The role of progression criteria in the design, conduct, analysis and reporting of external randomised pilot trials

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Abstract

External randomised pilot trials aim to assess whether a future definitive Randomised Controlled Trial (RCT) is feasible. Prespecified progression criteria help guide the interpretation of pilot trial findings to decide whether, and how, a definitive RCT should be conducted. Transparent feasibility assessment is crucial to ensure that pilot trials do not progress to definitive RCTs inappropriately. The research presented in this thesis examined the development, assessment and reporting of progression criteria throughout different stages of external randomised pilot trials.

As part of this DPhil I conducted four distinct but complementary research studies: a methodological review of progression criteria reported in randomised pilot trial protocol and result publications (published between January 2018 and December 2019); a cross-sectional study of progression criteria proposed in external randomised pilot trial research funding applications submitted to NIHR Research for Patient Benefit (RfPB) (with a funding decision between July 2017 and July 2019); a qualitative research study of thirty-five semi-structured interviews with key stakeholders (between December 2020 and July 2021) to understand pilot trial team member experiences of developing and using progression criteria in practice; a web-based follow-up survey study (between January 2022 and February 2022) of corresponding authors of publications included in the methodological review to examine whether identified pilot trials met their progression criteria (if applicable), were considered feasible, and progressed to further research.

I found that progression criteria were not always prespecified in pilot trial funding applications or reported in pilot trial publications. Where specified, researchers rarely stated how they had developed progression criteria, what specific criteria or targets were based on, or who had decided on them. My qualitative study findings highlighted varied and inconsistent approaches to progression criteria development, and suggest that a lack of knowledge, time and resources can lead to challenges when developing progression criteria. My findings also highlighted limitations associated with trial feasibility assessment, including the potential for biased pilot trial progression criteria, uncertainty about how to account for qualitative research findings and contextual considerations, and inefficiencies associated with non-progression of pilot trials that researchers considered to be feasible. Taken together, these findings indicate that progression criteria for external pilot trials might not always provide a comprehensive assessment of trial feasibility.

To address the challenges identified, I developed a set of proposed recommendations for progression criteria to guide researchers when (1) designing, (2) conducting, (3) analysing and (4) reporting external randomised pilot trials. These recommendations were refined following input from key stakeholders at two consultation workshops held in July 2022. Further research is needed to evaluate whether these proposed recommendations should inform future development, or update, of established guidelines for the design, conduct, analysis and reporting of external randomised pilot trials.

Table of Contents

List of Figures

List of Tables

List of Abbreviations

ADePT	A process for Decision-making after Pilot and feasibility Trials
AIC	Akaike's Information Criterion
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
COREQ	Consolidated Criteria for Reporting Qualitative Research
CROSS	Consensus-Based Checklist for Reporting of Survey Studies
CSM	Centre for Statistics in Medicine
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
CUREC	Central University Research Ethics Committee
DPA	Data Protection Agreement
DPhil	Doctor of Philosophy
GDPR	General Data Protection Regulation
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HiREB	Hamilton integrated Research Ethics Board
ICMJE	International Committee of Medical Journal Editors
IQR	Inter-quartile range
MISTIC	MethodologIcal STudy reportIng Checklist
MRC	Medical Research Council
MS IDREC	Medical Sciences Interdivisional Research Ethics Committee
NDORMS	Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
NGT	Nominal Group Technique
NIH	National Institutes of Health
NIHR	National Institute for Health and Care Research
OR	Odds Ratio

PAFS	Pilot and Feasibility Studies
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised Controlled Trial
RDS	Research Design Services
REC	Research Ethics Committee
RfPB	Research for Patient Benefit
SD	Standard Deviation
SoF	Summary of Findings
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TMG	Trial Management Group
TMRP	Trial Methodology Research Partnership
TSC	Trial Steering Committee
UK	United Kingdom
UKCRC	UK Clinical Research Collaboration
UKRI	UK Research and Innovation
UKTMN	UK Trial Managers' Network

Glossary

Analytical framework	A list of codes, with brief descriptions, that are organised into categories
Case	A unit of observation e.g. an individual participant or respondent
Category	A group of codes of similar content with linked properties and characteristics
Code	A descriptive word or short phrase assigned to excerpts of raw data in a process called ‘coding’
Content analysis	An analytical approach that involves establishing categories of data in a particular unit of analysis e.g. words or themes, and then counting the number of instances of those units to analyse the data
Epistemology	The nature of knowledge (what and how do we know what is true or real?)
Framework Method	An analytical method that sites within the broad family of thematic analysis methods, that can be distinguished by its highly ordered matrix outputs that help researchers analyse data by case and by code
Latent analysis	An interpretative analytical approach to qualitative research where the researcher aims to identify and co-create meaning within the data
Manifest analysis	A descriptive analytical approach to qualitative research where the researcher describes what respondents have said, using their words where possible, staying very close to the data
Framework matrix	A spreadsheet where 'cells' of summarised data is entered by rows (cases) and columns (codes), providing a structure into which the researcher can systematically reduce the data in order to analyse it
Ontology	The nature of reality (what is true or real?)
Pragmatism	A research paradigm where attention is focused on a research question, and available approaches that will best address the question are used. Rather than being based on a particular view of what ‘reality’ or ‘knowledge’ is, pragmatic researchers focus on the impact or consequences of their research, choosing the qualitative and quantitative research approaches, methods, and techniques that best meet their research purposes.

Reflexivity	The process of reflecting or critically thinking about the research process and the role of the researcher in influencing, or co-creating, the research findings
Thematic analysis	A well-established approach to qualitative data analysis that supports researchers to describe and interpret patterns identified by comparing and contrasting data across the data set (within and between cases)
Theme	Descriptive or interpretative concepts that describe or explain aspects of the data and are the final output of qualitative analysis. Themes go beyond codes and categories and are developed by comparing data within and between cases, therefore one theme can cut across several categories.
Triangulation	The integration of multiple research methods or data sources to develop a more comprehensive understanding of the topic to address the research question

Chapter 1 Introduction

1.1 Randomised Controlled Trials

Randomised Controlled Trials (RCTs) are regarded as the gold standard in generating evidence about the effectiveness (and harms) of health care interventions. RCTs are integral to the practice of evidence-based medicine [1], however they are often expensive, complicated, and can take a long time to set up, conduct, analyse and disseminate findings [2–5]. Despite researchers' best efforts to deliver gold standard RCTs, many RCTs do not adequately answer their research question [6,7], resulting in research waste and inefficiencies. RCTs might fail for many reasons: poor recruitment could mean that the prespecified sample size required to establish statistical significance is not met, low retention rates might mean that too few participants provide primary outcome data, or the study design might simply be flawed (e.g. a different method of randomisation might be more appropriate) [8,9]. A meta research analysis of 326 RCTs given ethical approval in 2012 by research ethics committees in Switzerland, the United Kingdom (UK), Germany, and Canada highlighted that 30% of included RCTs were discontinued prematurely, and that 71% of all discontinued RCTs were discontinued for reasons that the authors considered to be preventable [10]. To give RCTs the maximum chance of success and avoid wasting time and resources on trials that might fail, researchers frequently conduct Pilot and Feasibility Studies (PAFS) in advance of the main RCT.

1.2 Pilot and Feasibility Studies

PAFS aim to assess uncertainties that researchers might have about a future definitive RCT [11], and are a critical component of clinical trial feasibility assessment [12]. Historically the terms '*pilot*' and '*feasibility*' have been used inconsistently to define and describe conflicting study designs in research, healthcare and funding contexts [13–20].

To address this inconsistent terminology a conceptual framework for PAFS was developed and published in 2016, presented in Figure A1 [11]. The following standard definitions for PAFS were established, and are used throughout this thesis:

> **Feasibility studies** ask the question: can the future definitive trial be done, should we proceed with it, and if so, how [11]?
>
> **Pilot trials** are a specific type of feasibility study (asking the same question), but with a unique design feature: the future definitive trial, or a part of the future trial, is conducted on a smaller scale [11].

