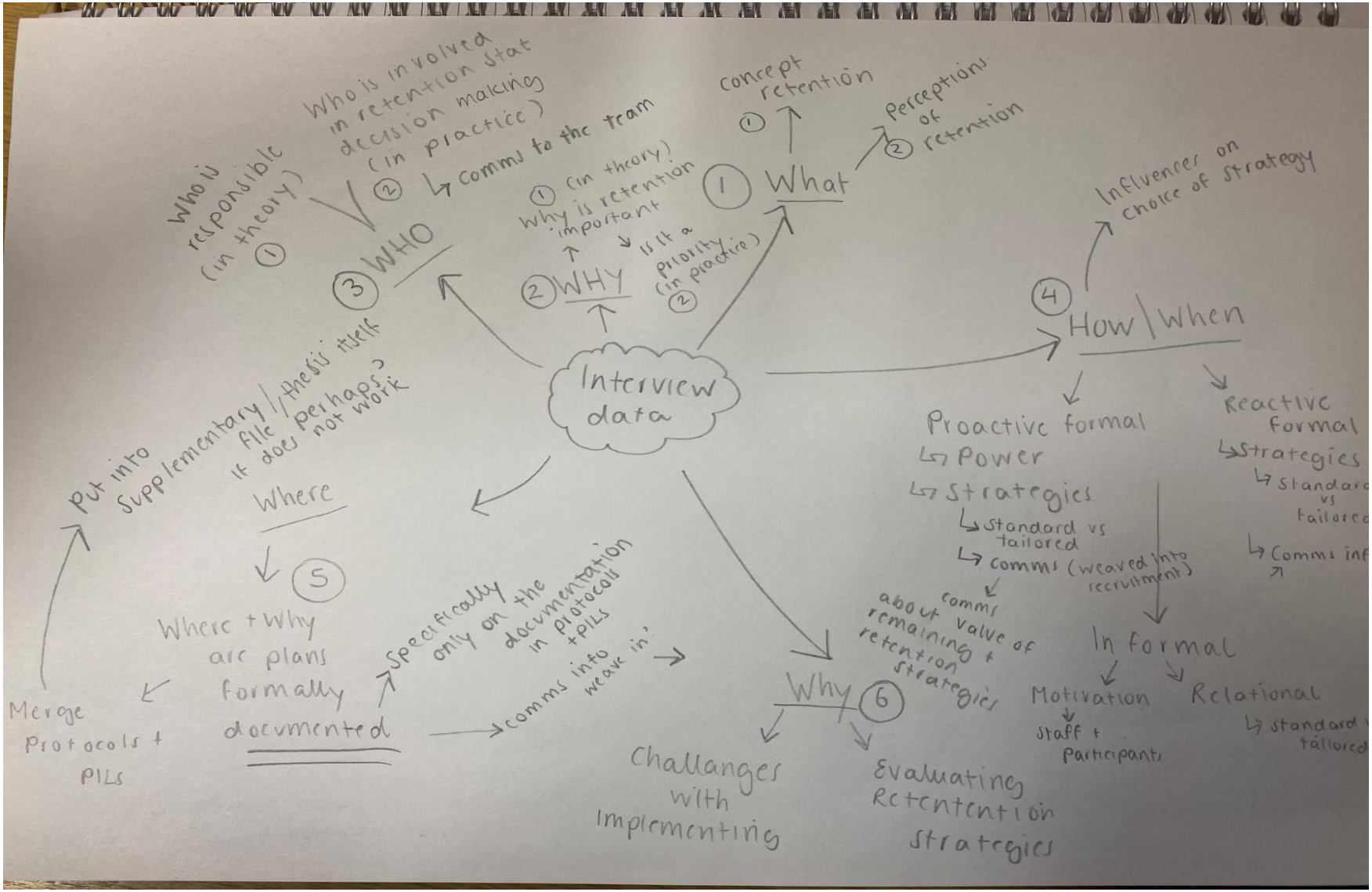


Appendix 9. Thesis Chapter Seven. Illustration of coding brainstorm.

Coding Brainstorm 1



Coding Brainstorm 2



Appendix 10. Thesis Chapter Seven. Supplementary File 3. Framework matrix.

Note for the submitted manuscript only aspects of the matrix for themes presented in the paper were submitted, the full version of Framework matrix for the thesis chapter in its entirety is presented in this appendix.

Abbreviations

Trial Manager; TM

Research Nurse; RN

Study Co-ordinator; SC

Principal Investigator; PI

Clinical Trial Monitor; CTM

Co-Investigator; Co-I

Clinical Trial Unit Director; CTUD

Head of Trial Operations; HTO

Clinical Trial Practitioner; CTP

Table A7.1. Retention conceptualisation, perceptions, importance and priority

Interviewee	Conceptualisation of retention	Perceptions of retention	Is retention important?		Is retention a priority?	
			Yes	No	Yes	No
12TM	Keeping participants involved and engaged and completing follow-ups	✓ Comparing to attrition rate	✓			✓ Gets overlooked at the start but sometimes it is a priority depends on the team
13TM	How much data can we collect for participants engaged in the trial	✓ Comparing to other	✓			

		research in the field				
16TM	How many remain but not only remain but getting data from	✓ Comparing to attrition rate	✓			✓ Believes most prioritise recruitment but their view is the opposite
20TM	Procedures in place to keep participants in the trial	✓ Based on monitoring follow-up outcome assessment completion	✓			✓ Not a priority from the outset of the trial – when problems occur
2TM	Maintaining engagement to get the primary outcome and maintaining the relationship with participants	✓ Compared to attrition but also length of follow-up and population (elderly, expected greater deaths)	✓			✓ Over emphasis on recruitment – incentives towards recruitment
3TM		✓ Monitoring follow-up rates	✓			✓ Recruitment is priority
4TM	Participants stay in until the end and get all the follow-up data – also adhere to the interventions	✓ Length of follow-up – longer you expect poorer retention	✓			✓ Recruitment is the priority
5TM	Keep them engaged and responding to questionnaires	✓ Opinions of senior trial staff	✓			✓ Recruitment priority – build in retention to sample size and compensate for it
6TM	Keeping participants engaged and also sites and remaining on the intervention		✓			

7TM	Did we get a primary outcome for the participant and are they still engaged	✓ Comparing to attrition rate	✓		✓ Yes from a TM point of review but not from a site view – but there is more of a focus on recruitment due to money for sites to recruit	
17RN	How to encourage people to stay in the trial and be in for the long haul		✓			✓ More emphasis on recruitment but thinks retention needs to be prioritised
18RN	Getting participants who are fully informed and staying on the study as per the protocol	✓ Comparison to rate for going full scale trial	✓			✓ More emphasis on recruitment but thinks retention needs to be prioritised
10SC	Staying in the trial and completeness of the data	✓ Comparing to attrition rate	✓			✓ Recruitment focus, retention prioritised if it is not performing well
14SC	Retaining people in the trial and ways to do this	✓ Comparing to attrition rate	✓		✓ Unsure but believed they prioritised in their trial	
1SC	One the patient is involved to keep them involved in throughout the study		✓			✓ Underestimate importance of retention
9SC	Not losing participants to follow-up	✓ Comparison to attrition rate	✓			

8PI	Retention of participants and retention of data – keeping them in so minimal loss to follow-up		✓		✓ Think they have a good level of retention prioritisation within their trial	
21PI		✓ Depends on the study design, more loss expected in decentralised studies	✓			
24PI	Maximising participation in the trial throughout and anything that can be done to achieve that	✓ Constantly monitoring follow-up rates	✓			✓ Recruitment and intervention adherence are priorities over retention – once recruitment is finished retention is focused on (but they have strategies planned and to be implemented from the outset)
11CTM	Staying in the trial, collecting as much data as possible while protecting their right to withdraw		✓			✓ Not sure, depends on the trial team
15Co-I		✓ Comparing to other trials	✓			✓ Recruitment and intervention adherence are priorities over retention
19CTUD	Entering and staying in until the last visits/study is completed		✓			
22HTO	Stay in until they meet discontinuing withdrawal criteria	✓ Experience and own comfort levels	✓			✓ Not enough value placed on retention

		with retention rates				
23CTP	Completing all visits all the way to the end of the trial	✓ Let's the main site deal with this and inform	✓			✓ Focus on recruitment due to funding

Table A7.2. Retention responsibility and who is involved retention strategy decision-making

Interviewee	Who is responsible for retention	Who is involved in retention strategy decisions
12TM	✓ Trial office and site staff responsible	✓ Project management group or in-house team; TM, CU, stats, co-applications, PPI – not as much the sites only when problems
13TM	✓ All stakeholders from the top down	✓ Trial Management and Steering Committee
16TM	✓ Trial team and particularly data co-ordinator	✓ Whole trial team, PPI, if problems site staff involved
20TM	✓ Trial office and site staff responsible	✓ Trial Management team
2TM	✓ Ultimately the CI, but everyone who interacts with the participants is responsible for retention	✓ Trial Management team, TM, Co-ordinators, steering committee input perhaps and PPI – thinks sites would be beneficial to include
3TM	✓ Trial and site staff but more site staff role in retention	✓ Trial Management team, PPI, - not site staff despite important role in retention because otherwise too many involved in the decision
4TM	✓ Ultimately the CI but also some responsibility with CTU staff, site staff very important role in retention	✓ CI and Trial Management team, PPI
5TM	✓ Everyone is responsible for retention but in reality thinks most lies with the trial unit staff and site staff	✓ Senior Trial Manager, Research Managers writing the protocol, PPI, data co-ordinator
6TM	✓ Trial Manager and team	✓ Senior Trial Managers, CI, Co-investigators, Data Manager
7TM	✓ Trial Manager and team with site staff at a level removed	✓ Trial Management team, PPI
17RN	✓ Everyone who is in contact with the participants, everyone involved in planning and implementation of the trial	✓ Depends on study set up, main site/outside sponsor vs in-house trial influences who makes the decisions on retention, even when get protocol from sponsor they have a in-house approach

18RN	✓ Ultimately the PI but in reality people on the ground doing the day-to-day trial work	✓ Research Nurse and Research Assistant running the study with PPI input – inherited a protocol and adjusted as much as possible to make it work
10SC	✓ Ultimately CI, but supported by the trial management team – site staff step removed not involved in retention	✓ PI and Trial Manager decided retention strategies but had input from whole team, PPI, co-investigator, stats.
14SC	✓ Depends on how the trial is run but feels it is the trial management team especially felt personal responsibility as a co-ordinator doing the follow-ups	✓ Trial team; TM, CI, core team members, PPI, unsure about site staff
1SC		✓ PI/CI, and trial management team, PPI, think site staff should be involved
9SC	✓ Entire trial team – office and site staff but perhaps more so with people on the ground	✓ CI, steering committee, PPI, Management team
8PI	✓ Everyone who comes in contact with participants but mainly the site staff – feels office staff no influence on retention	✓ CI with the trial management team, PPI, site staff best knowledge from on the ground experience
21PI	✓ Ultimately the CI but overall, the trial team responsibility	✓ Trial Management team and PPI
24PI		✓ Trial management team and PPI
11CTM	✓ Sponsor but also the trial management team – site important but perhaps a level removed	
15Co-I	✓ PI, trial team and research nurses at recruitment sites	✓ Clinical trial team, onsite team input important, PPI,
19CTUD		✓ Protocol more or less finalised when received from sponsor but negotiate with sponsor/funder prior to signing the contract to include activities to facilitate retention e.g. reimbursements but have in-house follow-up procedures also – trial team.
22HTO	✓ Ultimately the sponsor but everyone has a role	✓ CI academic trial /Sponsor for industry but some input from wider team
23CTP	✓ Main site	✓ Main site but if not in the protocol the site staff decide how to retain and follow-up – think it is important to have input from site staff

Table A7.3. Planning for power and proactively implemented retention strategies

Interview	Planning for Power	Proactively implementing strategies			
		Participants	**Sites**	**Blanket**	**Tailored**
12TM	✓ Previous research and experience over the years of conducting trials influence the figure but also thinks it is standard when trial teams not familiar with the research area	✓ Different methods of follow-up, pay for visit parking – contact GP to get contact info	✓ Try keep sites engaged – newsletters with trial updates, teleconferences to discuss the trial and keep engagement, send trial merch. ✓ SIV training about the importance of retention and to communicate that to participants	✓ Blanet unless being tested in a SWAT	
13TM	✓ Influenced by previous research in the field and clinical knowledge but also erred on caution and increased estimate to prevent underpower	✓ Cover parking costs. Reminders, booking appointment in advance, prompts. Explain to them clearly of what will happen in the trial – at each visit they are clearly told when their next visit is and what to expect. Appointments when it suits the	At a site level they are flexible but nothing targeted at the sites to boost retention		✓ Initially blanket but once they get to know the participants it is tailored to those who need more support

		participant/being flexible			
16TM	✓ Previous research, but if not it is just standard approach across the board	✓ Different methods of how to complete follow-up. Offered control intervention at the end. Reminders. Pre-paid envelopes		✓ Blanket	
20TM	✓ Does not know – did not provide insights		✓ Only proactive strategy is payment for sites per participant – only if follow-up is completed		
2TM	✓ CTU wide experience based on statistical papers – but a trial with elderly and long term follow-up attrition was higher	✓ Offering different methods of follow-up ✓ Pre-paid return envelopes ✓ Pens with questionnaires	✓ Training sites about handling the withdrawal conversation to make sure it is done properly and not just outright withdraw immediately	✓ Blanket unless SWAT	
3TM	✓ Influenced by the patient population and how you collect the data – lower rate in trials where patients were coming in for routine care vs higher rates	✓ In line with routine care ✓ Follow-up done by staff who recruited participants ✓ Pay for parking/travel	✓ Train staff on follow-up and the importance of retaining participants ✓ Pay sites for full datasets	✓ blanket for all participants	

	if they are coming in outside of this				
4TM	✓ Think it is quite arbitrary figure and not much science behind it				
5TM	✓ Does not know – did not provide insights	✓ Christmas cards ✓ Newsletters ✓ Stamped return envelope ✓ Try make questionnaires as short as possible ✓ Reminders ✓ Voucher	✓ Newsletters to site ✓ Merch and stationery ✓ Payment if participant completed	✓ Blanket	
6TM	✓ A standard approach to estimate but have to balance inflating sample size and pragmatism of what funders are willing to fund. Have less problems with trials with shorter follow-up periods	✓ Reminders ✓ Prompts ✓ Vouchers	✓ Couple of trials where sites receive payment for follow-up	✓ Blanket but reminders only applicable if missed	
7TM	✓ Influenced by literature in	✓ Reminders ✓ Newsletters	✓ Training sites on reminding participants	✓ Blanket – don't know which participants	

	similar trials and stats experience. The longer the follow-up the more likely you reach the attrition rate calculated	✓ Incentive ✓ Message from the PI/CI on the follow up	to things for outcome measures ✓ What the main site expects of site staff for retention	are more likely to leave at the start of the trial	
17RN	✓ Did not provide insights – feels recruitment is more of a challenge	✓ Keeping good communication with participants with newsletters. Report findings back to participants. Vouchers/reimbursement – car parking or coffee voucher. Being flexible for appointments. Options of completing follow-up ✓ Clearly setting expectations at the start of the trial	At a site level they are flexible but nothing targeted at the sites to boost retention	✓ Blanket	

18RN		✓ Had input from PPI on the trial time and burden and modified based on their feedback. ✓ E-consent and showing them they could complete the online surveys ✓ Clearly setting expectations of the trial and the follow-ups and reminders. ✓ Reminders ✓ Routine care visits			✓ Initially blanket but once got to know participants would tailor reminders and follow-ups
10SC	✓ Not sure what influences – think it is standard figure but still high	✓ Reminders, short questionnaires, different options of completion	✓ Not involved in retention but ask sites to collect as much contact info but really not involved in retention or targeted with strategies	✓ Blanket but to only those applicable for reminders	
14SC	✓ Does not know – did not provide insights	✓ Different options of completing follow-up. Reminders. Gift vouchers	✓ Updated sites with newsletters about the trial and nurse forums	✓ Blanket	
1SC	✓ Previous research	✓ Vouchers if budget allows ✓ Reminders ✓ PPI champion to communicate to participants to help with retention ✓ Newsletters			✓ Target participants with call that think need more engagement

		✓ Call outside of follow-up to maintain engagement ✓ Pay for parking ✓ Routine data/medical records ✓ Seasonal Cards			
9SC	✓ Based on data from other similar studies	✓ Align visits with routine care ✓ Cover transport to hospitals ✓ Reminders ✓ Minimal number of questions ✓ Travel to the house if participant cannot make clinic if possible	Nothing targeted to sites but at a site level making it efficient and having flexibility with appointments Tries to make the workload as light as possible for the site	✓ Blanket but can be dynamic and might change as you progress but don't do targeted it is always blanket	
8PI	✓ Influenced by previous research and side effects but errs on side of caution and inflates to prevent underpower.	✓ Recruit participant they think will remain in the trial ✓ Participant reimbursement ✓ Keep phoning if miss a follow-up call	✓ Site payment at the end for retained participants and completing follow-up		
21PI	✓ Experience from similar trials – due to longer follow-	✓ Visit with routine care		✓ Blanket	

	up with less face-to-face contact they estimated greater levels of attrition	✓ Pay for travel if the visit it outside of routine care ✓ Prompts ✓ Seasonal cards			
24PI	✓ Don't factor in attrition – factor in numbers that will stop study treatment – based on similar trials	✓ Different options of how to contact participants – telephone, medical records, GP practice ✓ Newsletters ✓ Reminders ✓ Prompts ✓ Run-in period	✓ SIVs tell site staff the importance of retention and the nuance of the withdrawal conversation and train the nurses on the follow-up methods		
11CTM		Does not do anything to encourage complete data sets and feels staff should know to do this to make their own job easier and avoid deviations etc			
15Co-I	✓ Does not know – did not provide insights	✓ Reimbursed for their time – vouchers. Visits co-inside with routine care. Reminders		✓ Blanket across all sites – all the sites will send the reminders	
19CTUD		✓ Clearly educate participants on the trial and what is involved in terms of follow-ups to make sure expectations are set so they can accommodate			✓ Case by case basis when the nurses get to know the Experience470 and some need more attention than others

		✓ Participant stipends, overnight accommodation and travel. ✓ Close follow-up with nurses ✓ Letters to employers ✓ Try transfer participants to differ trial sites if they are moving to keep them in the trial. ✓ Reminder (in-house SOP) ✓ Selecting participants they think will stay in the trial			BUT from the outset they would tailor based on the type of participants/disease area
22HTO	✓ Does not know – but said you need to look at the invasive nature of the trial and the level of benefit as if the participants are unlikely to benefit, as there is likely to be less motivation	✓ Travel reimbursement ✓ Looking to see if visits can be in line with routine care	✓ Training sites to clearly set participants expectations about trial follow-up	✓ Blanket – think it would be too complex to target.	

	and higher attrition in these trials				
23CTP	✓ Does not know – did not provide insights	✓ Clearly set expectations about the trial at recruitment ✓ Recruit participants think will stay on the trial ✓ Having a user ID on the telephone number so participants answer follow-up calls ✓ Prompts ✓ Try sort parking ✓ Vouchers			✓ Always aim to individualise when dealing with participants

Table A7.4. Reactively implemented strategies

Interviewee	Reactively implementing strategies					
	Mainly reactive or mix?	**Participants**	**Sites**	**Blanket**	**Tailored**	**Challenges with being reactive**
12TM	It is a mix of both proactive and reactive – depends on when the interviewee becomes involved in the trial	✓ Newsletters – keep building more in if needed	✓ Put up posters at the site to make sure staff/participants are aware of the importance of the trial	✓		

	Constantly monitor follow-up rates during the trial – if it is looking like it is dropping more newsletters might be implemented					
13TM	Both Proactive and Reactive Constantly monitoring follow-up rates – but finds recruitment more so the issue	✓ Had to recruit more participants to compensate as changing the primary outcome measure was not possible				✓ Cant change the primary outcome measure to actively address poor retention - instead overrecruiting
16TM	Mainly proactive (used to be more reactive but now mostly proactive) Monitor retention rates continuously throughout the trial – if had issues conversations with the trial		If they have issues would discuss with the sites to see what is possibly going wrong			✓ If it is not considered up front it is not going to be properly costed or resourced (taking more generally not in relation to what they do in their trial)

	teams, steering committees etc					
20TM	Mainly reactive for participants (bar site fee) Constantly monitor rates and see what the issue is – discuss with the sites	✓ Vouchers ✓ Reminders	Discuss and work with the sites to see what the issues are		✓ Targeted at sites but within sites it is blanket	✓ Has had to be reactive and it is difficult because of the time it takes to go back to ethics and make an amendment Note (thinks strategies around communication or engagement would be more effective than payments in the long term)
2TM	Mainly proactive– reactive if seeing issues but has not really had to be reactive Constantly monitor rates and see if there are any red flags		Discuss with the teams and the sites to see what is going wrong but has not seen issues with retention so this is so hasn't have to be reactive			

3TM	Both proactive and reactive when needed if issues arise		✓ Contact site with the issues and work with the site to figure out how to improve the issue s and also meeting regularly with all sites to share experience		✓ Initially blanket but if there are issues then it is targeted at the sites	✓ If you need to be reactive you are more limited in delivering a similar trial experience – cant fundamentally change things so you can still compare trial experience
4TM	Mainly Reactive Monitor return rates and that dictates whether vouchers or other aspects are needed	✓ Vouchers – reactive since they are higher cost you don t want them in from the start if not needed ✓ Brought in electronic option for follow-up ✓ Reactively did reminders – reactively did not feel it was necessary laying out a huge cost to set it up automatically, so nurses did it themselves		✓ Blanket		✓ Would have been easier to have things in from the start and potentially have better retention throughout – reactive in approach but unsure if then you are able to see any benefits – inflate costs to take from other areas if needed

5TM	Both proactive and reactive when needed if issues arise Monitor retention rates along the way	✓ Brough in a cover letter with wording to try encourage participants to complete and return questionnaires	✓ Go to the sites and find out what is going wrong and work with them to resolve the problem – maybe take more of the admin work to the main site to allow site staff more time to follow-up participants		✓ Bread and butter of the job being reactive – have to consider the time left I the trial and the length of time an amendment would take and if it is worth it for improving rates in the time left – can use different pots of money for retention strategies if needed but thinks like participant fees would not be brought in unless already planned
6TM	Both proactive and reactive Monitoring rates – risk assessment trigger based on calculated attrition rate – not meeting	✓ Reactively building in newsletters ✓ Looking at increasing forms of communication with participants			✓ Challenge with ethical approval time – cannot increase budget need to work with what already have

	targets has prompted additional action					
7TM	Both proactive and reactive Monitor continuously throughout the trial and look for trends in dropouts	✓ Prompt - Sent comms to participants to outlined the importance of completing and returning questionnaires – reactively	Talk to sites to see if they can help with the follow-up of participants ✓ Ad hoq send correspondence to sites to try motivate		✓ Tailored to sites reactively if they are struggling with retention	✓ Not really a challenge in being reactive – straightforward and crack on with amendment if needed
17RN	Mostly proactive but if needed are reactive Monitor retention throughout the trial – not has any issues with retention – mostly issue with recruitment	✓ If participants have issues traveling have previously gone out to homes to collect data				
18RN	Mainly and in this case seems to be only proactive					There was a dip in the penultimate follow-up timepoint but did not do anything differently as had faith and knew

	Monitor through completion of follow-up surveys					participants would come to the final follow-up – there was a dip in the final to come back to clinic but higher than penultimate as felt participants knew it was the final one
10SC	Both proactive and reactive - reactive monitoring the follow-ups but unsure	✓ Participant newsletters	✓ Reactive planned to go back to sites to get primary outcome via medical records	✓ Go back to all sites – blanket – all newsletters blanket but if participant did not give email then they will not get the newsletter		✓ When reactively implementing strategies – mostly straightforward but aspect of pushback from site but not really a problem ✓ Newsletters don't think it is any more difficult reactively vs proactively
14SC	Mainly and in this case seems to be only proactive Constantly monitored retention rates					

1SC	Mainly and in this case seems to be only proactive Does not see issues with retention during the trial – would need to discuss the issue and try figure out the cause				✓ When reactive it can take time and effort and difficult with resourcing the change perhaps with the amendment and has knock on impact on other trial docs like PIL – talking more generally not specific to their trial
9SC	Monitor but not had issues with poor retention as using routine data if needed				Lost participants for some if the visits were not along the clinical care pathway but felt it was outside of their control
8PI	Mainly proactive but also reactive if needed Monitor throughout the trial to look at drop out rates - if it looks like it will threaten the power of the study		✓ Talk to the trial site tell them what the problem is and see how to go about fixing it via a motivational email and perhaps reassessing if participant reimbursements are needed		✓ Generally speaking it is hard to increase sample size as it requires re-costing and a deviation from what is registered on clinicaltrials.gov

21PI	Both proactive and reactive – have strategies from beginning but if things are not going well more are added Monitor and if the attrition rate is higher than expected or higher than you've allowed for in the sample size – where less experience with the type of trial it is more of a gut feeling rather than having something to compare it too	✓ Additional reminders			✓ Generally speaking if you are reactive you have less money to do things so you only do what is free or cheap ✓ One of the studies has miscalculated sample size so had to stop recruiting early and now key focus is emphasise to staff that importance of retention to get the primary outcome
24PI	Mainly proactive but have been reactive to tackle issue of challenge of going to the GPs to get data		To tackle the challenge of it being difficult to go to the GPs to get participant data they introduced – send a letter to GPs with offer of reimbursement to get the information to send to the research		

	Monitor throughout the trial		nurses to put it onto the system One trial introduced electronic follow-up over the years as there was an improvement in technology (but not in particular response to poor retention)		
11CTM					
15Co-I	Mainly reactive – do not plan from the outset only consider retention once the first follow up is complete Compare follow-up to similar trials or in similar participant populations – compare sites to see if one site has problems	✓ Vouchers or raffle prize draw ✓ Reminders for visits		✓ If issues tailored to the site with the retention problems as it is a site-specific issue	Somethings are outside of the control of the trial – if the clinic moves location
19CTUD	Mainly and in this case seems				

	to be only proactive Retention not a major issue – recruitment more difficult				
22HTO	Mainly proactive but if issues reactive Monitor throughout the trial – no specific threshold		Issue with one trial and looking at changing the randomisation ratio		✓ More limited in what you need to deliver – redesign it is substantial amendment that would impact scientific integrity to redesign so now considering a 2-1 randomisation.
23CTP	Mostly proactive If can't get hold of participant it prompts action				

Table A7.5. Influences on the choice of strategy

Interviewee	Influences on the choice of strategy			
	Experience	**Cost /Resource**	**Other**	
12TM	✓ Mainly experience or see what other trials have done	✓ Keep an eye on budget, has to be considered	✓ Try keep up to date with the literature	
13TM	✓ Experienced based just part of day to day they know what needs to be done as have 10 plus years of experience		✓ Existing literature not really relevant to getting participants to clinics	✓ More of a focus from funders now on methodological pieces looking at issues of retention etc
16TM	✓ Experience and prior success with the strategy (success not formally evaluated)		✓ Consider digital literacy – different follow up options ✓ Look at evidence but it is not great. ✓ Cohort in the trial – feeds into digital literacy and impacts how follow-up is completed ✓ Ethics and what is seen as the non-hassling approach and personal feeling about the amount of follow-up ✓ Has to be a cut off level for resource and management	
20TM				
2TM	✓ Experience	✓ Budget constraints can play factor	✓ Age of participants – paper vs digital ✓ Keep eye on literature	
3TM			✓ How follow-up is completed	
4TM				
5TM	✓ Experience of the team	✓ Not certain but thinks the budget would need to be tight to be	✓ Ethics – balance between follow-up and hounding	Note – budget can be taken from other aspects if needed

		competitive to it is a factor		
6TM	✓ Experience with other trials and what was successfully implemented in these trials	✓ Need to balance resource – lots of things that can be done but cant stretch the team ✓ Consider the staffing needed	✓ Ethics – perceptions of what ethics would and will not approve impacts choice – difficulty with incentives and it takes time ✓ PPI feedback ✓ Environmental considerations for certain things – like toys and stickers ✓ Length of follow-up ✓ Is it for the primary outcome or not	
7TM	✓ Experience	✓ Strategies need to be resourced and budgeted – all about balancing the resource you have	✓ Type of participants – age ✓ Literature	
17RN			✓ How the follow-up is completed as some trials participants may not need to come to clinics	✓ Already in the protocol from the main site but if it is an in-house study they can make the decisions in terms of being flexible with appointments and vouchers etc ✓ Decision is driven by the sponsor
18RN	✓ Experience and just knowing how things need to work and be organised		✓ Literature ✓ PPI reviewed things and told them what would and would not work	

10SC	✓ Experience – balance between follow-up and hassling – not gone through the evidence for any strategy		✓ Age of participants – wide range so need to consider digital savvy and other methods to accommodate for everyone	Don't think they are making decisions differently to other trials
14SC	✓ Experience from other studies but unsure on how the choice was made			
1SC	✓ Experience and learn from other trials	✓ Vouchers only if budget allows – budget considered ✓ Manpower and resource	✓ Length of the follow-up ✓ PPI champion would be influenced by the cultural demographic of participants	
9SC			✓ Geographical spread of where participants are coming from – transport to clinics	Does not look at literature as don't think it would be helpful
8PI				
21PI	✓ Experience		✓ Ethics can be funny about incentives but have more recently stated the team need to provide. ✓ PPI input	
24PI	✓ Experience	✓ Build in costs for data linkage and contacting GPs, newsletters		
11CTM				
15Co-I				