These definitions are not mutually exclusive: Randomised pilot trials, non-randomised pilot trials, and non-pilot feasibility studies are all types of feasibility studies. Therefore, randomised pilot trials can also be legitimately called randomised feasibility studies.

The conceptual framework also highlights non-linear movement between different feasibility study designs to adequately address uncertainty before the decision is made about whether to progress to a future definitive trial [11]. Although any type of feasibility study can precede a definitive RCT, it is most common for randomised pilot trials to be conducted with the intention to proceed to a definitive RCT [11], since piloting of the randomisation aspect introduces other variables, e.g. equipoise, that researchers might have uncertainty about. This thesis focuses on randomised pilot trials (specifically external randomised pilot trials); however, parts of this thesis might be applicable to other feasibility study designs.

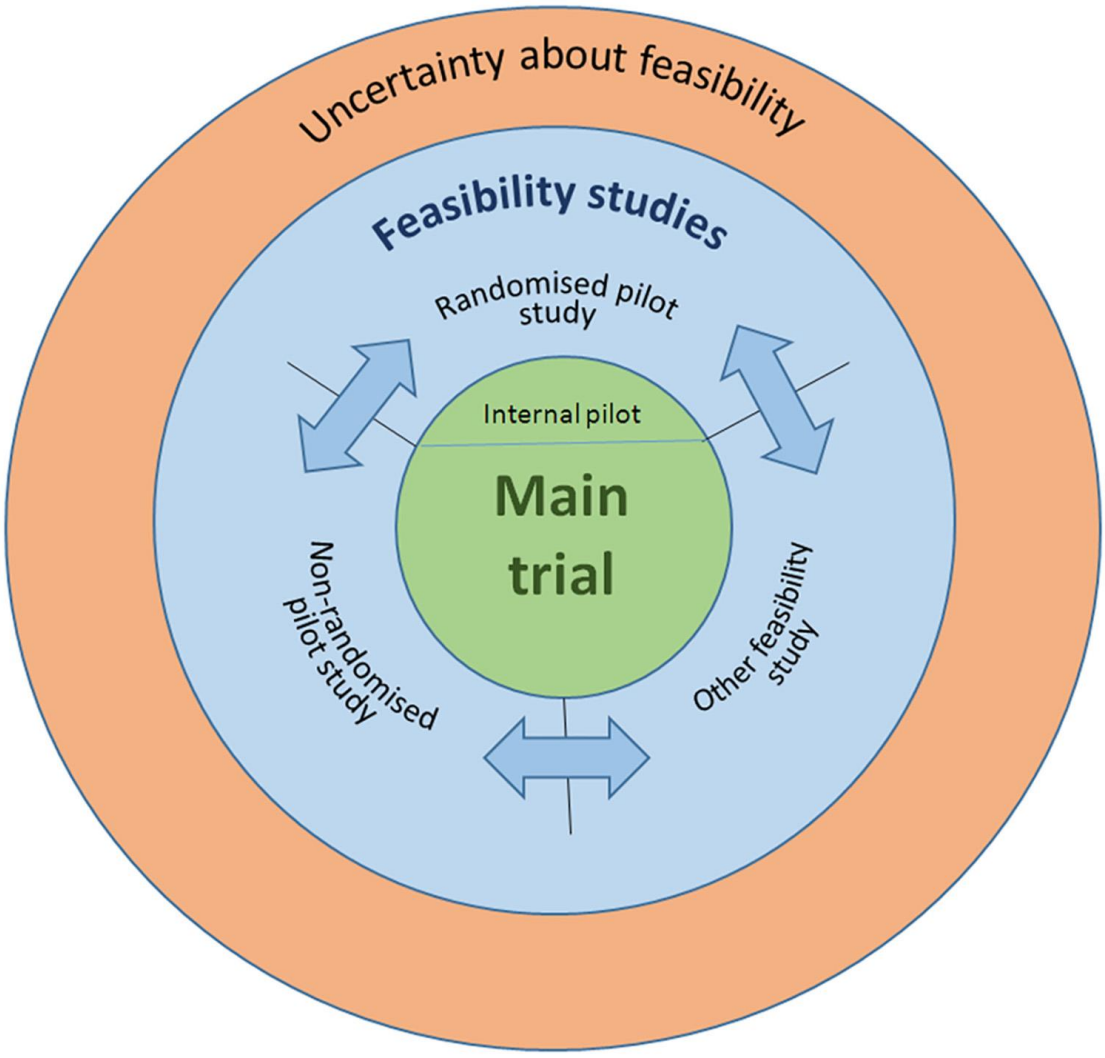

Figure A1 Conceptual framework for defining feasibility and pilot studies

Reproduced from Figure 7 Eldridge et al (2016) PLoS One **11**:e0150205, published CC-BY 4.0

1.2.1 The distinction between internal and external pilot trials

As indicated in Figure A1, randomised pilot trials can be distinguished into those that are internal or external.

> **Internal pilot trials** are embedded within a definitive RCT, where a portion of the main RCT (e.g. the first 6 months), is designated the internal pilot phase [21]. Following the internal pilot phase the decision is made to continue, adapt or abandon, the RCT [22]. National Institute for Health and Care Research (NIHR) guidance for applicants submitting to the HTA programme states that '*where requested, any internal or embedded pilot study should have clear and robust progression criteria*' to inform whether to proceed from the pilot to definitive RCT stage [23]. If the internal pilot trial proves to be feasible, any outcome data that has been collected during the internal pilot phase may contribute to the final trial analysis [21].
>
> **External pilot trials** are small stand-alone trials that do not form part of the definitive RCT. The key difference from an internal pilot trial is that any outcome data collected during the external pilot trial does not contribute to the final trial analysis [11]. When an external pilot trial completes, the pilot trial findings are interpreted (with reference to a priori progression criteria where reported) [24], and if the findings suggest that a definitive RCT is feasible, funding is sought for the definitive RCT as a separate study.

The pilot trial design, i.e. embedded internal or stand-alone external, should be prespecified during the study design stage to avoid introducing potential biases associated with making this decision after the pilot trial data are available [25]. However, there is

no formal guidance for when each design is most appropriate. External pilot trials, that are not embedded within the definitive RCT, are generally considered more appropriate where researchers have significant uncertainties about trial design [26]. Internal pilot trials are considered to be more efficient than external pilot trials because all participants are recruited to the main RCT during the internal pilot phase, therefore less resources are required [21]. However, they are much less flexible to change since any data collected will contribute to the definitive RCT dataset. Therefore, internal pilot trials are often considered more appropriate where it is unlikely that the trial design will change significantly.

These nuances are explored in an extension to the conceptual framework for PAFS (under review). Figure A2 highlights considerable overlap between external and internal pilot trial objectives and the uncertainties they address, reinforcing that choice is often pragmatic and not always based on methodological requirements. Further demonstrating the lack of clear distinction between the two study designs, the framework also highlights the potential for an external pilot trial to proceed to a definitive RCT and retain data collected, effectively becoming an internal pilot. The authors identify this as an area for future enquiry.

Although the internal/external pilot trial terminology is becoming commonplace in the research literature, some researchers have suggested that this taxonomy is sub-optimal and does not recognise the process of '*refinement*' that occurs during the set-up of most RCTs, irrespective of whether this is formally described as an internal pilot or not [27].

To acknowledge this ongoing debate and ensure clarity of results and interpretation, the focus of this thesis is on external randomised pilot trials, and future use of the term '*pilot trial*' is in reference to those that are external unless otherwise stated.