19CTUD			✓ Age, elderly phone in advance and help with any mobility issues. Also depends on disease cohort ✓ Depends on the study and depends on the funder – funder has influence from a financial perspective.	Will negotiate with funder before signing the site contract about participant travel and accommodation costs
22HTO			✓ In industry the risks would be flagged by people reviewing the protocol ✓ Similar in current role but often the protocol is already set by the time they get it so have less influence on the protocol ✓ Ethics recommend reimbursement for visits outside standard care ✓ PPI involvement ✓ Type of participants – old and very sick or if they need to travel a large distance ✓ Nature of follow-up	In industry interviewee would be reviewing protocol and feeding back red flags in terms of risks for poor retention to the trial team but in academia not very dissimilar but have less room to change things but can work with sponsor but some things can't change
23CTP	✓ Experience		✓ Levels of comfort with the amount of time to follow-up someone ✓ Depends on the type of participants – age, if older less likely to have email. ✓ Feedback from main site	Protocol already more or less complete but if people not turning up need to do something e.g. vouchers come from main site

Table A7.6. General challenges with retention strategies

Interviewee	Challenges with strategies generally speaking
12TM	
13TM	
16TM	
20TM	
2TM	✓ Challenges with timings of the postal system in terms of windows for data collection to prevent crossover
3TM	
4TM	
5TM	
6TM	✓ Challenge – admin workload of paying sites for data received – not worth the effort. ✓ Difficult to monitor if site staff are completing all required participant follow-up as no formal way of evaluating this
7TM	
17RN	
18RN	
10SC	
14SC	
1SC	✓ Mentions difficulties with using routine data as it is not certain it is up to date
9SC	
8PI	
21PI	
24PI	✓ Getting more challenging to contact relatives and carers so less used. Also more costly to contact GPs and the trial is not a priority for them
11CTM	
15Co-I	

19CTUD	
22HTO	
23CTP	✓ Getting more challenging to sort parking for participants

Table A7.7. Informal retention strategies

Interviewee	Informal ways to improve retention	
	Motivation and investment	**Relational**
12TM		✓ Conversations and chat, being approachable and being available to answer questions
13TM	✓ Having motivated staff and generating more research culture in staff not directly involved in running the trial – different staff have different motivations	✓ Building relationships important – consistency in staff – face to face helped with this – knew who to target
16TM	✓ Training people to do things for themselves and very engaged	✓ Having an extra chat with participants, relationship is important with participants – telephone calls helped with extra chat
20TM		
2TM		
3TM		✓ Relationship important
4TM		✓ Relationship important
5TM	✓ Invested sites and participants	✓ Being available and having a good relationship with sites
6TM		
7TM		✓ Building rapport important
17RN	✓ Participants motivated to find an answer and within their practice the importance of retention is embedded in their practice	✓ Relationship and being available to answer questions etc – having a good relationship with other staff like PIs also helped
18RN	✓ Empowering participants and giving them the feeling of ownership over the trial ✓ Motivated staff and participants	✓ Built relationship important, knowing where they are at and having empathy important – those who didn't have the relationship in the control arm didn't come back as no relationship built up – good communication between site staff and PIs and patients

10SC	✓ Participants were not invested but still had good retention	
14SC	✓ Motivated and engaged participants	✓ Being polite and appreciative, build up rapport – doing telephone calls follow-up helped built up the rapport and they like to chat
1SC		✓ Not treating them like a subject is important and building rapport important – talking on the phone regularly helped build the rapport
9SC		✓ Going the extra mile important
8PI	✓ Motivated and invested staff	✓ Having good rapport and being friendly
21PI	✓ Motivated and engaged participants	✓ Harder to retain with less participant contact as they don't have the relationship – relationship makes the biggest difference
24PI	✓ Engaged sites	✓ Consistency in staff important
11CTM		
15Co-I		✓ Built up rapport with clinicians helps with retention in the sites
19CTUD		
22HTO		✓ Important to make participants not feel like a number and to give them time and answer questions
23CTP	✓ Having invested staff	✓ Building relationship with participant important – human contact either face to face or phone calls

Table A7.8. Effectiveness of retention strategies

Interviewee	Are retention strategies effective?	Formal evaluation of retention strategies	
	Yes	Yes	No
12TM	✓	✓ Once but most not evaluated	
13TM	✓	✓ Retention is secondary outcome	
16TM	✓	✓	
20TM	✓ unsure of effectiveness		✓
2TM	✓ unsure of effectiveness	✓	
3TM	✓		✓
4TM	✓		✓
5TM	✓		✓
6TM	✓	✓	
7TM	✓ unsure of effectiveness	✓	
17RN	✓		✓
18RN			
10SC	✓		✓
14SC	✓		✓
1SC	✓		✓
9SC	✓		✓
8PI			
21PI	✓		✓
24PI	✓		✓
11CTM			

15Co-I	✓		✓ Perhaps at main trial office
19CTUD	✓		✓
22HTO	✓		
23CTP	✓		✓ Perhaps at main trial office

Table A7.9. Communication of retention strategies to the trial team

Interviewee	**Communication of retention strategies to trial team**			
	Yes			**No**
	Meeting	**Protocol**	**Other**	
12TM	✓	✓ Vaguely to allow for flexibility		
13TM			✓ Study specific procedure – not in protocol (thinks more guidance/framework would facilitate better planning and documentation)	
16TM		✓	✓ Site via SIVs told about retention strategies	
20TM				✓ Not in protocol because solely reactive
2TM		✓ Integrated into protocol/trial design	✓ Sites via trainings about how to follow the follow-up processes	
3TM		✓ Integrated into protocol/trial design	✓ Emails and training and newsletters to sites and wider team about retention updates and trainings on how the trial will retain participants	
4TM	✓ Core team (reactively)	✓ Only if amendment but likely vaguely and depends on the amendment	✓ Sites via Newsletters or email for amendments on retention strategies if they are implemented but will keep sites updated on retention rates generally	

5TM	✓ Core team, only site if it is applicable	✓ Yes but some aspects not such as merch to sites		
6TM	✓	✓ But vaguely	✓ When there are issues sites are looped in and told	
7TM	✓ meeting	✓ but not in fine detail	✓ SIVs about how they plan to retain participants or if amendments might be via email or letter	
17RN		✓ Interviewee finds out via the protocol from main site unless it is in house then via team meeting		
18RN	✓	✓ Less detailed compared to procedure docs and informal aspects not written in	✓ Policies and SOPs	
10SC	✓ core staff, site not really involved so not first to know	✓ Thinks yes but unsure		
14SC	✓ Core team	✓ Think yes but unsure	✓ Sites via SIVs told about how the trial will retain participants	
1SC	✓	Thinks having mandatory requirements in the protocol would be beneficial		
9SC	✓	✓ Integrated into the design but unsure		
8PI				✓ Not in protocol – not in the template

				requirements of what is needed – if nobody asks it is not going to be there
21PI	✓	✓	✓ Sites via SIVs told how the trial will retain participants	
24PI	✓	✓ Only vaguely	✓ More detailed in SOPs and sites find out via training documents on how to tackle retention	
11CTM				✓ Has not seen this
15Co-I	✓ Core and site staff meetings	✓		
19CTUD			✓ Site contract with Sponsor (not in protocol) – in-house reminders are in a SOP.	
22HTO	✓	✓ But some aspects are not such as training sites on the importance of clear comms and aspects integrated into the design	✓ Sites via SIVs about informed consent training to make it clear to set expectations about number of visits (that is not something in the protocol)	
23CTP		✓ Sometimes yes and sometimes no – depends on the experience of the research writing the protocol	✓ Site staff finds out how to retain participants via newsletter, email or perhaps joint meeting	

Table A7.10. Communication of retention strategies to trial participants

	Outline Retention strategies to participants		Outline importance of retention to participants	
	Yes	**No**	**Yes**	**No**
12TM	✓ vaguely in PIL		✓ in newsletters perhaps and not sure if it happens during consent	
13TM	✓ Verbally, not in PIL. PIL more for general information		✓ PIL and verbally	
16TM	✓ PILs		✓ Follow-up comms – ethics committee more allowing	
20TM	✓ Thinks yes but unsure - retrospectively		✓ Verbally and in PIL/ICF	
2TM	✓ PILs		✓ Follow-up comms	
3TM	✓ PILs but depends on the type of strategy		✓ Verbally, not in PIL	
4TM	✓ Only for those still in follow-up when amendment is implemented via PIL but also perhaps via conversation but not sure			✓ Don't think it is emphasised enough in the PILs interviewee has read – balance with withdrawal

5TM	✓ PIL		✓ Follow-up comms, PIL and if in convo they feel participant is thinking of leaving they will outline the importance	
6TM		✓ Not outlined – don't need this level of detail and also try to keep PIL short	✓ Via email and letter prompts- follow up comms	
7TM	✓ PILs		✓ PILs	
17RN	✓ Mainly verbally but thinks also outlined in PIL		✓ Verbally	
18RN	✓ Not in PIL but verbally told			✓ Not directly told but knew the more data provided the better for the study – also because it was feasibility not as important
10SC	✓ Only vaguely in PIL – depends on the strategy and not about the reactively implemented strategy		✓ During follow-up communications like reminders and PILs but not sure about consent discussion	
14SC	✓ PIL		✓ Overall thinks yes but unsure but mentions it defo happens if participant raises, they might withdraw but is	

			balanced with information to withdraw	
1SC	✓		✓ Depends on the participant if it felt it was needed to if participant showing signs of withdrawal	
9SC	✓ PIL and Verbally			✓ Don't think explicitly but told about the benefits of the research for others
8PI	✓ Verbally		✓ Verbally	
21PI	✓ PIL as they need to consent to aspects		✓ Verbally with the caveat of withdrawal with participants indicating withdrawal	
24PI	✓ PIL for only aspects they need to consent too but not perhaps explicitly		✓ Newsletters and PIL	
11CTM				✓ Has not seen this
15Co-I		✓ Not in PIL and doesn't think it does but perhaps other methods like verbally but unsure	✓ Verbally at the site	
19CTUD		✓ no		✓ Not directly but through outlining the visits and it is

				important to adhere to visits otherwise it is a deviation
22HTO	✓ PIL		✓ Verbally	
23CTP	✓ PIL as they need to consent but also verbally		✓ Verbally but might also be in PIL if it is outlined by the main site in it	

Table A7.11. Insights into results from PIL analysis

Interviewee	Reason for inconsistencies across protocols and corresponding PIL regarding retention strategy information
12TM	✓ Rush to get all documents together to submit for approval to get the trial started – just missed – human error
13TM	✓ Human error that things get missed – really busy and tight deadlines for submitting
16TM	✓ Poor version control, not really sure as ethics would normally pick up that type of thing
20TM	✓ If it is a multi-country trial the different countries have different templates so sometimes the requirements of what to be included is different across countries for the protocol and the PIL
2TM	✓ Lack of synergy between the documents – usually ethics committee would pick it up but sometimes just slip through the cracks
3TM	
4TM	✓ Human error
5TM	✓ Human error
6TM	✓ The PIL does not need the same level of detail as the protocol as previously mentioned
7TM	✓ Effort to keep PIL brief as possible
17RN	✓ Doesn't know why this would happen
18RN	✓ The documents are different in their nature of what is to be included as previously mentioned
10SC	✓ Hypothetical – depends on the strategy and how telling participants may influence behaviour as previously outlined – not to overload the participant with information in the PIL
14SC	✓ Human error and the time pressure to get documents through ethics so just gets missed
1SC	✓ Things just get missed due to human error in the version controls and updating documents
9SC	✓ Efforts to keep the PIL as brief as possible to avoid overload of information

8PI	✓ Human error, not deliberate but need a good trial manager to harmonise the documents
21PI	✓ Human error, try minimise what is outlined in the PIL as to not overload
24PI	
11CTM	✓ Not sure but perhaps due to human error omission of information or decisions made about what is relevant to outline in the PIL and what information needs to be prioritised
15Co-I	✓ Not deliberate but through different versions of the document's things get missed – human error
19CTUD	✓ The documents are different in their nature of what is to be included
22HTO	✓ Not sure why this would happen but perhaps the PIL does not need lots of detail
23CTP	✓ Issues in version control of the documents

Appendix 11. Thesis Chapter Seven. Supplementary File 2. Topic guide and RREAL sheet

First Version of the Topic Guide

Disclaimer: The topic guide is an iterative and flexible document that is responsive to the data that comes out during the interviews therefore the questions asked may differ from the topic guide but will stay within the broad topic of retention in clinical trials.

This this topic guide will be refined with the input from the PPI group.

Opening questions – general questions about retention in clinical trials
All trial staff
What does "retention" in clinical trials mean to you?
What do you know about retention in clinical trials?
What do you know about promoting participant retention in clinical trials? - Do you consider it important to promote participant retention in clinical trials? - Could you explain why you think this?
Do you consider promoting participant retention as part of your role within the clinical trial team? - If yes = Can you tell me about this aspect of your role and what is involved / can you tell me about your experience of retaining trial participants? - If no = Can you tell me why you do not consider retaining participants as part of your role? Who do you think this role belongs to within the trial team?
Opening questions specific to Trial Managers/Principal Investigators/Study Co-ordinators
Have you ever provided training or information courses to trial staff on participant retention? - If yes = what prompted you to provide your trial staff with this training/information?

- If no = would you consider this going forward – why/why not?
Opening questions specific to Research Nurses/Research Assistants
Have you received any training/information on participant retention in clinical trials? - If yes – what did this look like? Did you find it beneficial? - If no = would you like to receive this type of training/do you think it is important to receive this training/information?
Opening questions for PPI contributors we interview
How did you become involved as a PPI contributor? What is your experience like? What does your involvement look like?
Questions about retention strategies
All trial staff
Are you aware of any retention strategies/activities that are used in clinical trials to promote participant retention? - Can you explain what these strategies are? - What do you know about these strategies? - How did you learn about these retention strategies?
Are there any retention strategies used in the trials that you are involved in?
If yes (to the above) - What are these strategies? - Do you know/think these strategies have had an impact (positive and/or negative) on the retention rates in the trial? - If successful - why do you think this is? – What factors do you think contributed to the success of this retention strategy - in what way/could you explain? - If not successful - why do you think this is? – What factors do you think contributed to this? - In these situations what do you do? Can you talk me through the process if this situation were to occur / can you tell me about what happened when this occurred in the trial? - Do you think these activities are suitable to the participants in the trial? – Can you elaborate – If no – why do you think they are not suitable – what strategies do you think are more suitable methods of improving retention? - Are there situations where you do not think it is appropriate to use retention strategies – can you explain - why do you think this is?

- *(If involved in implementing retention strategies)* - Do you feel comfortable implementing retention strategies – situations where do think it is not appropriate? Or where you do not feel comfortable using retention strategies? – are there any strategies in particular?

If no (to the above- (Are there any retention strategies used in the trials that you are involved in?))

- Is there any reason you have not used retention strategies in trials? / Do you know why retention strategies have not been used in the trial?
- Do you think it would be beneficial to use retention strategies? – Can you elaborate –
- If you were to introduce a retention strategy what strategy would you most likely use and why?

Questions about the choice of retention strategy

Who makes the decision about the type of retention strategy that is used in the trial?

- Are there other individuals who you think should be involved in this process?
- What are your opinions about involving PPI members in this research decision? – Can you elaborate on this further

<u>If the individual is involved in the decision about the type of retention strategy</u>

- Can you describe the decision making process?
- What factors are taken into consideration when choosing the most suitable retention strategy to use in the trial?
- Are there any barriers within the trial that prevent you from implementing certain retention strategies?
- Are there any factors that enable the implementation of certain strategies more than others?
- Do you think other factors need to be considered when choosing a retention strategy?

<u>If the individual is not involved in the decision about the type of retention strategy</u>

- Do you think you should be involved in choosing the type of retention strategy that is used in the trial – can you explain why?
- Is there any reason why you think you are not currently involved in this decision making process?
- Since you are not involved in the choice of strategy – are you involved in implementing the strategy/what is your role?

Often when trial teams plan retention strategies we have found that they tend to implement multiple strategies within the trial – for example send out reminders for upcoming visits and also provide monetary incentives for participants – is using multiple strategies something you have considered? - can you elaborate? – have you found using multiple methods to promote retention beneficial?

We know from the literature that there is very little evidence to show retention strategies are effective at actually retaining participants – if you implement/were to implement a retention strategy would you consider evaluating how effective it?
From looking at trial protocols that outline retention strategies they are all generic and broad strategies – have you ever considered using different types of strategies within the trial to target individuals from specific sociodemographic or cultural background? Or is this taken into consideration when you develop retention strategies?
Questions about communicating information about retention strategies
Do you think it is important to communicate information about retention and the importance of retention to potential trial participants? - Can you explain From previous research looking at the content of PILs, often participants are told about their right to withdraw from the trial but not often told about the importance of remaining in the trial - Is this your experience – why do you think this is?
Do you think it is important to tell trial participants about retention strategies that will be used in the trial? - Can you elaborate on this? - Do you think there are any positive/negative impacts on communicating this information to participants? - In your experience when is this type of information communicated to participants? – Why is this? - How is the information typically communicated to the participant? (via PILs, verbally during recruitment consultations) - At what point in the trial do you think would be most suitable to inform participants about the retention strategy? - What factors influence the communication of retention strategies?
Often retention strategies are planned and implemented when retention becomes an issue in the trial, in this case how would you inform participants about the activities you intend on implementing to improve retention - If they are not planned for and included when the protocol is being developed how are you informed about these plans? / Do you need to get protocol amendments – what is this process like? – do you need to re-consent the trial participants?

We know from previous research that strategies are often not planned at the beginning of the trial but instead planned when retention becomes an issue – is this the approach you take in your trials? – What influences you to take this approach?
If retention strategies are planned during trial development, are they included in the trial protocol - Can you elaborate on this? - Do you think it is important to include retention plans in the trial protocol?
As part of previous research in my PhD we reviewed trial protocols and despite there being recommendations to include plans to promote participant retention – it was often not included in the protocol – Can you think why this may be?
As part of my PhD research we looked at how retention strategies are communicated in PILs – we found they are often communicated however when compared to the information provided in the corresponding protocol – there was a mismatch of information provided – participants were not provided with as much detail or different details about retention strategies compared to the information in the protocol – could you tell me why this could be? - Do you think this miscommunication has an impact on participant retention?

Final Version of Topic Guide

Introductory questions Can you give me an overview on the types of trials that you work on? How did you end up in your current position? Years in role, number of trials, clinical area, number of participants?
Group 1 Questions (Retention in trials) How do you conceptualise retention in clinical trials? Do you think retention is important? Why? Is retention a priority among trial teams? Why?

Can you tell me what you know about retention in trials – Generally or your own experience from the trials you are involved in
(Any differences between trials with good vs bad retention?)
(Key predictors of retention?)
(Any reason you think retention has been good/bad in the trials?)
(why do you think participants drop out?)

What informs your perspective on whether retention rates are good in a trial or not?

Group 2 Questions (Planning and decision making)

When calculating attrition rates for the trials – what is the rate chosen? - Why? How is it decided? What factors are considered? Is the rate decided usually Accurate? Are the rates chosen Different across trials?

Do you use any retention strategies in the trials you work in/any activities to promote and encourage participants to remain in the trials and facilitate data collection?

How do you choose them? What goes into that decision? What factors are considered? (Budget, Scientific literature, Participants, Environmental impacts)

Is it the same retention strategies used across all trials? - What dictates whether some trials get X, and some trials get Y?

Do you use multiple retention strategies within the trial?

Anything that you do at a site level to improve retention?
How is it decided what to do at a site level?

When implementing the retention strategies do all participants receive the same strategy or are certain participants targeted with the strategy (who you deem might be more likely to leave the trial)?
Do you plan different strategies for people who actively drop out versus those who passively drop out?

When implementing retention strategies, are they implemented from the outset of the trial or are they implemented only when a certain drop out rate has been reached?

Do you think the strategies that you use are effective? Why do you think this? Do you formally evaluate the retention strategies to see if they are effective? Why/Why not?
Before we move on are there any other strategies that you use to encourage or facilitate continued trial participation? – pay for parking, organise transportation, offering alternative follow-up methods, paying for return postage?

Group 3 (Planning and decision making continued)
When does the planning and decision making about retention strategies happen? At what stage of the trial? Why at this stage?

Who is responsible for retention in the trial?
Who is involved in the decision making about retention strategies?

Influences on the planning process? The funders? Are they always willing to fund what is proposed or do they influence what is chosen in anyway?

Mid trial
How is it identified that a mid-trial or additional strategy is needed in the trial? How is it highlighted to the team that there is a retention issue that needs addressing at this stage?
Does the mid trial planning of a retention strategy differ to if it were to be planned at the start of the trial? Who makes the decision start vs mid trial?

Group 4 (Communication)
How are retention strategies communicated to the trial team?

Are retention strategies outlined in trial protocols? Why/Why not? If additional strategies are added are these documents updated and amended?

Are participants informed about retention strategies? Why? How? Do you think it is important that participants know about retention strategies?
If there is a strategy added mid trial are participants reconsented?

Are participants told about the importance and the value of remaining in the trial? Why? How? Do you think it is important they are made aware?

Questions on previous PhD findings
In previous research we found that there were often inconsistencies in how retention strategy information is communicated in corresponding trial protocols and PILs – (provide example) why do you think this is?

RREAL Sheet

Introductory questions	**Key points and notes**
Can you give me an **overview of the types of trials that you work on?**	
Group 1 Questions (Retention in trials)	
How do you conceptualise retention in clinical trials?	
Do you think retention is **important? Why?**	
Is retention a **priority among trial teams? Why?**	
Can you tell me **about retention in the trials you have worked on?** (Any differences between trials with good vs bad retention?) (Key predictors of retention?) (Any reason you think retention has been good/bad?)	

(Why do you think participants drop out?)	
What **informs your perspective on whether retention rates are good** in a trial or not?	
Group 2 Questions (Planning and decision making)	
Planning at the start for sample size What is it? Why? How is it decided? What factors are considered? Accurate? Different across trials?	
Do you use any retention strategies?	
How do you **choose** them? What goes into that decision? **What factors are considered?** Budget Scientific literature Participants Environmental impacts	
Is it the **same strategy across all trials?** **What dictates whether some trials get X, and some trials get Y?** Do you plan different strategies for people who actively drop out versus those who passively drop out?	
Multiple strategies within a trial?	
Anything that you do at a **site level to improve retention?**	

Blanket approach or everyone gets the same?	
Effective? Formally Evaluate? How? Why is it not?	
Implemented regardless of dropout rate or only when a certain number of participants drop out?	
Before we move on are there any other strategies that you use to encourage or facilitate continued trial participation? – pay for parking, organise transportation, offering alternative follow-up methods, paying for return postage?	
Group 3 (Planning and decision making continued)	
When does the **planning happen**? **Why?**	
Who is **responsible for retention** in the trial team?	
Who is **involved in the decision making**?	
Influences on the planning process? E.g., Funders?	
Mid trial? **How is it identified that a mid-trial or additional strategy is needed in the trial?**	
Does the **mid trial planning** of a retention strategy **differ** to if it were to be planned at the start of the trial?	
Group 4 (Communication)	
Are strategies communicated to the trial team? **How?**	

Protocols? **Mid trial – these docs updated and amended?**	
Are participants informed? How?	
Do you think it is **important they know** about retention strategies?	
If it is **Mid-trial amendment** – are participants **re-consented**?	
Are they told about the **importance and value of remaining in the trial?** **Why? DO you think it is important** for them to be told? Why?	
Mismatch of information? Why? Do you think a **lack of transparency could impact retention?**	

Appendix 12. Thesis Chapter Seven. Supplementary File 1. Standards for Reporting Qualitative Research Checklist.

Topic	Item	Page of thesis
Title and Abstract		
S1 Title	Concise description of the nature and topic of the study identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	213
S2 Abstract	Summary of key elements of the study using the abstract format of the intended publication; typically includes objective, methods, results, and conclusions	214-215
Introduction		
S3 Problem formulation	Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	216
S4 Purpose or research question	Purpose of the study and specific objectives or questions	216-217
Methods		
S5 Qualitative approach and research paradigm	Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g., positivist,	217

	constructivist/interpretivist) is also recommended	
S6 Researcher characteristics and reflexivity	Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, or transferability	253
S7 Context	Setting/site and salient contextual factors; rationale[a]	217
S8 Sampling strategy	How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale[a]	218-219
S9 Ethical issues pertaining to human subjects	Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	217
S10 Data collection methods	Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale[a]	221, 217-218, 219
S11 Data collection instruments and technologies	Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for data collection; if/how the instrument(s) changed over the course of the study	218

S12 Units of study	Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	222-223
S13 Data processing	Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/deidentification of excerpts	220-221
S14 Data analysis	Process by which inferences, themes, etc., were identified and developed, including researchers involved in data analysis; usually references a specific paradigm or approach; rationale[a]	220
S15 Techniques to enhance trustworthiness	Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale[a]	221-222
Results/Findings		
S16 Synthesis and interpretation	Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	222-238
S17 Links to empirical data	Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	222-238
Discussion		
S18 Integration with prior work, implications, transferability, and	Short summary of main findings; explanation of how findings and conclusions connect to, support,	239-242

contribution(s) to the field	elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	
S19 Limitations	Trustworthiness and limitations of findings	243-244
Other		
S20 Conflicts of interest	Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	246
S21 Funding	Sources of funding and other support; role of funders in data collection, interpretation, and reporting	246

Appendix 13. Thesis Chapter Seven. Supplementary File 4. Additional Quotes.

For the submitted manuscript only additional quotes for themes presented in the paper were submitted, the full version of additional quotes for the thesis chapter in its entirety is presented in this appendix.

Themes and quotes
Conceptualisation and perceptions of retention
"So the word that would make me feel that retention is something once that patient is involved in the study we would like to retain them throughout the study" (Interview 1, Study Co-ordinator)
"It's trying to ensure that patients are staying within the trial and not withdrawing or being lost to follow-up. I suppose, it also comes down to looking at the actual data and the primary outcome data, as well. The completeness of the trial data is overall" (Interview 10, Study Co-ordinator)
"keeping participants in the study for the purpose of collecting as much relevant data as possible but of course protect, having their rights protected" (Interview 11, Clinical Trial Monitor)
"It is keeping the participants involved and engaged to completing their follow-up outcomes in clinic appointments or whatever that is" (Interview 12, Trial Manager)
"how many participants remain in the trial, but not only remain, we're getting the data so I suppose you've got your participant retention, where they're physical doing something like returning a questionnaire. But actually, they might opt out of that but depending on the data collection we still might have retention." (Interview 16, Trial Manager)
"To me that means how can I encourage them to stay with us and not give up on the trial, to be in there for the long haul" (Interview 17, Research Nurse)
"I mean, for me retention is they stay in until they meet discontinuing criteria in the trial." (Interview 22, Head of Trial Operations)
"Yeah, so you'd expect a better retention rate the closer it is to the intervention, certainly from my experience. There's various factors that fell into that. I mean some of them it is literally if you're dealing, as I said, dealing with an elderly populous that

you'd expect a certain level of deaths throughout the trial, so you'd then expect that number of participants who could be involved to actually be going down just because it's a smaller sample size." (Interview 2, Trial Manager)
"I guess the reassurances is that the Senior Trial Manager will bring to the meetings for the Chief Investigator when you're looking at that information on a regular basis" (Interview 5, Trial Manager)
"when I'm saying, you know, a trial retained well or didn't retain participants very well it's around those thresholds for pre-defined loss to follow up, yeah" (Interview 7, Trial Manager)
"when you plan the sample size you expect a certain amount of withdrawal and I think ours was below that" (Interview 9, Study Co-ordinator)
"I suppose just by comparing to research in the field that others have undertaken" (Interview 13, Trial Manager)
"I think that depends on the study design as well. So I think you know, most of our studies we look at around 10% if they're clinical sensible studies, and most of the stuff that I do is, and most of it's around that kind of level. Whenever we're into survey questionnaires or the remote stuff, then I think your realistic assessment has to drop quite a lot and it's likely to take off over time you know, we know that we're going to lose sequentially more people, and we try to minimise that but it's difficult." (Interview 21, Principal Investigator)
"I would definitely not want it creeping above 10%, that would be kind of where, well what informs that? I probably can't really tell you, it's more just maybe experience or just from a, yeah and I think above that just doesn't, I wouldn't be comfortable" (Interview 22, Head of Trial Operations)
Retention against competing trial priorities
"It's fundamentally important. I mean apart from anything else, from a personal perspective I very much dislike the idea of the waste that's associated with a trial, and not only from a trial level perspective, but actually from a person perspective. So if you're not retaining participants then that makes ... if you get to a level where you're not going to get information, you've actually wasted the information that you have received from the participants." (Interview 2, Trial Manager)
"Ultimately [poor retention] leads to underpowered, less valid research. Ultimately, it can be a bit of research waste which is not what we want. It's really, really important to maximise the strength and quality of the research we produce" (Interview 13, Trial Manager)
"if you have poor retention it can really affect your data and the overall outcomes that you get from the end result." (Interview 14, Study Co-ordinator)