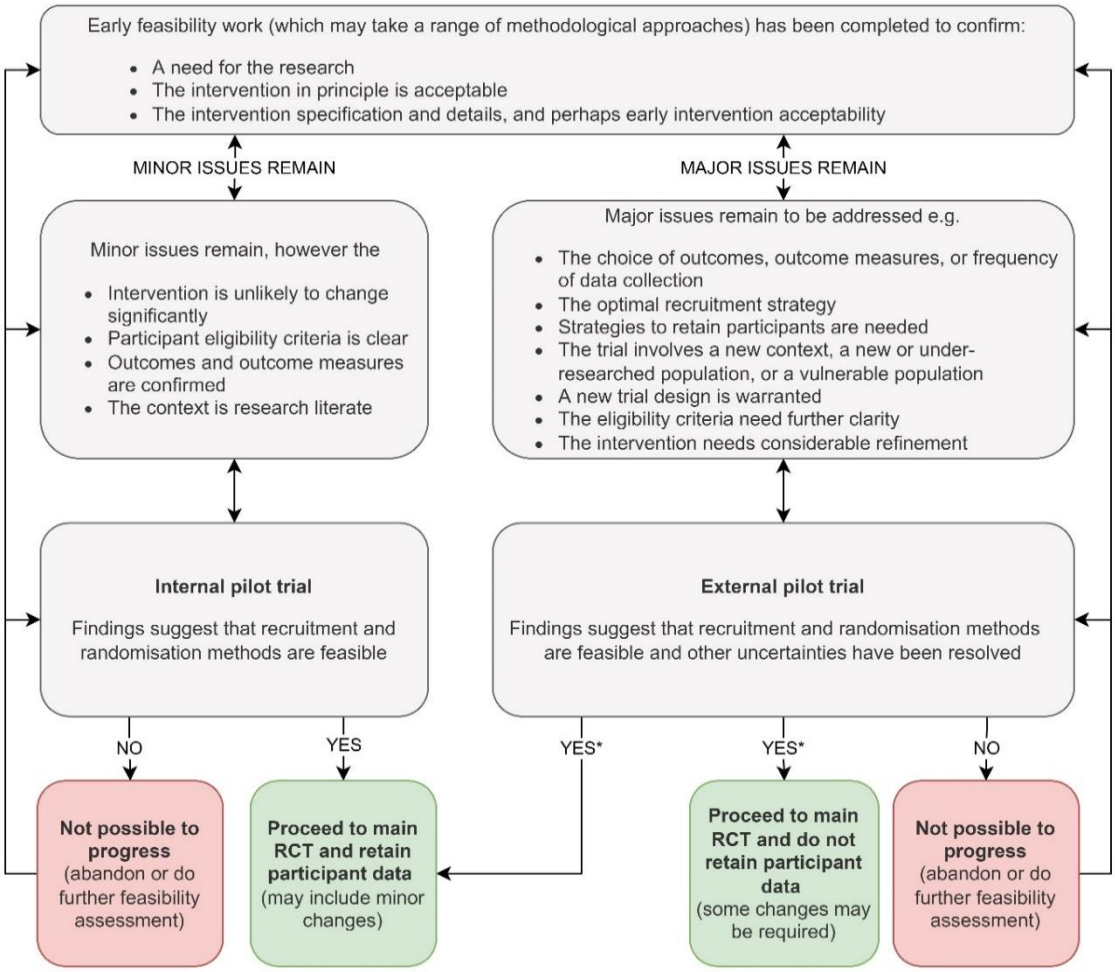

Figure A2 Flow chart to distinguish internal and external pilot trials

Reproduced from Figure 2 Bond et al (under review) *Pilot Feasibility Stud*

*Whether an external pilot trial can become an internal pilot if nothing has been changed is identified in this manuscript as an area for further enquiry

1.2.2 Existing recommendations for the design, conduct, analysis and reporting of external randomised pilot trials

To provide context for how the research that I present in this thesis can inform future randomised pilot trials, I will first summarise and present existing sources of guidance for the design, conduct, analysis and reporting of randomised pilot trials. I have highlighted where recommendations were written with other feasibility study designs in mind but may also be applicable to external randomised pilot trials.

1.2.2.1 PAFS reporting and the CONSORT 2010 statement for randomised pilot trials

PAFS have historically been underreported in the research literature. However reporting is improving. Articles indexed in PubMed that include the terms '*pilot*' or '*feasibility*' in their title show year on year increase and have doubled over the last ten years (5,153 articles in 2011 to 13,987 in 2021, searched in July 2022). Publishing PAFS is widely encouraged, as any lessons learned in one feasibility study could be applicable to other trials and avoid unnecessary duplication of research effort [15,28]. In 2015, the *Pilot and Feasibility Studies* (*PAFS*) journal was launched to promote and encourage PAFS publication [29]. Despite these efforts, recent reviews have found that protocols and results publications for PAFS are still widely unpublished [30–32].

Where pilot trials are published reporting standards vary. It is thought that some researchers have used the term '*pilot*' to justify smaller, underpowered or even poorly designed research studies [33], or those with surrogate endpoints despite resembling a definitive study (i.e. a trial that assesses efficacy, not feasibility) [34]. To address inadequate PAFS reporting, in 2016 an extension to the CONSORT 2010 statement for

randomised pilot trials was published [24]. CONSORT is arguably the most well-known reporting guideline and is widely endorsed by medical journals and organisations worldwide [35]. Trials published in journals that endorse CONSORT are more likely to be clearly and completely reported compared to trials published in journals that do not endorse CONSORT [36]. Therefore, the development of a specific CONSORT extension for PAFS would also be expected to improve reporting of randomised pilot trials [37,38]. The full CONSORT extension for PAFS checklist is presented in Appendix A1 and research has been conducted, with more studies planned, to evaluate the impact of the CONSORT extension for PAFS on pilot trial reporting [37,39,40]. Editors of *PAFS* have also suggested researchers use the CONSORT extension for PAFS as a reference document when reporting pilot trial protocols in the absence of a Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) extension for pilot trials [41].

1.2.2.2 Pilot trial objectives and outcomes

External randomised pilot trials, like all feasibility studies, should aim to address uncertainties about a future definitive trial to determine its feasibility. Researchers have previously consolidated and outlined reasons to conduct a pilot trial [15,42] and have suggested which types of feasibility study might be best placed to address different feasibility objectives [43], highlighting the non-linear process of feasibility assessment as alluded to in the conceptual framework (presented in Figure A1 [11]).

It has been suggested that the reasons for doing a pilot trial can be classified into four domains: process, resources, management and scientific, presented in Table A1 [15]. Despite these broad domains, there have been calls for pilot trials to expand their objectives to ensure all aspects of feasibility are assessed. For example, it has been recommended that pilot trials focus on assessing intervention fidelity [44,45], participant

burden and acceptability [46], and that health economic data collection is piloted (e.g. healthcare utilisation, reference costs, and a quality of life measure) to inform a future economic evaluation [47].

Table A1 Broad domains to present reasons for doing a pilot trial

Domain	**Description**
Process	Assesses the feasibility of the steps that need to take place as part of the main study
Resources	Deals with assessing time and budget problems that can occur during the main study
Management	Covers potential human and data optimization problems such as personnel and data management issues at participating centres
Scientific	Deals with the assessment of treatment safety, determination of dose levels and response, and estimation of treatment effect and its variance

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1.2.2.3 Sample size and the hypothesis testing debate

There is conflicting guidance about what sample size is appropriate for a pilot trial [48–54]. Researchers have suggested including a minimum of 30 patients [48], 12 per group [49], 35 per group [50], 50 per group [51], 9% of the sample size of the planned definitive study [52], and 0.03 x the proposed sample size of the definitive study [53]. Others have recommended that the sample size should depend on the study aim, for example those aiming to assess instrumentation (or outcome measure) adequacy might be able to adopt a smaller sample than those aiming to estimate statistical concepts such as test-retest reliability [55].

It is generally agreed that the primary focus of an external randomised pilot trial should be to assess feasibility rather than efficacy or effectiveness. However, guidance for whether it is appropriate to estimate effect sizes from pilot trials is conflicting. Some

researchers and funders, including the NIHR, support the use of PAFS to generate data that might be useful for determining the sample size of the definitive study [56,57]. Others argue that since pilot trials are small and not statistically powered, the analysis should be mainly descriptive, and any results from hypothesis testing should be treated with caution as estimates can be imprecise and biased [13,15,42,52,58–64]. Research has shown that using a pilot trial effect size to inform definitive trial sample size can lead to an underpowered RCT [59,65], and that pilot trial effect sizes are often overly optimistic and can even be misrepresentational [66]. This has also been demonstrated through simulation studies describing the misuse of pilot trials, illustrating how error can occur from using pilot trial effect sizes to inform a definitive trial power calculation [44]. It is recommended that sensitivity analyses should be used to assess the robustness of pilot trial estimates that inform definitive trial design [67]. The National Institutes of Health (NIH) advises against the use of effect sizes from pilot trials to power definitive trials, instead recommending that definitive trial sample size calculations are based on estimates of a clinically meaningful difference [68] which could be informed in other ways, e.g. based on investigators' clinical experience [66].

1.2.2.4 Interpreting pilot trial findings

Since the aim of a pilot trial is to assess whether a future definitive trial is feasible, the process for assessing feasibility should be built into the trial design. If this process is not established a priori (before the pilot trial results are known) there is the potential for bias to be introduced. Adequate feasibility assessment also avoids research waste associated with pilot trials progressing to definitive trials that are still unlikely to answer their research question, and non-progression of pilot trials that were likely to be feasible [30].

1.3 An introduction to progression criteria

Progression criteria help researchers interpret their pilot trial findings to decide whether, and how, to proceed with a future definitive trial. It is important that progression criteria are specified before the pilot trial begins (a priori) to avoid introducing bias associated with establishing progression criteria once external pilot trial findings are known. If progression criteria are not set a priori, there is a risk that pilot trials may be optimistic in reporting that a future RCT is feasible [31] and progress to a definitive RCT without modification or acknowledgement of potential limitations [69]. The subsequent progression decision may take one of three scenarios: (1) proceed to the definitive trial, (2) proceed with amendments to the definitive trial design, or (3) not proceed to the definitive trial (e.g. instead conduct further feasibility assessment) [24].

Young et al. have developed an everyday analogy of progression criteria to facilitate understanding among patient and clinician groups, provided in Figure A3.

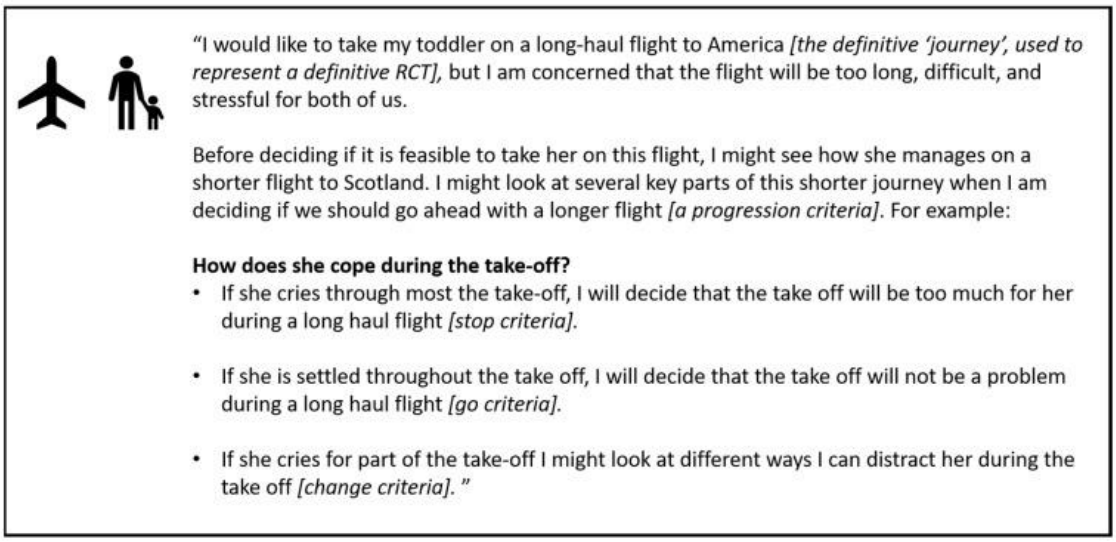

Figure A3 Example analogy to explain progression criteria

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1.3.1 Existing recommendations for progression criteria

An editorial published in 2014 advised that researchers should specify a priori criteria for success of feasibility and pilot studies [14]. In 2016 the CONSORT extension for PAFS was published and included the recommendation that researchers report progression criteria in pilot trial publications [24]. In 2017 the NIHR Research for Patient Benefit (RfPB) published guidance on applying for feasibility studies to stipulate that applications for feasibility studies should include clear progression criteria [17]. Although there are other references to progression criteria in the research literature, there are currently no clear evidence-based recommendations for how researchers should develop and assess progression criteria [70].

In this section of the introduction, I will summarise and present existing suggestions that have been made with regards to progression criteria (not all are necessarily specific to external randomised pilot trials) and highlight areas of remaining uncertainty.

1.3.1.1 Rationale for progression criteria

Although it is generally agreed that progression criteria should be defined prior to PAFS commencement, there is no evidence-based guidance for how researchers should decide on progression criteria, whether numerical targets should be used, and if so, what data should underpin these targets. A NIHR guidance document for Research Design Service (RDS) advisors suggests that not all feasibility outcomes might inform progression criteria, some might instead be used to refine processes should a definitive trial be feasible [57]. This guidance document, which was based on common mistakes identified through a survey of RDS advisors who support PAFS applications, also suggests that target values for progression criteria are most useful when they are justified in terms of their

implications for a future main study [57]. Where there is no empirical data to inform progression criteria, Jones et al. advise that researchers base progression criteria thresholds on what can be justified from an economic, resource or ethical basis [46].

There is conflicting opinion around whether effect size estimates should inform progression criteria [61,64,71]. Some researchers argue that small and underpowered sample sizes can lead to misguided decisions on whether to progress to a main trial [61,64]. Others suggest that although a formal hypothesis testing approach is inappropriate for clinical outcomes, it might be appropriate when evaluating feasibility outcomes [71]. To demonstrate this, in 2021 Lewis et al. published a methodology for devising a pilot trial sample size based on formal hypothesis testing of proposed progression criteria cut-off values, generating sample size look-up tables that correlate with perceived progression criteria targets [71].

1.3.1.2 Emphasis on flexibility

The CONSORT extension for PAFS advises that progression criteria may be best viewed as guidelines, rather than strict thresholds [24]. This is echoed in the NIHR RDS guidance which suggests that using numerical cut-off values can be inflexible and restrictive [57]. Instead, the CONSORT extension for PAFS recommends using a traffic light approach to progression criteria, with values linked to red (stop), amber (changes required/amend) or green (go) domains, rather than strict thresholds (e.g. a stop-go approach) [24]. Hypothetical examples of these formats are presented in Figure A4.

The suggestion to format progression criteria in a '*traffic light approach*' is also recommended for RCTs with internal pilot phases. Ten top tips for progression criteria for RCTs with internal pilot trials have been previously developed and are presented in Appendix A2 [22]. A number of these tips might also be applicable to external pilot trials,

such as the suggestion that criteria *strike a careful balance between being firm enough to promote ambition in the trial team yet being flexible enough to allow opportunities to remedy early problems* [22].

Figure A4 Examples of stop-go versus stop-amend-go progression criteria format

The CONSORT extension for PAFS also advises researchers to report implications for progression from pilot to future definitive trial, including any proposed amendments to definitive trial design [24]. This is supported by NIHR guidance for RDS advisors which promotes judgements based on whether changes can be made where progression criteria are not met [57]. Therefore, not meeting prespecified progression criteria might not necessarily indicate that a definitive trial is not feasible, but instead identify changes that can be made to the study protocol [46,72,73].

Progression decisions might become more complicated where there are several progression criteria to consider. This could result in a '*trade-off*' between different criteria, with certain criteria deemed to be more crucial to the success of a definitive study

than others. However, there is no guidance as to how this ordering might be determined, and what this might be based on.