"Retention is important. You work backwards based on a sample size. A sample size is calculated on the basis of the power of the study. Now, if you don't have sufficient power at the end the whole work which you have done, as well as the money which is spent is a waste" (Interview 15, Co-Investigator)
"it's hugely important because, you know, you set out to answer a question and if you're not retaining the patients then you risk not being able answer that question. If you're not retaining patients and it's due to a particular arm then you're really quite jeopardising and potentially introducing a bias, so it is very important yeah…I mean, if they don't complete the trial, as to how valuable that data is, is questionable and, you know, so much effort, energy, time, resources, money, everything goes into trials, like if you do one and then it can't answer your question, I mean that's not going to serve anybody." (Interview 22, Head of Trial Operations)
"I'm going to say yes, from a Trial Manager point of view yes, attention to that potential thing to jeopardise a study yes. I think that overall in a trial team from like a CI perspective and the site perspective and other people on maybe, like, the frontline of delivery, I think they possibly have different concerns. But when you're sitting in a CTU and you're seeing the numbers stacking up then yes, and so it's something we always report at TMG level obviously and then onwards." (Interview 7, Trial Manager)
"Could we do better? They've [the trial team] probably got it [prioritising retention] about right." (Interview 8, Principal Investigator)
"First step is, obviously, are we meeting the recruitment targets. The second thing we need to make sure is whether the patients are adhering to therapy. The retention only comes up when we move towards the first follow-up visit." (Interview 15, Co-Investigator)
"I think a lot of people focus on recruitment more than retention but my view is probably the other way." (Interview 16, Trial Manager)
"I think it should be when you do your initial assessment I think it should be up there at the top of agenda how we're going to retain people where, with the trials there's a lot of talk about how we're going to recruit people" (Interview 17, Research Nurse)
"I think it's a very, it's a key area that's often overlooked. I think a lot of I suppose the priority can sometimes be putting on numbers getting on and not always keeping them on." (Interview 18, Research Nurse)
"This is the only trial I've worked on so I can't give you a generalised answer, but from my experience I would say no. I would say a bit more information a bit more emphasis could be put on it" (Interview 20, Trial Manager)

"Number one is recruitment when you're recruiting big numbers. Number two is keeping people on the intervention, and number three is retaining them until the end of the trial" (Interview 24, Principal Investigator)
Retention responsibility and decision-making
"Ultimately the trial team. 99% of the things on the trial fall to the Trial Manager and the trial team." (Interview 6, Trial Manager)
"I don't think it's one person. You know, putting aside the sponsor being responsible for the whole thing and CI being, you know, I think, I know it's a bit of a pithy answer but it's definitely a TM, I think it's TMG level responsibility, but then the Trial Manager is a mechanism for doing some of the operational stuff, CTU are, but, and obviously trial managers bring their knowledge and expertise into the discussion but it's got to be a consensus of the TMG I think." (Interview 7, Trial Manager)
"I think, ultimately, the chief investigator but they need to be supported, by a team, to show them the information on what retention levels are" (Interview 10, Study Co-ordinator)
"Well from the recommendations and regulatory point of view that would always be sponsor because they are responsible for the conduct of the whole trial, you know, and outcome and then publication. But, but they, if, I think it's, it's the project management, it's whoever, whoever is responsible for the, for managing clinical trial project, but in most cases that would be the, either sponsor or delegated party" (Interview 11, Clinical Trial Monitor)
"We all are. Everybody that comes into contact, you know, with the patients and everybody that's involved in planning how the study is implemented and how the study is designed" (Interview 17, Research Nurse)
"Well the team, which means the buck always stops with the CI, but I think the team in general" (Interview 21, Principal Investigator)
"Usually the trial management group, so the PI, the trial manager, but you usually ... so most trials have a trial steering committee, and they're usually made up of experienced statisticians, trialists et cetera, and you always run through all your strategies with them and the co-investigators who ... so you have a big meeting with co-investigators, the trial steering committee and you do all of that so that you have got lots of big brains in a room to give you strategies, and hopefully people who have come from different areas as well and run different trials, so have different thoughts….we also have a PPI member who sits on the trial steering committee, and we have PPI groups all through. (Interview 3, Trial Manager)

"It would be the chief investigator in discussion with the trials team and a good trials unit will have lots of experience and will give some advice… we tend to have a local group and a national online group of PPI and that's exactly the sort of thing we'd ask them" (Interview 8, Principal Investigator)
"The Chief Investigator and then as part of the steering committee, you have sort of clinical expert advisers who are working within the site but also outside the site as well. Like statistical advisers, advisers from outside your own institution and of course Patient Public Involvement Team as well. They're the key people on the steering committee." (Interview 9, Study Co-ordinator)
"It would be trial manager, the chief investigator. Statisticians might get involved or your co-applicants on the ground. You would just try and engage everybody as much as possible to come up with a strategy." (Interview 12, Trial Manager)
"The full team I think, I was very glad to see more and more equal say is coming to the patients and public." (Interview 16, Trial Manager)
"Well that would be the study, you know, if it's an in house study, if it's a study that we're providing from here, from in house, then it is, we're more in control over it, yes obviously, and you can make it more suitable, say to your local population. But if it's a study that's come from an outside sponsor then you're very much dependent on their protocol. But what you can do is when you communicate with the sponsor you can tell them what's challenging, you know, what you're finding difficult and then you can, between the two of you, you can discuss how you might overcome that" (Interview 17, Research Nurse)
"The management team, usually led by the global project manager over in Australia, I guess that's where the ideas come from, and then it's approved by the management and then goes to ethics. So at the end of the day it's ethics who decide whether we can implement it first." (Interview 20, Trial Manager)
Proactively planning for retention
Planning for Power
"I believe it's the CTU wide experience. I imagine there's quite a few statistical papers that have built that over the years, it's just ... yeah, it seems to be an experiential thing within the department, within the statistical community that that's the kind of levels you're expecting." (Interview 2, Trial Manager) *"So 20% is the worst response rate I'm hoping for, certainly for that portion of it. Obviously that long term follow up that I worked on when I was an administrator that was significantly more because it was that elderly populous. Yeah, for the whole sample size I think that was 50%, but that was because it as a ... and it was a long term follow up." (Interview 2, Trial Manager)*

"So for one of our trials it was 80%, we had an 80% retention rate, so we anticipated that we would lose 20%. For another one of our trials I think it was something we thought that we would only lose 6%, so again, it all depends on one, your patient population, and two, how you're gathering that data." (Interview 3, Trial Manager)
"It's difficult because I don't think you'd really expect only 10% for two years but again it's statistically influenced but there's probably also an element to you can only inflate your sample size to a certain level before it becomes unviable to fund. And you can't necessarily, it's probably very hard to inflate your sample size by 20% to account for that. It's a degree of balancing and pragmatism over what lost to follow up would be and what the funders willing to fund" (Interview 6, Trial Manager)
"I think, predominantly, it has been by looking at the literature and seeing what other people have done…it's a mix of judging it on previous research and then also using clinical knowledge to inform that" (Interview 13, Trial Manager)
"If there's been research done in that field before, it will very much look at the data from previous research. If there's no data the 20%'s going to take us as a standard methodological approach" (Interview 16, Trial Manager)
"I mean I think it is mostly experience from before and from similar trials…..it'll probably be about ten or 20 or whatever, but you've then got to really think about the study design and what patients are getting out of it and see" (Interview 21, Principal Investigator)
Implementing retention strategies
"But I think trials now are perhaps trying to think about this more in advance and plan more things in from the start because it just makes things easier." (Interview 4, Trial Manager)
"we're planning a retention strategy from the beginning" (Interview 7, Trial Manager)
"How likely is it that people will be attracted to it for whatever reason or not? And how likely is it that people will abandon the research along the way?" So it has to be part of that initial conversation around the protocol because I'd say there's no point in recruiting people if you're going to lose them in a week's time or, yeah." (Interview 17, Research Nurse)
"*We had retention strategies from the word go really" (Interview 18, Research Nurse)* *"It was in infancy really. It was while we were building up the study really…. no retention studies came in once we started recruiting really. They were all prior to it. They were built in." (Interview 18, Research Nurse)*
"*Oh, I mean right from the start we try and maximise the plans that we have" (Interview 24, Principal Investigator)*

"so right at the beginning when we do the site initiation visit we train the teams in the importance of retaining patients, and also a lot of trials when they do their grant application they only put in that they'll pay a site, so for example, for accrual, a consent or a randomisation. But what we have done is we will also pay the sites for a full data set." (Interview 3, Trial Manager)
"R-And you said you look at, you know, data sets and you monitor data, is there anything that you do at a site level to encourage them to have complete data sets and to get them to, you know, follow up participants and get that information from them? *P – From my side, so you see, like, there would be a general requirement that I will be checking for the completeness, like. In some cases if this is related to primary outcomes or safety related data that, that, I don't actually, in most cases I wouldn't need to encourage them because they would end up with deviations and, and some, I don't know, like non-compliances that we'll have to manage then together. So basically explaining them that it's easier to do their job from the very beginning, accordingly, you know, like properly, would prevent from losing this data or you, not documenting it properly or, or, yeah basically yeah, it's, you're right actually. It's just I don't think that from my perspective I was ever thinking this way but it actually, it helps, it helps to, you know, ensure the completeness, it's how, what strategy is big in work with sites" (Interview 11, Clinical Trial Monitor)*
"I know when I do training, part of the training to the sites, is all about the importance of retention and making sure that's communicated to the participant so that they're aware of how important it is as well. You hope that comes across but we don't have a way to monitor that" (Interview 12, Trial Manager)
"So at the beginning everyone gets the same training at site initiation, but then we will target it because some sites won't have an issue but other sites you will notice, "Oh, actually you're not following ... we're losing these patients, what's happening?" and we will target those sites." (Interview 3, Trial Manager)
"The vast majority of it will be across the board. If we said that everyone gets a voucher, nobody would not get a voucher. And if we were doing a newsletter, everyone would get a newsletter irrespective. Whether or not you get the reminder emails obviously depends on whether you've responded to the questionnaire that we're doing. That's influenced by the participants behaviour." (Interview 6, Trial Manager)

"They've, I think they've pretty much been a blanket approach. I think especially at the beginning of a trial because you don't know if some different characteristics will emerge, and also from a deployment point of view, if you've set something up to go automated you've set it up for a reason and that's because that's the resource and the budget, so, but we would be open to looking at if there was a different behavioural sort of characteristic within a particular, maybe site or something" (Interview 7, Trial Manager)
"It would be a blanket approach and I think that that probably is more ethical because trying to maybe decide between the patients I think adds a whole other level of complexity that I think would be difficult to achieve. Maybe if you'd more staffing and things like that you could work out some sort of criteria system but I think in the, you know, kind of in the system that we're working with I think that, yeah that blanket approach is what we would apply anyway." (Interview 22, Head of Trial Operations)
"hopefully it's [good retention rates] got something to do with the way we're doing things, as in, you know, making sure the patient understands what their commitment is before they sign up… What's expected of them, being clear about that, not being woolly, you know, not saying like, "Oh you'll have a few questionnaires to do along the way." If you've got six questionnaires and each of them is 20 pages long, you know, be truthful and open and honest about what's expected" (Interview 17, Research Nurse)
"I always, I also think being very clear of what it entails. Our study was follow up for 12 months. Really it was being very clear of what was involved the whole way through and in that you will be getting surveys every two months, you would have to fill them in. You would be contacted by the nurse. You know what I mean. That they were clear the whole way along of what was involved." (Interview 18, Research Nurse)
"in the patient information leaflet which is given to the patient at the beginning of the study so it's at that stage when we're telling the patient about the study, we're saying, "Okay listen. This study is quite involved. There'll be 12 visits per year. Means it you're to come into the clinic every visit. Every visit could take two to four hours or whatever length of time it is." I think at the very beginning you have to educate the patient correctly so that they know." (Interview 19, Clinical Trial Unit Director) *(recruiting participants that will stay in the trial)* *"Well I guess it starts from the beginning as in selecting the patients. If you were selecting a patient for a clinical trial, you have to ensure that the patient will meet their appointments anyway. It starts at educating the patients from the beginning. If you*

had a patient who didn't seem to be attending clinic much or there were numerous DNAs or that type of thing, they probably wouldn't make a very suitable clinical trial participant." (Interview 19, Clinical Trial Unit Director)
Communicating the importance of retention in the trial (reported under Implementing retention strategies)
"I think from patient information sheets I've read, that's probably not emphasised enough. But I think it's a balance between you want to make sure the patients are fully informed but then it's also, you don't want to provide too much information because then they won't read it properly. You want to be succinct but obviously they do need to be fully informed about what they're signing up to. Explain the importance of retention in that perhaps might make it too long, I don't know." (Interview 4, Trial Manager)
"I think we do include that in the patient information leaflet and we do include it in the letter that goes out with the questionnaires……It's more prescriptively in the written letters and in the patient information leaflet but we do a lot of work with the data co-ordinators so that they can respond to those questions so that they know it's important for people if they haven't had the operation to, we still have that information. They can almost give that same response to explain to the people that whatever their data is it's always important to us. However much they don't feel that it might be, it is." (Interview 5, Trial Manager)
"It, yeah according to those sort of, that sort of terminology. "You are really important to us, regardless of the group that you get allocated to or put in, your information" we, sort of, say data, but, "Your information, your questionnaires, your visits are really important to the success of this study…. That's in the patient information leaflet, that's the sort of terminology in the patient information sheet for sure" (Interview 7, Trial Manager)
"I think that would be probably recorded in the information leaflet and then also when we come to the end of each assessment it would be like, now we'll get you to come back in three months' time. We want to see how these measures have changed and we'd be as encouraging as possible for them to come back to each follow-up assessment" (Interview 13, Trial Manager)
"one time I did a follow up call they were like, "Oh, do you know, I feel like maybe I'm not really any use to you anymore because I'm not using a catheter so I don't really see where my data ..." So in that instance we always say, "Well actually all the data we still get from you is really, really valuable data, however it's entirely up to yourself whether you want to continue or not", and we obviously highlight the whole that if they decide to withdraw their care's not going to be affected in any way, all the things that's said on the consent form. But we would always say to them, "That data, actually what you're contributing is still really, really valuable so if you are happy to continue then we would love to have you still being part of the study. However we totally understand if it's not suitable for you anymore…." (Interview 14, Study Co-ordinator)

"that will be done by their meeting clinician and the on-site trial team. How this is important to the follow-up visits are for the trial." (Interview 15, Co-Investigator)
"I know the ethics committee can sometimes put a hand in the way about wording and say that that sounds too coercive. I think, hopefully, that's actually in the past. We've had that in the past about it but it was a good few years ago until we could have demonstrated that, actually, they need to be shown in a way that it is important." (Interview 16, Trial Manager) (talking about the communication of the importance of retention in the trial)
"Yes, yeah absolutely,…that's more, more likely to be in the verbal conversation, yeah." (Interview 17, Research Nurse)
"Yes, that would be definitely a bit part of getting consent, the PI will sit down with them for half an hour, as long as they need and would definitely go into that, being the follow ups. The outcome assessments i.e. the follow ups, "They are our most important part of the trial, they are how we determine the results of the trial, so it's really important that you give thought to whether you'll be willing to do that six months down the line", because it is six months down the line, a lot can change in that time. But yeah, an emphasis is definitely put on that" (Interview 20, Trial Manager)
"I think that's definitely discussed with again, a caveat that, "You can withdraw at any time and you're completely within your rights", and whatever. I mean I would have quite an honest conversation with patients who do want to withdraw. I would never obviously try and persuade somebody from not doing so, but if you can fix whatever issue it is like doing questionnaires at home or not participating in some bits of the study or something, to explain that, "Some of your data is still useful even if you're not willing to fill in the questionnaires", or whatever it is, I think that would be helpful" (Interview 21, Principal Investigator)
"R -And would they be told about the value of remaining in the trial and how it's important that they continue to provide follow up information? *P – Yeah, so the expectations around their participation in the trial would be and should be discussed with them and communicated to them again prior to consent, yeah that would be" (Interview 22, Head of Trial Operations)*
"R – Are participants told about the importance of staying in the trial and continuing to provide follow-up information? Regardless of what trial group they're in or anything like that? It's just important for them to keep in contact and keep providing follow-up data.