There have been suggestions that when there are '*extensive changes*' or '*major modifications*' identified e.g. to the intervention or to a specific aspect of the study design, researchers should conduct further feasibility assessment to address areas of uncertainty before proceeding to a definitive trial [43,74,75]. For example data collection tools (e.g. questionnaires), might be re-piloted and refined until no further changes are required and they are considered suitable for use in a definitive trial [76]. However, it is unclear which changes would be major enough to warrant re-piloting, and which are minor enough that re-piloting would not be necessary. MRC guidance also supports re-assessment of feasibility where uncertainties remain, and advises that additional pilot or feasibility assessment may be required [16].

1.3.1.3 Who should decide on, and assess, progression criteria

Although there is no formal guidance for who should be involved in deciding on progression criteria for external randomised pilot trials, it has been suggested for internal pilot trials that researchers agree progression criteria with their funders [22]. This is supported by the NIHR whose *HTA Tips for Applicants* document states that '*clear success criteria for progression should be identified*', and that applicants may be given '*some steer on this in the feedback from the committee*' [77].

Two case studies were also published in 2019 to describe how researchers co-produced progression criteria with PAFS stakeholders. In one commissioned programme, different stakeholders (including delivery teams, commissioners, intervention-monitoring teams, academics and community representatives) ranked seven potential progression criteria that had been previously identified by the Medical Research Council (MRC) for trial

progression [78] in terms of importance, and agreed traffic light '*cut-off'* values [79]. In a separate feasibility study the Nominal Group Technique (NGT), a structured approach to reaching consensus through small group discussion [80], was used to co-produce progression criteria with patients, clinicians and researchers [81]. Stakeholders also identified potential changes that could be made to improve the future trial design. However, the researchers described that this process was challenging and recommend that more creative, interactive and visual methods are used in future to facilitate understanding. In addition, researchers advised that a co-production approach to determining progression criteria should be pre-planned and fully accounted for in funding applications due to the increased time and resources required [81].

There is no guidance for who should assess progression criteria for external randomised pilot trials. However, for internal pilot trials it has been suggested that researchers involve a Trial Steering Committee (TSC) when assessing progression criteria [22].

1.3.2 Alternative approaches for determining trial feasibility

Other approaches to determining trial feasibility following an external randomised pilot trial, that do not mention progression criteria, have been previously described in the literature.

1.3.2.1 The ADePT framework

In 2013, Bugge et al. published the '*A process for Decision-making after Pilot and feasibility Trials*' (AdePT) framework [82]. This framework was informed by a case study of issues identified in a pilot trial of a complex intervention and led to the development of a 3-stage decision making process (the full framework is presented in Appendix A3 [82]):

1. Deciding on the problem type (e.g. a trial problem, a real-world problem, or both)
2. Identify solutions to the problem (e.g. using literature searching, consulting the wider research team including lay participants, or if available by analysing feasibility data)
3. Assessment of optimal solution (e.g. by using a ranking method of optional solutions, or include cost assessments)

Bugge et al. suggest that identifying solutions to problems that effect both trial and real-word contexts can be more complicated, and the trade-off between internal and external validity can be minimised by involving wider stakeholders to identify and assess solutions. The authors also suggest that researchers justify how any identified solutions address the specific problem faced.

1.3.2.2 Foregrounding qualitative research findings

It has been suggested that progression criteria should be stated in terms of '*clear quantitative benchmarks*' against which feasibility is judged [72], for example the number of patients who are accrued, complete the study, complete study assessments, or are randomised [83]. However, the importance of embedding qualitative research in trials has been widely promoted [84,85], for example to gain an insight into intervention acceptability, implementation and deliverability [43], or to explore challenges that are faced when conducting the pilot trial [82].

In 2015, guidance was published to maximise the impact of qualitative research in external PAFS. These recommendations consist of 16 items across five domains: research question, data collection, analysis, teamwork, and reporting, and are based on author experience and workshop discussions [75]. The guidance describes various scenarios where qualitative research might enhance feasibility assessment. For example,

researchers might fall short of a quantitative criterion but have enough qualitative understanding of why this happened and what changes are required, making it possible to proceed to a definitive study, or qualitative research may identify potential harms at the feasibility stage, which could lead to modifications to the intervention or study process prior to a definitive study. This approach to determining trial feasibility is also supported by NIHR guidance for RDS advisors which encourages researchers to acknowledge the contributions of qualitative data when assessing feasibility objectives [57]. However, there is currently no clear guidance for whether, or how, qualitative findings should be incorporated into or considered alongside progression criteria to inform feasibility assessment, or how to proceed if qualitative and quantitative findings do not align.

1.3.2.3 A realist approach

In 2016 Fletcher et al. described how realist evaluation principles can be used in randomised pilot trials for developing and evaluating complex interventions. The authors promote a realist approach to progression decision-making following randomised pilot trials focusing on *'what is feasible and acceptable for whom and under what circumstances'* [86], as opposed to determining feasibility based on binary indicators. The authors suggest that instead of over-relying on progression criteria, pilot trials should present an opportunity to collect and analyse rich qualitative data and refine hypotheses before moving to a definitive RCT. For example, multi-arm pilot trials might be an appropriate way to assess and pilot different interventions or intervention components separately, with arms dropped or merged in the definitive RCT depending on the pilot trial findings [86].

1.4 Rationale for thesis

Although progression criteria are now expected by some research funders in pilot trial funding applications [17] and are specified as a reporting item in the CONSORT extension for PAFS [24], existing recommendations are largely based on case studies of individual pilot trials or have not been developed specifically for external randomised pilot trials. There are also unaddressed areas of uncertainty around progression criteria in the literature, including conflicting opinion (e.g. whether it is OK to use effect size estimates in progression criteria) and unanswered questions (e.g. should qualitative research contribute to progression criteria, and how?).

The purpose of prespecifying progression criteria is to promote adequate assessment of future trial feasibility and avoid pilot trials progressing to larger definitive RCTs inappropriately. Not only is adequate assessment of trial feasibility crucial to avoid research waste, but it also has wider ethical implications for the participants who give their time to participate in these research studies, and for the public since many pilot trials and definitive RCTs are supported by public funding. Therefore, to facilitate and promote adequate feasibility assessment of external randomised pilot trials, it is unclear whether it is simply enough to ask researchers to include and report progression criteria in funding applications and publications, or whether further evidence-based guidance is needed.

1.5 Research question

The overarching research question that I have aimed to address throughout this thesis is: how should researchers use progression criteria in external randomised pilot trials to determine future definitive trial feasibility?

1.6 Thesis aims and objectives

The aim of this thesis is to examine whether, and how, progression criteria for external randomised pilot trials should inform assessment of future definitive trial feasibility.

The overarching objectives are to:

- Examine the reporting of progression criteria in pilot trial publications
- Examine the inclusion of progression criteria in research funding applications
- Explore researchers' perceptions and experiences of using progression criteria in practice
- Examine how progression criteria inform feasibility assessment and subsequent progression decision making
- Identify challenges and barriers to using progression criteria in practice, and outline practical recommendations to support researchers using progression criteria in external randomised pilot trials

Individual study aims and objectives are presented in each chapter.

In addition to the research presented in this thesis, on the 19th of February 2020 I was awarded a UK Research and Innovation (UKRI) and Mitacs Globalink Research Placement funding (grant reference NE/T014059/1), for an additional 12-week internship in Canada to study the inclusion of progression criteria in pilot trial ethics applications. Due to the ongoing impact of Covid-19 throughout the duration of this DPhil I was unable to do this additional 12-week internship within my research timeframe. This proposed research study is described in further detail in the discussion chapter and is a recommended area for future research.

1.7 Thesis outline

This thesis follows a mixed methods triangulation approach [87]. In mixed methods research, multiple research methods are used to address a research question that cannot be addressed though using quantitative or qualitative methods alone [88]. The findings of these distinct, but complementary studies are then triangulated to provide a comprehensive understanding of a topic.

Each study reported in this thesis focused on progression criteria during different pilot trial stages (funding application, conduct, reporting and progression) and the findings were triangulated to inform the development of recommendations for the design, conduct, analysis and reporting of progression criteria for external randomised pilot trials.

I have formatted this thesis into seven distinct chapters to present the research I conducted as follows:

Chapter 1, this introductory chapter introduces feasibility studies and the external randomised pilot trial design, the concept of progression criteria, any existing recommendations of relevance and presents the rationale and aims of the thesis.

Chapter 2 will present a methodological review of progression criteria reporting in a recent sample of published randomised pilot trial protocol and result publications (published between January 2018 and December 2019).

Chapter 3 will present a cross-sectional study of NIHR Research for Patient Benefit applications (with a funding decision between July 2017 and July 2019) to examine how progression criteria are proposed in external randomised pilot trial research funding applications.

Chapter 4 will present a qualitative research study of thirty-five semi-structured interviews (conducted between December 2020 and July 2021) with key stakeholders to understand pilot trial team member experiences of developing and using progression criteria to evaluate the feasibility of external randomised pilot trials in practice.

Chapter 5 will present a web-based follow-up survey study (survey conducted over a four-week period between January 2022 and February 2022) of the sample of external randomised pilot trials included in the methodological review (Chapter 2) to examine pilot trial progression to further research, and how progression criteria inform assessment of trial feasibility.

Chapter 6 will outline key concerns identified through the previous chapters and present a set of proposed recommendations for progression criteria to guide researchers when (1) designing, (2) conducting, (3) analysing and (4) reporting external randomised pilot trials.

Chapter 7 will conclude this thesis with a summary of the findings, present the strengths and limitations of the research, outline the potential implications of these findings for different stakeholder groups and point to areas for future research.

I have indicated on chapter cover pages where the research reported in this thesis has been disseminated, and I have provided lists of publication and presentation outputs at the start of the appendices.

Chapter 2 A methodological review of progression criteria reported in external randomised pilot trial publications

Associated research outputs:

The protocol for this chapter is registered on the *Open Science Framework* [1] and the results are published in *BMJ Open* [2]. I presented the findings from this study at two sessions at the *Society for Clinical Trials* conference (2021, virtual).

[1] Mellor K, Hopewell S. An investigation of the current use of progression criteria in external randomised pilot studies: a systematic review protocol. *OSF* 2020. doi:10.17605/OSF.IO/BN35K

[2] Mellor K, Eddy S, Peckham N, et al Progression from external pilot to definitive randomised controlled trial: a methodological review of progression criteria reporting. *BMJ Open* 2021;**11**:e048178. doi:10.1136/bmjopen-2020-048178

2.1 Chapter introduction and rationale for study

2.1.1 Rationale for methodological review

As presented in Chapter 1, prespecification of clear progression criteria avoids biased progression decision making by promoting transparent assessment of external randomised pilot trials, based on a priori rules, to determine future definitive trial feasibility. However, previous research has identified that progression criteria are not always reported in pilot trial publications. A review of pilot trial protocols published in three major journals between 2013 and 2017 found that less than 20% reported clear progression criteria [69]. Furthermore, a review of feasibility studies on the ISRCTN registry that had an end date between 1995 and 2019 also found that many did not stipulate, or had unclear, progression criteria [31]. Both of these reviews included pilot trials that were designed prior to publication of the 2016 CONSORT extension for PAFS [24,89], which has likely increased progression criteria reporting in more recently published pilot trials.

Although previous research has focused on whether progression criteria are reported, the consistency of this reporting and approaches to progression criteria are unclear. For example, it is unclear how progression criteria are established, what they are based on, and how they inform conclusions about trial feasibility. Questions like these, that aim to evaluate methodology of studies with the aim of improving the methodology of future studies, are best addressed through a methodological study [90]. In this chapter I present the methods and findings of a methodological study of the characteristics of progression criteria, where reported, in pilot trial publications.

2.1.2 Aim and objectives

I aimed to assess progression criteria reporting in external randomised pilot trial reports.

The primary objective was to describe progression criteria reporting including which uncertainties most frequently contribute to progression criteria, reporting format, whether any rationale or justification for choice of progression criteria are given, and whether it is reported who was involved in determining and assessing progression criteria.

The secondary objectives were to:

- review publicly available prepublication peer reviewer reports to assess the extent, and context, in which progression criteria are discussed during peer review
- conduct a linear regression analysis to determine whether any trial characteristics are associated with reporting progression criteria as opposed to reporting only a recruitment or sample size target
- for completed pilot trial publications, to assess whether progression criteria are specified a priori in an earlier protocol publication or trial registration
- for completed pilot trial publications, to determine how many of the reported pilot trials had met their progression criteria, and how many reported the intention to progress to a definitive RCT

2.2 Methods

2.2.1 Protocol and registration

I published a protocol for this methodological review on the Open Science Framework (osf.io/bn35k) [91]. A checklist for reporting methodological research studies is currently being developed (MethodologIcal STudy reportIng Checklist; MISTIC) [92]. In lieu of formal reporting guidelines for methodological studies I opted to report this chapter following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 checklist [93], presented in Appendix B1. The PRISMA checklist has been previously recommended to guide reporting of methodological studies where the study follows a systematic approach to data selection (i.e. selection of the research studies for inclusion) [94].

2.2.2 Eligibility criteria

I included reports of completed external randomised pilot trials and protocols, published between January 2018 and December 2019 inclusive. I placed no restriction on reported trial intervention, health-related context or research setting. Publications reporting any external randomised pilot trial design were eligible (e.g. parallel group, cluster, factorial), provided that the primary focus was to investigate feasibility of a future definitive RCT (i.e. reported objectives related to feasibility). In addition, included publications reported some form of progression criteria which I defined as a statement or wording to reflect how (against what criteria, values, threshold or conditions) the decision will be made to proceed with the future definitive trial.

2.2.3 Information sources

I used a purposeful sampling method to target journals that were likely to include eligible studies [90]. I searched four journals that are indexed in PubMed: *British Medical Journal (BMJ) Open*, *Pilot and Feasibility Studies (PAFS)*, *Trials* and *Public Library of Science (PLoS) One*. I chose these journals because they are known to publish pilot trial protocol and results publications and they had the most PubMed indexed publications that included the terms '*pilot*' or '*feasibility*' (and) '*trial*' or '*protocol*' in their title between January 2018 and December 2019.

These four journals all direct authors to the CONSORT statement for reporting [95] and require that the completed checklist is included as part of the article submission. *PAFS* directs authors to the specific CONSORT extension for PAFS [24,96], *BMJ Open* and *Trials* advise authors to use the most appropriate CONSORT statement extension for their submission [97,98], and *PLoS One* directs authors to the CONSORT statement only [99].

2.2.4 Search strategy

The search was designed in accordance with published guidance for defining PAFS, in which randomised pilot trials might also legitimately be called '*randomised pilot studies*' or '*randomised feasibility studies*' [11]. Terms that have previously been used to describe pilot trials such as '*proof-of-concept*', were not included as these resulted in the inclusion of many ineligible studies when developing and piloting the search strategy. In addition, '*external*' was not included as a search term since this resulted in the exclusion of eligible reports. To ensure that recent publications were included, the search was repeated periodically throughout the screening process to allow time for indexing and linking of

eligible reports to PubMed, with the last search conducted on the 6th of January 2020. The search strategy used is presented in Table B1.