P – Yeah. That's all part of that conversation. Yeah. Without trying to overload them. Yeah (Interview 23, Clinical Trial Practitioner)
"Absolutely yes, now that is absolutely something that we do play up in the newsletters you know, as a routine almost, we would certainly play that up in general to all participants whether they've expressed any concern in continuing or not, so, yes." (Interview 24, Principal Investigator)
Reactively planning and implementing retention strategies
"I would say post the first follow-up visit is when you will devise any strategies required in terms of retention." (Interview 15, Co-Investigator)
"Well the only time it will possibly change if we were seeing a particular issue in terms of withdrawals, or, where that would start to become at risk. So it would be engaging with the research teams at the hospitals in particular just to see if there's something particular that ... and try to find anything anecdotally that might ... whether it's the structure of the trial or something like that and perhaps something more fundamental like that where it might be an issue with the protocol or something like that, but those are the big problems. So it would have to be kind of base method and then ... and subtract, people have ideas that they'd like to check or implement and then something a bit more robust if the trial is at risk." (Interview 2, Trial Manager)
"There would always be a standard baseline of retention that would be done, like the vouchers and reminder emails. But the extra thing that, the extra work that is ongoing now is driven by not meeting our targets. That's prompted that." (Interview 6, Trial Manager) *"Obviously if you've hit a risk assessment trigger as is kind of happening in this trial per sae where we're going over the lost to follow up that we'd anticipate, then that triggers additional action which is why a more involved follow up campaign has been created" (Interview 6, Trial Manager)*
"I think we constantly monitor it so we just keep an eye on everything. If it is looking like it is dropping off then we, maybe, put in more newsletters or things that we might think about." (Interview 12, Trial Manager)
"I guess if it's higher than you expect, and particularly higher than you've budgeted for in your sample size, that's probably the defining feature…"[Name of study] is my real first foray into studies of that size so I probably came in with a lot less

understanding of what was likely to happen. So I think that's a little bit more gut feel rather than having something to compare it to" (Interview 21, Principal Investigator)
"When we've used vouchers it's tended to be later on in the trial where I don't think we've ever, certainly a trial I've worked on, we haven't used vouchers upfront. It's always been later on where you're looking at the form return rates and then you think okay we could perhaps move some money around in the budget and make some funds available for purchasing vouchers and something we do for healthcare workers is prize draws and things like that. But so that's more reactive in that we haven't planned for that upfront. It's been something you'd use later on if you're struggling." (Interview 4, Trial Manager) *"I think from experience there's been no specific section about retention strategies you'd want to implement from the start, sort of outlining we expect these issues therefore we're going implement, these strategies will be used from the start of the study to combat that. Like you say, I think the only thing that is explicitly stated is about anticipated dropout rates so then you inflate the sample size by about 10% to combat that." (Interview 4, Trial Manager)*
"We wouldn't at that point look at anything around participant fees if that wasn't already implemented. But we would try and speak to sites and see if there was something that we weren't aware of and if it's specific site, and sometimes you've got sites where you've got research nurses who are much more engaged with you, so you can have a conversation with them. They might be seeing them in clinic and getting some feedback that we're not aware of or just trying the newsletters or putting something in there that states, it's really important that if you think it's the people that haven't had the operation or having to wait a long time, saying, "We thank you for your patience" or addressing what you think might be the issue or what you found to be the issue within that newsletter or within the site." (Interview 5, Trial Manager)
"It depends what we think is the root cause I think. Sometimes we'll need to contact sites and say, you know, "Please can you assist us with this?" Which might be more patient contact or something, it just really depends on what the issue was. If people aren't filling out a questionnaire and we see this trend happening we might introduce, what we did do once is we introduced a pre-questionnaire, I mean, email saying, you know, "This is coming, we just want to let you know this is coming." So it's a prior notification that a questionnaire's coming. The, you know, we could never tell whether it made any difference or not because we weren't, you know, set up to do that but we did do that one time. So just putting an amendment obviously to have a new communicate going out to all the participants to try and, to try and not make retention worse" (Interview 7, Trial Manager)

"Well it would usually start with a motivational email to the study staff saying, "This has gone wrong. How can we share best practice?" and it's all quite soft touchy feely type approaches to it highlighting to the team, "This is a problem", but you could potentially reassess whether you should be reimbursing participants for. But I think we would start by assessing what the perceived problem was, and you might need to simplify the study." (Interview 8, Principal Investigator)
"We would talk to the people on site. We would talk to the research nurses, to the principal investigators onsite to find out what are the reasons, what are the impediments to retention. If there are some things which are beyond our control. For example I think there was one site where the clinic was moving from one place to another place, that causes a problem. That is beyond our control and that will obviously have an impact on retention. Where reasons are where we could provide an incentive of a nudge, in terms of a phone call or a reminder from the research nurse, we will, obviously go with that." (Interview 15, Co-Investigator)
"No, not really [no reactive strategy when issues identified with penultimate questionnaire return] because we'd followed the same process in that the survey went out and we had a good return [rate to this point] and I think these people knew it was the end of study….I kind of trusted that they'd come back up at the end of study and they did" (Interview 18, Research Nurse)
"We'll definitely re-evaluate, because we deal with multiple different countries a lot of our ethics forms are ... sorry, our consent forms go through ethics and they're national templates, and our monitoring visits there have been situations where we kind of we're like, "Oh, why does this site have a high loss to follow up?" or things like that, and we'll then go to our consent forms and they could be worded quite harshly so then we have to review that. So there is, there's constant reviews of things like that based on retention I suppose. But there's no strategies from what I've gathered that have been placed from the beginning, it's very much touch and go." (Interview 20, Trial Manager)
Influences on the choice of retention strategy
"Yeah, there's a couple of journals that we keep an eye on like Trials and those that might provide information … so you don't fall into the notion of well if you do something rather than do nothing." (Interview 2, Trial Manager)
"So it all depends on what trial you're doing and the design of that trial because some patients will be coming in for regular appointments, whereas some patients will come to a clinic and they won't ever come back to a clinic, so all the further research appoint..., all the further follow up appointments will just be purely for research. So it all depends on the population of the patient that you are designing your trial around." (Interview 3, Trial Manager)

"And then you get also into environment considerations. People don't like plastic. People don't like cheap things that have come from abroad. You get into this whole realm of what's appropriate and what's not." (Interview 6, Trial Manager) *"What we think an Ethical Committee would approve. Like I say with money they were quite sensitive to that. I don't think that they would approve one group getting info and another group not getting info. And also, kind of the timescale that's involved in getting that ethical approval. It does influence some. It will be very common that we'll say we can't do that because we have to go to ethics". (Interview 6, Trial Manager)*
"We try to keep up to date with what's gone on and what new things are emerging in the literature. Yeah. We always have to keep an eye on the budget, we can't just be sending out lots of letters without thinking this is going to cost so, yeah, that absolutely has to be thought about." (Interview 12, Trial Manager)
"I actually think that we probably do a lot of those things pretty just innately without really giving much consideration or formal planning to them….I think just because we're so experienced in delivering these studies but it just happens as part of our day-to-day thing. It's just like, oh, okay. Well, so and so's got this assessment, well make sure you send them a text message" (Interview 13, Trial Manager) *"It's experienced based. As I said, a lot of the evidence for retention is coming from returning of patient reported outcomes. There isn't as much evidence in support of how you maximise retention in the studies where you're getting them to come in for inpatient visits. For us, we've been relying on our experience of running these trials for the last 10 years." (Interview 13, Trial Manager)*
"Yeah, there's obviously need for a lot of evidence out there to see which strategies but things like Shaun Treeweek's work for Christmas cards and things like that, we don't do that" (Interview 16, Trial Manager) *"I think because we have had success with that, we would just repeat that process." (Interview 16, Trial Manager)* *"I also think just myself as well, I wouldn't like to be hassled or something more than three times, I think. Yeah. There's got to be a cut-off for resource or management of the trial, as well, it would be too hard to keep a track of five different methods" (Interview 16, Trial Manager)*

I don't think you would ever get past an ethics committee to have more than three reminders. We've discussed that in our committee quite a lot. I think somebody had up to five reminders in their application and it wasn't approved. I think three's very much seen as the, not-hassling approach (Interview 16, Trial Manager)
"Well again, you know, that's [retention strategy] driven by the sponsor, yeah, if it's a sponsor's study then it's up to, you know, we can't, we don't have that control over that" (Interview 17, Research Nurse)
"I just know that's how people's lives work. Giving them an actual printout and telling them what is going to be happening, put it in your diary, this is how it's going to happen. Not surprising them with anything. But I don't know is that a personal thing? I don't know, you know, that I just felt that is how it should work. I think that worked. I think there's a bit of the person experience and other research really would be the key things" (Interview 18, Research Nurse)
"It very much depends on the study and very much depends on the sponsor and the budget associated with it." (Interview 19, Clinical Trial Unit Director)
"I don't think we know. I think we sort of make it up. It depends on what people think and what their experience is and what we've got funded." (Interview 21, Principal Investigator)
"I would probably do two telephone messages, an e-mail or a letter and ask for a little bit of in and then if they don't respond to those, then actually I will say that's enough. I don't want to harass people because you don't know what's going on in their lives, do you?" (Interview 23, Research Nurse)
"I would say we build in approaches based on probably previous experience of what worked, and most of them are not particularly costly I would say, but we do build in costs for newsletters or costs for data linkage to the central registries which can be more costly these days, so those costs absolutely going from the start" (Interview 24, Principal Investigator)
Challenges with planning and implementing retention strategies
"Sometimes I feel it's better to contact the participants because the records are not very updated, because I think the Cerner thing isn't very much updated, the nurses tell me that. Because usually when I ask them, "Can we not check the records on there?" then they would say, "Oh no you can't." It's just because we are not very 100% sure that this is updated and we crack on calling the patient" (Interview 1, Study Co-ordinator)
"I guess it's just bread and butter. It can be and I think sometimes depending on where you're at in the study might influence where, what you do. Well, I guess it depends what you're implementing but it might mean quite a large amendment that has to

go to the Ethics Committee and that can take time to pull together. If you're six months from the end of your study, by the time you've got that and implemented it, it's probably not going to be worth the impact but if you've got several years and you feel that it's going to impact on that, then that might be useful" (Interview 5, Trial Manager)
"If we have to be reactive like we have in this trial where retention has fallen off much more quickly then we were expecting, we can't increase the budget. We've just got to work with the staff that we've got available" (Interview 6, Trial Manager)
"I think it's been quite straightforward mostly. I think we have had a bit of pushback from sites regarding contacting them to look in the medical records. Because it wasn't something we initially decided to do so at some sites we're very fine to do that. But it is a little bit time consuming so we did have a little bit of pushback but it has not been any problem. I think there's one site we have that isn't going to be looking at medical records and the one out of the 50, it really isn't too bad. So, I suppose, if that had been decided right at the beginning, probably wouldn't have had that one site not agree to do it. Mostly the sites are very positive and happy to follow our lead of what we need so, yes, I don't think there's been any particular challenges about those specific strategies that we've been adding" (Interview 10, Study Co-ordinator)
"It's not possible or practical, mid-trial, to change the primary outcome so the only way we've been able to mitigate that loss in primary outcome data is by actually extending the accrual target which is what we're doing now. We're recruiting an extra 12 participants. That's the only way that was feasible to mitigate that loss in retention in that trial" (Interview 13, Trial Manager)
"if you're not thinking of that then protocol, at the start, it's not going to be costed correctly or resourced correctly. Because it takes time, these letters. Follow-up calls and things all take a great amount of time" (Interview 16, Trial Manager)
"I mean if it was done at the start we wouldn't have to then implement it, we could just do it as needs be and ethics in every country seems to be a time consuming process, a back and forth process. So yeah, it would delay things and it's just more of a frustration for the trial, yeah." (Interview 20, Trial Manager)
"If you've thought of things later and you haven't got the money, which happens quite a lot, then you've got to try and do things that are cheap or free. If you've obviously thought about that more upfront then you can cost for it" (Interview 21, Principal Investigator)
"Yeah it is more limited, we did, for that particular trial we did question whether we should look at redesign, that at the stage we're at it would kind of too much of an impact on the scientific integrity, certainly in terms of crossover. What we are now discussing is whether we actually should randomise 2-1, and so just boosting the number of patients that are in the control arm to kind of allow for the drop out so that when we actually do the comparison at the end there'll be enough data there. So it is more challenging though, absolutely, and it does involve, you know, it will involve a substantial amendment and, you know,

looking at the stats piece, obviously in terms of the, and when you're doing it in the middle as well you need to really home in on what the reason is and whether it is something that you can or can't address, and sometimes it might not be something so yeah" (Interview 22, Head of Trial Operations)
"We've never organised transportation but I do go out of my way to help with parking. It's getting more and more challenging but it used to be quite nice I could smile nicely to our reception team at the main hospital and they would just sign the ticket off but it's less simple now which is a real pain" (Interview 23, Clinical Trial Practitioner)
"I mean one thing we've noticed in one trial is that historically if it was difficult to track down a patient, that contacting their GP practice to get information was effective, but that has changed. GP practices are so overwhelmed with work that our incoming requests about a chronic disease trial is not at the top of their list and can easily go ... I wouldn't say ignored, but they've got other things to do. We do often get comments back saying, "This is not part of our contract, we need payment", so sometimes it goes nowhere. So for example, phoning up a GP practice, trying to explain what you're looking for is proving more problematic than it used to be" (Interview 24, Principal Investigator)
Informal ways to improve retention
Motivation and investment
"The more invested the site team are then the more invested they are with following up participants as well, whether that's chasing them for a phone call if they're doing that or whether it's actually seeing them in clinic" (Interview 5, Trial Manager)
"in our department the whole thing's run on a shoestring with a lot of goodwill. We're under resourced but we just have a team who are highly motivated, yeah…….you can have all the policies in the world, but if you've got someone who's dynamic, enthusiastic and really cares for the patients people will do anything for you….it's better to have kind and caring and enthusiastic nurses who can retain the patients and be motivated" (Interview 8, Principal Investigator)
"I think, actually, compared to some of the other trials, just the patient group that are taking part in our trial, they're less invested in *the study…In this case, the surgery the patients are having is nothing to do with, really, the trial. It's just the so often I think, actually, I would say that the patients aren't too invested, really, in the study. Actually it is quite good to still see the levels of follow-up that we've been having" (Interview 10, Study Co-ordinator)*
"Our 97% was a questionnaire study so yeah, just really invested women, I think, in that trial" (Interview 16, Trial Manager)