Table B1 PubMed search strategy [6th January 2020]

No	Search terms	Results
1	**Pilot[Title]**	68704
2	**Feasibility[Title]**	31478
3	**1 OR 2**	98358
4	**Trial[Title/Abstract]**	576760
5	**Study[Title/Abstract]**	7478840
6	**Protocol[Title/Abstract]**	300466
7	**4 OR 5 OR 6**	7872797
8	**((((("Pilot and feasibility studies"[Journal])) OR "Trials"[Journal]) OR "BMJ open"[Journal]) OR "PloS one"[Journal]**	245189
9	**3 AND 7 AND 8**	2529
10	**9 AND 2018.01.01"[Date - Publication] : "2019.12.31"[Date - Publication]**	1030

2.2.5 Study selection

I screened the title and abstract of all identified publications and excluded those that did not satisfy eligibility criteria. I retrieved the full text for each that appeared to be eligible and screened these against an eligibility checklist, presented in Appendix B2, to determine inclusion. I maintained a record of eligibility assessment in Microsoft Excel (Office16). I saved all included publications in an electronic library on my personal password protected University of Oxford server (H: drive) and kept a record in EndNote X9 for Windows reference management software. I manually checked for multiple publications by comparing trial descriptors (title, publication year and authorship), and

confirmed that there were none using the EndNote 'Find Duplicates' function. External randomised pilot trials which satisfied all eligibility criteria, except only reported a prespecified sample or recruitment target instead of detailed progression criteria, were also included as part of a separate descriptive sub-study (I have called these 'comparator' publications throughout this thesis).

2.2.6 Data collection process

I conducted data extraction starting with the earliest publications to allow time for more recent publications to be correctly indexed and linked to PubMed. I produced data extraction forms in Microsoft Excel (Office16) which I piloted on the first 10 publications to ensure usability and completeness (the data extraction form used can be obtained from osf.io/fxv4n).

For quality assurance, double-data extraction was conducted for a random 25% sample of included publications, shared equally between second reviewers Saskia Eddy (PhD student; Queen Mary University of London) and Nicholas Peckham (Medical Statistician; Centre for Statistics in Medicine, University of Oxford). The decision to conduct double data extraction for 25%, rather than all included publications, was pragmatic and based on what was feasible at the time given time and resource availability. I used the rand() function in Microsoft Excel (Office16) to provide each publication with a random number value, which I then ordered from smallest to largest (and by publication type, i.e. completed trial or protocol) to obtain the random 25% sample. I provided both second reviewers with guidance notes and training for using the data extraction form. Double data extraction forms were completed by second reviewer and shared via email in small rolling batches of five publications. I compared data extraction forms for any discrepancies which were discussed at virtual meetings with the second reviewer until

consensus was reached. All data that I collected, and copies of data extractor forms completed by second reviewers, were stored and maintained on my personal University of Oxford H: drive.

2.2.7 Data items

The data items I extracted were informed by the CONSORT extension for PAFS [24] and other sources of guidance and recommendations that might inform pilot trial progression criteria development and reporting, as previously described in Chapter 1. See Appendix B3 for a full list of data items collected and the corresponding coding strategy used for data collection.

In brief, from protocol and results publications I extracted: trial characteristics (including author, year, journal, country, randomisation design, therapeutic area, intervention type, sample size target, number of arms, number of centres); feasibility objectives, outcomes, and instances of hypothesis testing; progression criteria details (wording, rationale or justification, format, process for establishing, and process for assessing); and references to progression criteria in publicly available prepublication peer reviewer reports, where these were published online and linked to the publication.

From publications reporting completed pilot trials I also extracted: whether progression criteria were met; any reported intention to progress to a definitive RCT; any proposed changes to the definitive RCT design; any refinement of hypotheses; any comment on data quality; whether progression criteria was prespecified a priori in a published protocol or trial registration, and if so, whether the a priori progression criteria reported was the same as that reported in the result publication.

From comparator publications for external randomised pilot trials that only reported a prespecified sample or recruitment target instead of detailed progression criteria, I extracted details about the recruitment target such as whether this was an overall trial target or site target, and whether any justification or rationale for the target was provided.

2.2.8 Synthesis of results

I produced descriptive summary statistics (frequencies and mean, median and interquartile ranges for sample size) using Stata (version. 15.0; StataCorp) [100] to describe reported trial characteristics, reported progression criteria, and the number of prepublication peer reviewer reports that mentioned progression criteria.

I examined the frequency with which different areas of feasibility assessment (such as recruitment, retention and proportion of missing data) contributed to progression criteria, and reported these in line with prespecified domains of reasons for conducting pilot trials: process, resource, management and scientific, see Table A1 [15]. I also calculated the average number of progression criteria per publication.

I used narrative synthesis to describe the context in which progression criteria were mentioned in peer reviewer reports. I aimed to take the reports at face value to simply assess whether progression criteria were mentioned, and if so, whether peer reviewer comments indicated that (1) progression criteria were not present in previous versions of the submitted manuscript or (2) reviewers queried rationale for progression criteria reported. The remaining content of the peer reviewer reports was not formally assessed, and no comment is made on the quality of individual peer reviewer reports.

2.2.9 Logistic regression

I compared specific trial characteristics between publications that reported progression criteria and those that only reported a prespecified sample or recruitment target using logistic regression. The characteristics I compared have been described to be relevant to methodological studies and associated with study design or reporting standards [90], including: journal, year, funding source, sample size, number of centres, country of origin and intervention type. I conducted this analysis in Stata (version. 15.0; StataCorp) [100] using the 'logistic' and 'glm' functions.

All study characteristics were categorical, and I recoded sample size target as a categorical variable with small defined as N=0-60 and large as N=61+ based on previous categorisation for PAFS sample size [69]. I also grouped countries into regions since some countries were less frequent and were not present in both groups. Where countries were present in at least ten publications across both groups they remained ungrouped.

I assumed a binomial distribution. I produced a multivariate model that included all variables with a relaxed p-value of ≤ 0.25 in the initial univariate analysis, and then a second reduced multivariate model that included only variables that were statistically significant at a p-value of ≤ 0.05 in the first multivariate model [101]. I did this to reduce the number of variables included in the final multivariate model. This is because models that are saturated with too many variables have reduced statistical power, meaning that important variables can be missed as there is not enough power to detect them [102]. When producing the first multivariate model I used the more liberal 0.25 p-value cut-off because more stringent cut-off values such as 0.05 might have led to important variables being dropped from the initial multivariate model [103]. Akaike's Information Criterion (AIC), an estimator of prediction error, was calculated for the full and reduced

multivariate models to assess model fit. In the results I report the odds ratio (OR), 95% confidence intervals, and p-values.

2.2.10 Risk of bias

Commenting on the quality of the evidence from studied randomised pilot trials was not an outcome of this review. Instead, I aimed to comment only on the completeness of progression criteria reporting in this sample of external randomised pilot trial publications. To an extent I was able to assess potential publication and reporting biases by determining (1) the proportion of included randomised pilot trials for which a published protocol could be sourced (indicating protocol publication bias) and (2) the proportion of randomised pilot trials with the same progression criteria reported in the protocol (where available) and result publication (indicating outcome reporting bias). I also calculated the proportion of randomised pilot trials that reported that a future RCT would be feasible as a potential indicator of positive reporting bias towards publication of pilot trials that were feasible.

2.3 Results

2.3.1 Screening and inclusion of publications

The search strategy identified 1030 publications. I screened the title and abstracts of all publications, then assessed 679 at full text stage for eligibility. During full text screening I excluded many randomised pilot trial publications because I was unable to identify explicit progression criteria reported (n=251). I identified 160 eligible publications (37 completed; 123 protocol) that reported progression criteria, and an additional 118 randomised pilot trial publications (34 completed; 84 protocol) that reported only a recruitment or sample size target that would inform progression. These 118 publications were included in a secondary comparator subset for the logistic regression. See Figure B1 for full PRISMA flow chart of publications included and excluded at each stage.

There were two instances where both the completed trial publication and protocol were identified. In these instances, both publications were included. Appendix B4 lists all included publications.