"I suppose it was my study, I was invested, very much invested in it. I could see the benefits for the patients and the patients could see the benefits along with me….They felt in control as well that the surveys are, that the study wasn't controlling the whole thing, that they had some ownership to it too which was very important" (Interview 18, Research Nurse)
Relational aspects of retention
"we find that it's because the patients feel as though they're supported all the way through the trial because they build up a relationship with the research nurses, the research nurses know them, they can do a bit of chat and not just ask research questions. I think that is really important if you want to try to retain patients, especially for a longer ... especially for 12 months, it's quite a long time to try to keep somebody in a trial" (Interview 3, Trial Manager)
"I guess it's just, it's that relation building with the research nurses. Being available to them. Always say, "Ask me a silly question because I can answer those" (Interview 5, Trial Manager)
"I'm also doing a trial where our follow-up is monthly phone calls. I think when you've got that amount of participant communication your retention's going to be high because quite often you have that extra chat with them that they like." (Interview 16, Trial Manager)
"I think the things that we concentrate on is, you know, that relationship we have with participants, about making it very, very friendly, very honest, very open, very available" (Interview 17, Research Nurse)
"I think knowing where the patient is at is very important. Understanding what they've been through to get to this point and what you're going to offer them and how can it benefit them is very important. Putting yourself in the patient's shoes I think is very important. Being empathetic with them of what they're going through is very important and having somebody on the inside that knows the clinical landscape is very important" (Interview 18, Research Nurse)
"they have a relationship with us through their clinical care as well which helps. I think that provides a bit more impetus to stay involved….I think it is mostly the relationship that makes the biggest difference." (Interview 21, Principal Investigator)
"I think the patient's experience and the site staff are really, really important from a retention point of view. And so, you know, that they feel engaged and that they are engaging, so with the trial that I suppose they feel well looked after, they feel like the trial staff are giving them the time, that they're answering their questions, if they do phone up with a query that, you know, it's heard, I think all of that is really, really important as well because if they start to feel like a number, you know, they're going to be less engaged and perhaps more likely to drop out" (Interview 22, Head of Trial Operations)

"wherever possible consistency of staff, retention of staff at a site, and that is often obviously outside control of the central centre, but constant changeover of staff is not great from a participant perspective. They do like the idea of seeing the same research nurse each time" (Interview 24, Principal Investigator)
"I would say we have a general blanket approach in terms of the initial reminder but we would have then, a targeted approach for more, I suppose, people who we deem to be high risk of low retention. We'd have a good guess on them, who needs, maybe, a bit more support to get the information back. We would support them to do that." (Interview 13, Trial Manager)
In terms of follow up and stuff like that, that's done kind of really on a case-by-case basis really. When the nurse gets to know the patients, some patients might need more attention than others and it's like a personalised tailored programme (Interview 19, Clinical Trial Unit Director)
"I will aim, always, to individualise something because folk like to be treated as an individual as opposed to receiving a perfunctory letter that doesn't really express much….I try and tailor it and individualise it a little bit more in accordance with who it is I'm trying to contact [for follow-up]" (Interview 23, Clinical Trial Practitioner)
Effectiveness of retention strategies
"I think we have not formally analysed it but I feel like it does really work, we believe it for some reason and we keep on doing it because I think it's not that we have analysed, you know, patient wise or study wise but I think newsletters, getting in touch with PPI has really helped for retention" (Interview 1, Study Co-ordinator)
"I have certain scepticism when it comes to some of them, so like does that actually work just you know, not quite a ... just a myth or confirmation bias, or. But there's a lot of work going on with, and a lot of encouragement to bring in SWATs into these trials. Worked on one a little while ago…." (Interview 2, Trial Manager)
"I'm going to say yes [retention strategies are effective] but I have no evidence to support that. It's a feel" (Interview 5, Trial Manager)
"To formally evaluate again you have to go through the Rec so the Rec, they weren't happy for some participants to get money and others not to get money. Everything has to be… I don't know. It's where the difficulty comes in. Would you get ethical approval to send one group a newsletter and another group not? Probably not" (Interview 6, Trial Manager)

"The voucher is effective because that's been researched and we did a SWAT analysis on it…so again because we've researched that, and we've seen it's effective then we would do it." (Interview 6, Trial Manager)
"If we don't do reminders for this within the, if we compare reminders or no reminders or reminders with different reminders, what if one of them really bombs and you've missed your chance, you can't go back. You can't go back and get that follow up data" (Interview 7, Trial Manager)
"Are the strategies formally evaluated in anyway or is it just through experience that you see that they are effective and they're working? *P – It's mainly through experience…We would have a system in place whereby we're tracking the patients visits so we know when a patient's due to come in and if they don't come in there's an alert on the system" (Interview 19, Head of Trial Unit)*
"I think it's just ... to be honest, the workload is heavy enough. I hate to say that, but I think that is what it is and this is just one tiny aspect of everything the project manager is doing, the assistants are doing, the research coordinators are doing and I'd say that is the only reason because it would be very beneficial and very useful to do something like that." (Interview 20, Trial Manager) *"I think it will be self-evident based on if loss to follow up reduces and then ... but there's no ... no, I don't think there's any actual evaluation on the strategies in place at this time" (Interview 20, Trial Manager)*
"I'm sure others have done methodological research with randomisation to look at which approaches work best, but we haven't done that kind of work ourselves" (Interview 24, Principal Investigator)
How are retention strategies communicated and documented in trials
Communication within the trial team and documentation in trial protocols
"Generally a meeting I think usually. I think that's, I mean obviously you can send them an email but I think a meeting is better because if you have, you can get feedback straightaway if your suggestion is a problem or if they think actually that's not really going to work because of this. discuss and come up with maybe a better plan." (Interview 9, Study Co-ordinator)
"We have regular trial meetings with just the trial manager and there's three other trial co-ordinators. I suppose it would definitely be discussed there first, before any wider group. Then it would probably be discussed within the wider academic

team, as well, with other trial managers with other studies. It would probably feed into a bit of a group discussion on those sorts of things." (Interview 10, Study Co-ordinator)
"Yeah, so it would be communicated in the team meetings and the project management group meetings and the main team and then it would be communicated to sites through, well obviously site initiation visits they would get told that this was what was happening and obviously it's in the protocol and they obviously got all that." (Interview 14, Study Co-ordinator)
"I would expect them [main site] to tell me. They're going to tell me in a newsletter. They're going to tell me at one of the joint meetings, they're going to tell me via e-mail. However they want to do it, they need to tell me. Yeah" (Interview 23, Clinical Trial Practitioner)
"I would say that your retention strategies aren't written as a specific point in your protocol, but your design should be incorporating your retention strategies. So it's not a case of it should be a specific section, but for example, for us "If you don't get them at three months, get them at six months, and if you don't get them at six months get them ..." that's all written within the protocol, so that would be your retention strategy… It's all in the protocol. So although it might not, when you're reading the protocols you might not have a specific retention strategy, but when you read the protocol as a whole you'll see, "Okay, we're trying to do clinic visits. We're trying to give them options in how to complete things. We're giving windows, we're saying, 'If you don't do this carry on here'", so they would be all your retention strategies." (Interview 3, Trial Manager)
"I think from experience there's been no specific section about retention strategies you'd want to implement from the start, sort of outlining we expect these issues therefore we're going implement, these strategies will be used from the start of the study to combat that. Like you say, I think the only thing that is explicitly stated is about anticipated dropout rates so then you inflate the sample size by about 10% to combat that." (Interview 4, Trial Manager)
"It [the protocol] needs to be loose enough to allow for all different forms of communication at different points in time. We don't want to pre-specify everything that we're going to be doing. And also, it is a nightmare if you create a really detailed protocol, then everything is a protocol deviation and you will wrap yourself up in knots doing incident forms. (Interview 6, Trial Manager)
"It's not a word document, it's not a policy document that we share. It's discussed and agreed in meetings and written up in minutes." (Interview 7, Trial Manager)
"R - For the trials you've worked on in terms of retention strategies, are they outlined in the trial protocol?

P - No. *R - Is there a reason that they're not?* *P - Because the trial protocol fills in a template and you answer all the questions, it's already 140 pages long, if nobody asks the question it's not going to be there." (Interview 8, Principal Investigator)*
"R – And in terms of the communication of retention, from your experience are retention strategies outlined in trial protocols? *P – I, no I don't think I've seen much in terms of retention strategies.* *R – Why do you think that's the case?* *P – You know, the trials that are in big demand, you know like, actually very promising substances, it's like, trust me they wouldn't need much of retention strategies" (Interview 11, Clinical Trial Monitor)*
"That's always a woolly one. Yeah. The trial protocol often just says newsletters or other regular. It's not specific. It's usually quite obtuse so that we can come up with something new or use the same old….. I think it's just in case we decide to do something different which doesn't often happen….. It's loose enough that we could still do it but it would still need amendment. Because if it's a thing that you're sending to participants, that still needs ethics approval" (Interview 12, Trial Manager)
"Because I think lots of people are just naturally doing all these things to try and maximise the retention. Because ultimately everybody wants to collect much of the data that they plan to collect as possible. You are going to do all of these things. I don't think I've defined most of those things in the protocol for our study to know but we just do those things anyway" (Interview 13, Trial Manager) *"We'd have a specific procedure document and we'd highlight those things and that" (Interview 13, Trial Manager)*
"It was written into our policies and procedures and our protocol as much as possible…. I suppose then there was parts of it just in my head which is terrible because it was kind of me leading the whole study and doing it all along the way… some of that personal contact that doesn't get down on the paper I suppose, yeah" (Interview 18, Research Nurse)

"I guess through the protocol in terms of the plan, site initiation visits, obviously the design of the study and the questionnaires and that kind of thing, and with the site meetings" (Interview 21, Principal Investigator)
"More often than not they are but some of the more kind of nuanced stuff such as, you know, what I just spoke about there around kind of making it really clear to the patients on the assessments and things like that, I mean, it's a given as part of the standard, the ICF process but at the same time we will just stress it, particularly from a retention point of view, but yeah normally there would be, obviously from a protocol design point of view it's going to be designed with retention in mind so that's already in the protocol. In terms of reimbursement and things like that, that will be already in the protocol as well, yeah." (Interview 22, Head of Trial Operations)
P – Well, some include retention strategies [in protocols] and some really don't. *R – Is there a reason you think they don't?* *P – I suspect that they're not seasoned researchers that are writing the protocol, yeah. (Interview 23, Clinical Trial Practitioner)*
"I mean our protocols tend to be I'd say quite light touch. We have a lot of separate SOPs that are intimately linked. We tend to have trial specific SOPs that fit with the protocol. We would not see something like a newsletter needing to be part of the protocol, or indeed reminders, and I don't personally think there'd be need to mention that kind of thing in a newsletter…. I think protocols are good for certain aspects where following the rule book is critical, but there's many aspects where you do want to have flexibility and where the approach to retain participants isn't really an ethical consideration. So the problem with writing stuff down is that it could be considered that you've left something out and then you're not allowed to do it, so it's more that. I mean if we put something like that in we would keep it very woolly or very flexible in terms of its wording because you don't want to constrain your ability to do something that's entirely reasonable." (Interview 24, Principal Investigator)
"If you make that thing mandatory, currently it's only the accrual rates they want to know how you would do that, which is only for recruitment, because everyone is more concerned about the milestones and the time lengths rather than the retention., So there is too much underestimated the problem, we take if for granted I feel, and if it's a part of the design right from the beginning as a mandatory placed in all the protocols, as a check list, even for the sponsor, how do you ensure you will retain it, you know… there's no formal column in there or in the protocol where they would say, "What happens if the recruitment goes

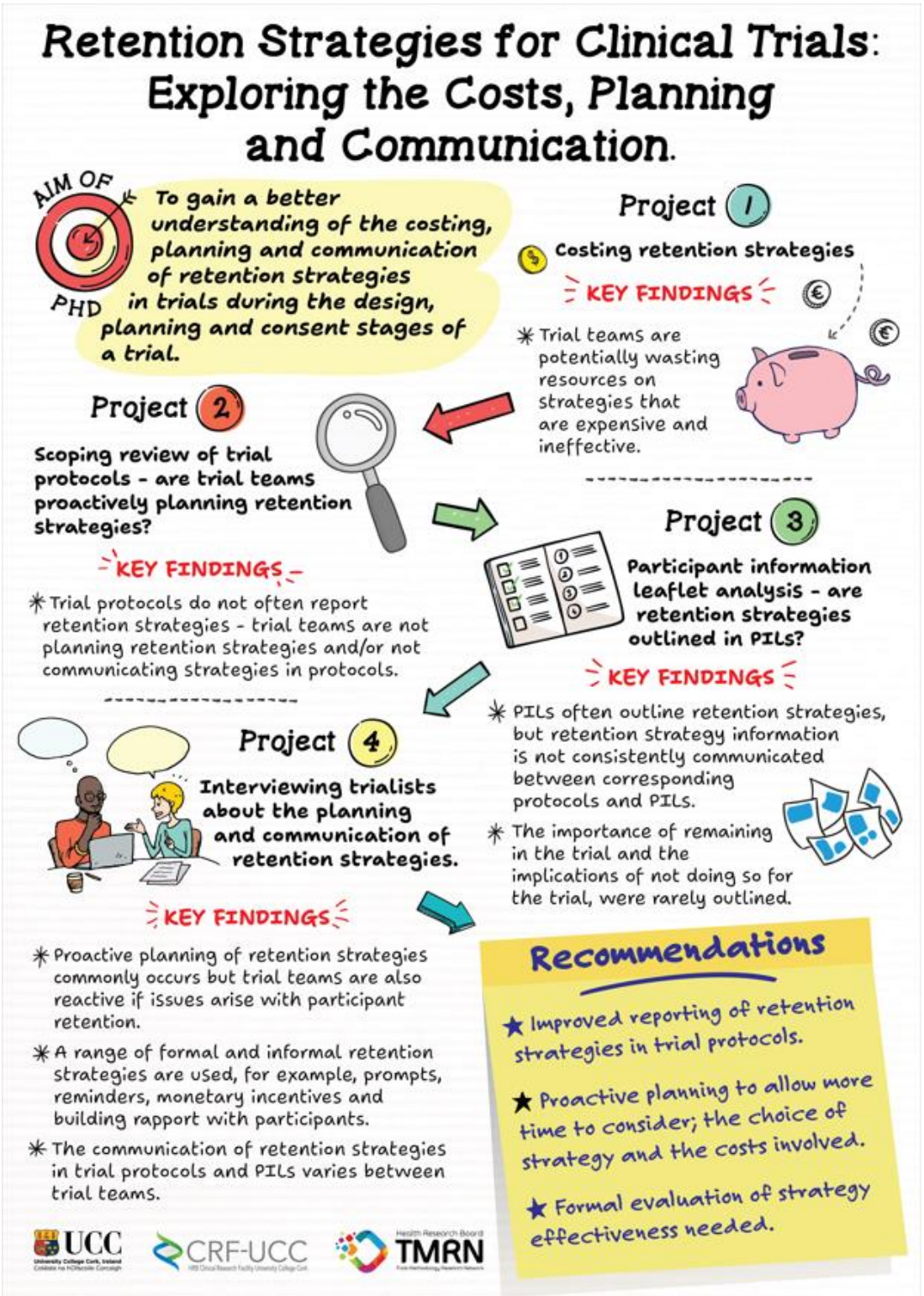
below this this, or retention goes below this, this, what are you going to do?" So it should be in the risk assessment, it should be in the protocol, then it becomes mandatory and we have to design something and follow it. (Interview 1, Study Co-ordinator)
"I think there is definitely space to develop, maybe, more of a framework or guidance for how we should be reporting retention planning in the studies that we do. I think, yeah, it could definitely. If there was more of a framework in terms of how we should be doing it then, maybe, we would see to it….I think it goes back to the guidelines need to be inclusive, very specific or there needs to be some kind of clearer framework in terms of the frame retention and also trialists need to be more aware of the importance of retention and how it can impact your research and how you should be focusing on it." (Interview 13, Trial manager)
Communication with trial participants and documentation in PILs
"With the participants themselves it would be the patient information sheets as they were developed and they'd be notified if there were any particular changes or anything like that, especially if it's something that's had to go to the research ethics committees or something like that" (Interview 2, Trial Manager)
"It's tricky because a lot of the strategies, you perhaps, need to think about by telling them, we're doing this to help you complete the questionnaire, it is sometimes a bit… I don't know, perhaps sometimes, that's going to then result in more issues. Well, it's clear that they know they're getting reminders so that's not hidden. Or clearly they know that it's going to be to get them to complete it so I suppose the information's out there. I can't remember if we put that they'll be getting reminders in the information sheet. I think we might just say, you'll be being followed up by these methods so it leaves room for, we don't say how any e-mails they're getting. I suppose, perhaps, erring on the side of not formally saying to the patient, this is what we're doing to help you complete the questionnaire but all these few methods that I've mentioned are taking place, if the patient thought about it, it's very obvious that you're getting these extra e-mails because you haven't completed it so they want me to complete it" (Interview 10, Study Co-ordinator) *"I think we've just said you'll be followed up by these methods and not stating there and then how many reminders they'll get. Because to be honest, I don't know if that would put them off, actually, to take part. I'm not sure." (Interview 10, Study Co-ordinator)* *"We're trying to change a behaviour subtly so by trying to change the behaviour, it's quite hard if you're clearly stating what you're looking for otherwise it might affect the normal process of changing the behaviour." (Interview 10, Study Co-ordinator)*

"If they get incentives, it will be in the patient information leaflet. Again, in the patient information leaflet, we might be quite obtuse in what we say. Yeah. We probably would say that we might keep in touch with them while we have newsletters or similar so it's not really clear." (Interview 12, Trial Manager)
"It'd be a verbal conversation, yeah….I'd say maybe information leaflet is just, maybe, more general about what's expected of them in terms of the assessments and not the kind of process of how the assessments will be organised. Again, it goes back to, say, frameworks for information leaflets. Retention isn't really considered in the information leaflets at all." (Interview 13, Trial Manager)
"Our patient information sheet for the trial which we are talking about, it certainly doesn't mention anything about incentives or retention strategies at all. That might be either communicated verbally or it may be communicated if they are sent an e-mail or an SMS. That might be part of that" (Interview 15, Co-investigator)
"We also would say that in the patient information leaflet that if they don't return they would get a reminder and then, potentially, they would get a phone call as well so that they know." (Interview 16, Trial Manager)
"Oh yeah, absolutely, that would be part of your initial discussion…, "We realise for example it's going to be a burden on you to come in to the hospital and the car parking here is challenging so, you know, we'll make sure that we don't keep you any longer than we have to and we'll have a voucher or whatever." Yeah, things like that yeah… I think there's always reference to it in the patient information leaflets but, and not always, but you would expect there would be, but at the same time I think the verbal conversation is more powerful, a bit more meaningful." (Interview 17, Research Nurse)
"I don't think I did because I think it was a very standard PIL, you know the way. It did all the necessities, tick box from a legal point of view but I had a one pager, a schedule for the patients so they weren't on the PIL. We had other information that we gave them outside of the PIL that had their schedule and would have mentioned about their reminders on that." (Interview 18, Research Nurse)
"We have got consent on the online study to contact people in between and, so we are doing kind of ... and we sent a Christmas card, like an e-card, and we're doing a summer newsletter because we've got the first data being presented at conference. So I guess they know that that's a possibility that we'll keep in touch with them about the study" (Interview 21, Principal Investigator)
"they [participants] may, you know, for example, like they may be embarrassed to say, "Oh you know what, God the cost of getting the bus whatever many times a week just might be…" so being up front and open about the retention strategies I think is very important from the patient perspective." (Interview 22, Head of Trial Operations)

"Well, sometimes it can be written out in the information leaflet. In that conversation where I say, how can you achieve this, is this achievable for you, then it comes into that conversation." (Interview 23, Clinical Trial Practitioner)
"I think it's probably an expectation from participants that they will. …To me it's you know, if I'm going to my GP practice I expect that they'll send me a reminder. Now they may or they may not, but I see it as a routine thing which is commonplace in all aspects of life whether you're going to the dentist or the doctor or whatever. So personally I don't think ... I'm not sure what you would achieve by asking separate questions. What if the patient says ... effectively I think we cover that in our approach to recording consent. If somebody's fed up and they just don't want to hear from you anymore then you need an approach to record that, but which applies not just to the issue of receiving a newsletter or having a reminder, but to receiving another telephone call from anybody else in the trial because there's multiple routes that a patient might be contacted and, so we kind of address that by using a central recording of consent with each patient where you can change individual shall we say, mini consents within the overall consent" (Interview 24, Trial Manager)
Insights into findings from the PIL analysis
"the only thing I could think of is that it would be because the patient information sheet and the protocols tend to be developed at the same time that sometimes there is that lack of synergy when developing it. I mean a lot of ... certainly our most recent experience with the research committee, they were very keen on looking at what the patient recruitment through line was, so they picked out that we were very consistent with ours, but. Yeah, those type of things I imagine can slip through the cracks" (Interview 2, Trial Manager)
"Maybe there's an effort, there's always an effort to keep the patient information sheet as brief as possible. I can only assume that someone or a team decide, you know decided or even perhaps out of necessity that they couldn't mention every single thing on the patient information sheet, and we try for, like, different tables or graphics to kind of illustrate things because, you know, they're 20 pages long, it's a perennial problem isn't it?" (Interview 7, Trial Manager)
"Carelessness. I don't think anyone deliberately wants to cause confusion or mislead people, it's just the study information start pack for a study will have at least 14 documents in it and if somebody suggests one thing you'd need a really good trials manager to harmonise all the documents." (Interview 8, Principal Investigator)
"The PIL I suppose we try to keep the information as informative but as simple as possible. Perhaps the reminders are an absolute… Whereas on the protocol you have to list everything. The PIL is more ensuring they're informed but not overloading them with information" (Interview 9, Trial Manager)

"Theoretically in a trial, your documents should be each reflective. The plan should be consistent across the board. It can be really busy working on research. Sometimes there can be errors in documents. You find things and it's really frustrating. Things like, maybe, the version numbers weren't updated. It can be really easy, like, human error. Sometimes it can be the resources. Working on trials they're quite tight. Sometimes there mightn't be the time to spend checking the documents are coherent like that. I suppose in the day-to-day of trials, sometimes jobs like that are things that go on long fingers because you're so engrossed in the day to day, trying to collect all the data. I think that's probably part of it." (Interview 13, Trial Manager)
"I suppose sometimes there is a lot of time pressure to get some of these documents in and through ethics and things like that, so maybe sometimes things just get missed because they're maybe under quite tight timelines and they're just trying to get it done and get it approved so that they can get on with it, I don't know." (Interview 14, Study Co-ordinator)
"I don't think the disconnect is happening purposely. It might be that these documents, they go through a number of different revisions. From my personal experience. I was involved in writing the protocol. I was also involved in writing the patient information leaflet for this particular trial. I've seen many multiple versions of documents going through a number of different hands, things can disappear. Things can get lost so I think that is, purely, a technical reason rather than anything purposely done." (Interview 15, Co-Investigator)
"I think the protocol is often related to the clinical scientific components of the study, so the operational activities and what to do when the patient is in and the activities you have to do. With the patient information leaflet, it is more patient focused in terms of how the study affects the patient." (Interview 19, Clinical Trial Unit Director)
"I mean I think it's very easy to get minor discrepancies between documents, so I suspect some of it is kind of cockup. Some of it is also trying to minimise what you put in a patient information sheet in that they might think you know, reminders are probably logical and normal rather than I guess offering additional stuff, or outlining additional information. I mean I think patient information sheets generally are terrible and are pages and pages of all sorts of legal nonsense that nobody ever reads….So I suspect some of it kind of benign neglect, some of it's trying to minimise what gets in and some of it is just kind of minor cockups and making sure it matches." (Interview 21, Principal Investigator)
"That's just version control Yeah. As far as I'm concerned, that's just about researchers they've got to go through so many loops and hoops to get their research running in the first place, that that level of detail gets lost in the version control." (Interview 23, Clinical Trial Practitioner)

Appendix 14. Thesis Chapter Eight. PhD Infographic.



Appendix 15. Thesis Chapter Eight. PhD in Pictures.

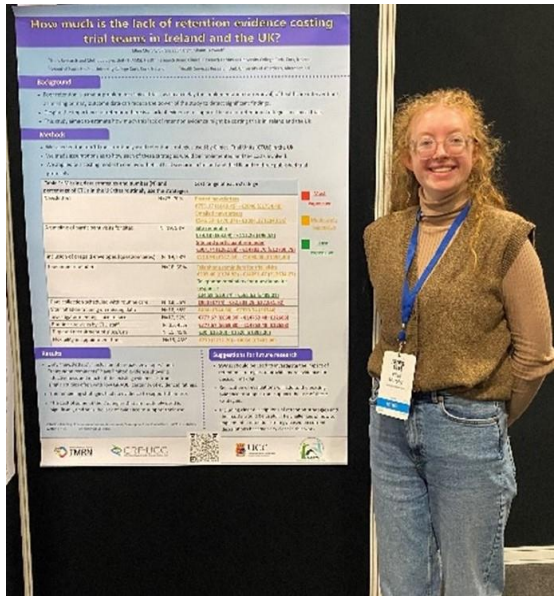
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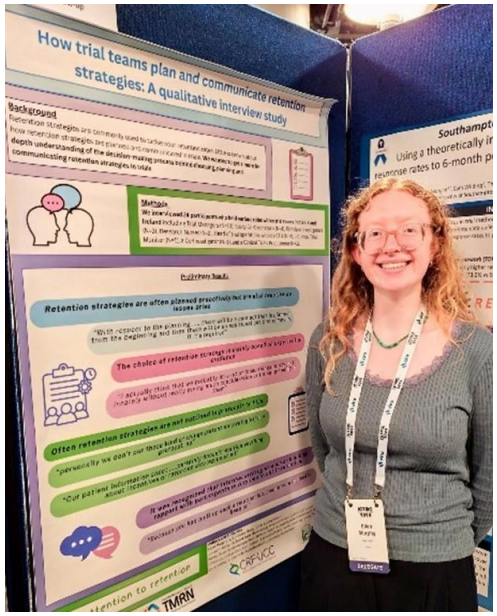
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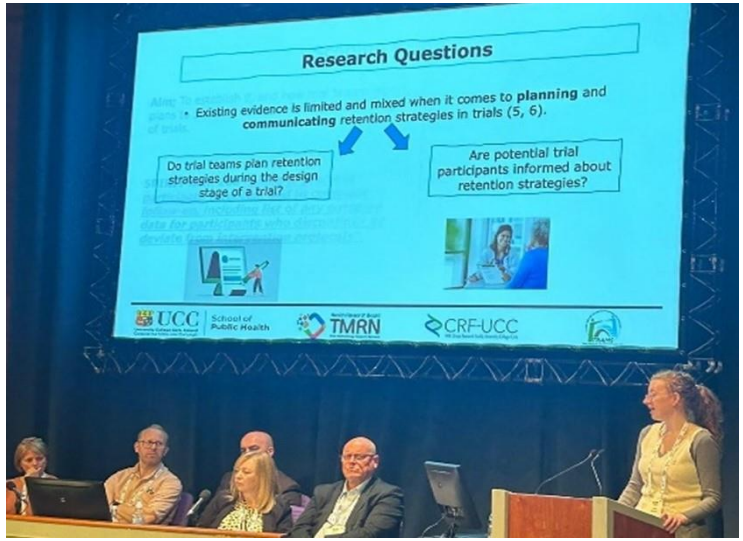
5


How much is the lack of retention evidence costing trial teams in Ireland and the UK?
Background
Method
Results
Suggestions for future research

6


How trial teams plan and communicate retention strategies: A qualitative interview study
Background
Methods
Retention strategies are often planned proactively but practice may change during the course of the trial
The choice of retention strategies is rarely based on explicit evidence
Often retention strategies are not noticed by study participants
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7


Research Questions
Existing evidence is limited and mixed when it comes to planning and communicating retention strategies in trials (5, 6).
Do trial teams plan retention strategies during the design stage of a trial?
Are potential trial participants informed about retention strategies?
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8


Background
Participant retention is an ongoing issue.
Little high-quality evidence to support retention strategies (1).
?
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1. Health Research Board, Trial Methodology Research Network. Spring School. Dublin 2023.
2. Health Research Board, Trial Methodology Research Network. 8th Trials Methodology Symposium. Presenters. Galway 2023.
3. Health Research Board, Trial Methodology Research Network. 8th Trials Methodology Symposium. PhD Cohort. Galway 2023.
4. Health Research Board, Trial Methodology Research Network. START Competition. Galway 2023.
5. International Clinical Trials Methodology Conference 2022. Poster. Harrogate, England.
6. International Clinical Trials Methodology Conference 2024. Poster. Edinburgh, Scotland.
7. International Clinical Trials Methodology Conference 2024. Oral Presentation. Edinburgh, Scotland.
8. HRB-TMRN Peer Pathway 2025 Conference. Dublin, Ireland.
9. Placement at Aberdeen Centre of Evaluation. 2023-2025.
10. Qualitative Research Course. Oxford. 2023.