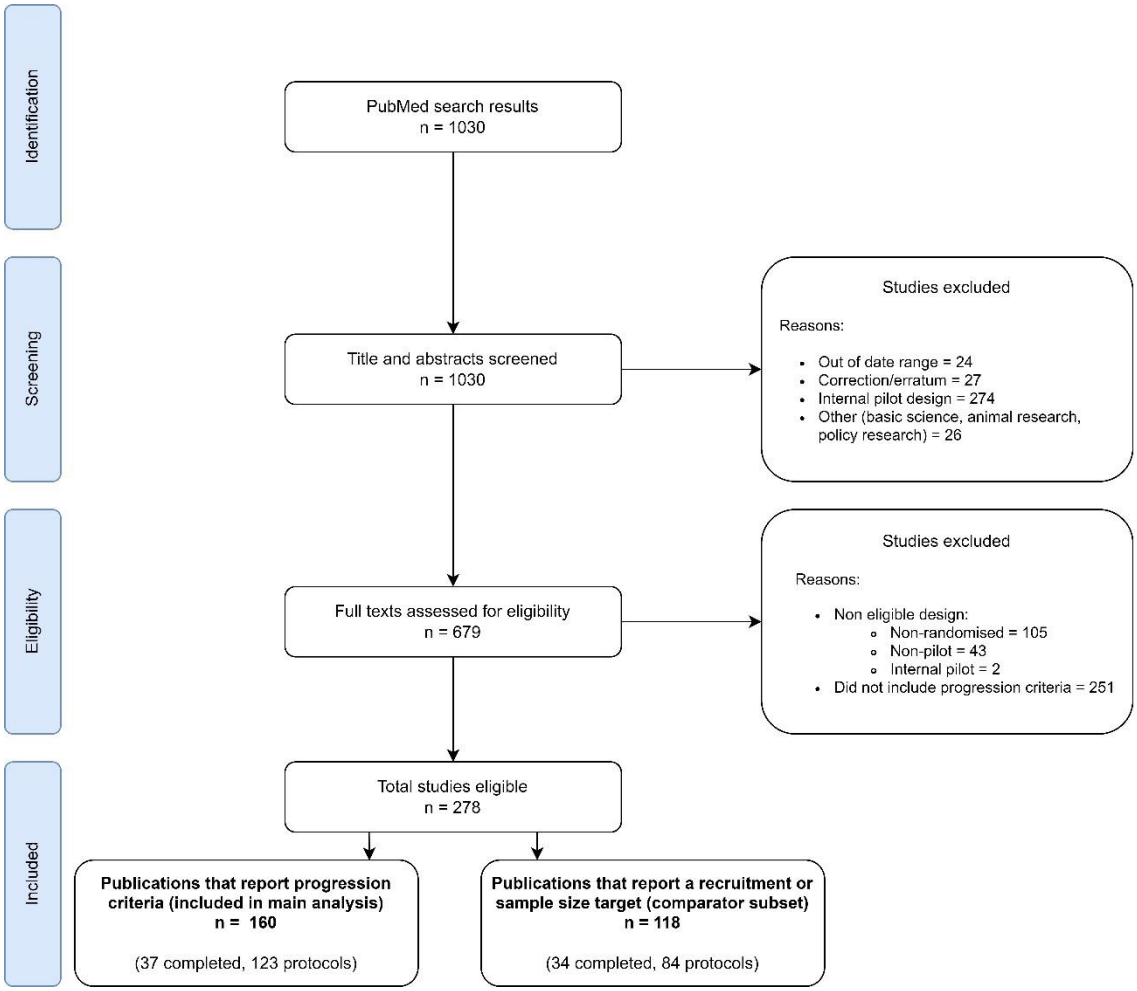

Figure B1 PRISMA flow chart

2.3.2 Characteristics of publications reporting progression criteria

Table B2 summarises the characteristics of all included publications. In this section of the thesis I present the characteristics of the publications reporting progression criteria (see Figure B1; n=160). Characteristics of publications reporting only recruitment or sample size target as a measure of progression (comparator subset) (see Figure B1; n=118) are presented later in this chapter (section 2.3.7) along with the logistic regression analysis.

Of the 160 publications which reported progression criteria, most included publications were for randomised pilot trial protocols (123/160, 77%) as opposed to completed trial result reports (37/160, 23%). The journal with the most eligible publications was *Pilot and Feasibility Studies* (77/160, 48%). Most publications described external randomised pilot trials that were two-arm (143/160, 89%), multicentre (102/160, 64%), non-industry funded (147/160, 92%) trials of counselling, lifestyle or physiotherapy interventions (94/160, 59%). The reported trials covered 27 therapeutic areas and were from 18 countries, mostly from the UK (87/160, 54%), followed by Canada (19/160, 12%) and the USA (16/160, 10%).

Primary feasibility objectives were explicitly stated in 71/160 (44%) publications and were more often stated in protocols than completed trial reports (50%, 62/123 versus 24%, 9/37 respectively). Most publications reported feasibility outcomes in the methods that addressed all the stated feasibility objectives (109/160, 68%) and more often in protocols compared to completed trials (74%, 91/123 versus 49%, 18/37 respectively). In 50/160 (31%) of the publications, the stated feasibility outcomes only somewhat addressed trial objectives, often because the objective stated was broad (e.g. ‘to determine whether a future trial is feasible’) and did not clearly define the specific aspects of

feasibility being assessed. Most of the pilot trial publications that reported the intention to conduct hypothesis testing stated that this was exploratory or advised caution in interpretation. All but one publication reported multiple feasibility outcomes. The place in the publication where the specific uncertainties related to trial feasibility were first reported varied, but most often this was within the pilot trial feasibility objectives (72/160, 45%), the data collection section describing the feasibility outcomes (26/160, 16%), or pilot trial assessments or measurements (23/160, 14%).

Table B2 Characteristics of included publications

	Report progression criteria						Comparator subset*					
	Total (n = 160)		**Completed (n = 37)**		**Protocol (n = 123)**		**Total (n = 118)**		**Completed (n = 34)**		**Protocol (n = 84)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Journal												
Pilot and Feasibility Studies (PAFS)	77	(48%)	21	(57%)	56	(46%)	36	(31%)	16	(46%)	20	(24%)
British Medical Journal (BMJ) Open	45	(28%)	11	(30%)	34	(28%)	46	(39%)	11	(31%)	35	(42%)
Trials	35	(22%)	2	(5%)	33	(27%)	35	(30%)	6	(18%)	29	(35%)
Public Library of Science (PLoS) One	3	(2%)	3	(8%)	0	(0%)	1	(1%)	1	(1%)	0	(0%)
Country												
UK	87	(54%)	19	(51%)	68	(55%)	66	(56%)	21	(62%)	45	(54%)
Canada	19	(12%)	4	(11%)	15	(12%)	4	(3%)	0	(0%)	4	(5%)
USA	16	(10%)	2	(5%)	14	(11%)	8	(7%)	4	(12%)	4	(5%)
Australia	10	(6%)	6	(16%)	4	(3%)	13	(11%)	3	(9%)	10	(12%)
Republic of Ireland	5	(3%)	0	(0%)	5	(4%)	1	(1%)	0	(0%)	1	(1%)
China	4	(3%)	0	(0%)	4	(3%)	2	(2%)	0	(0%)	2	(2%)
Nepal	3	(2%)	1	(3%)	2	(2%)	0	(0%)	0	(0%)	0	(0%)
New Zealand	3	(2%)	2	(5%)	1	(1%)	1	(1%)	1	(3%)	0	(0%)
Germany	2	(1%)	1	(3%)	1	(1%)	5	(4%)	2	(6%)	3	(4%)
Sweden	2	(1%)	1	(3%)	1	(1%)	1	(1%)	1	(3%)	0	(0%)
The Netherlands	2	(1%)	0	(0%)	2	(2%)	0	(0%)	0	(0%)	0	(0%)
Brazil	1	(1%)	0	(0%)	1	(1%)	1	(1%)	0	(0%)	1	(1%)
Denmark	1	(1%)	0	(0%)	1	(1%)	2	(2%)	0	(0%)	2	(2%)
Korea	1	(1%)	0	(0%)	1	(1%)	1	(1%)	0	(0%)	1	(1%)
Norway	1	(1%)	1	(3%)	0	(0%)	3	(3%)	1	(3%)	2	(2%)
Tanzania	1	(1%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)

	Report progression criteria						Comparator subset*					
	Total (n = 160)		Completed (n = 37)		Protocol (n = 123)		Total (n = 118)		Completed (n = 34)		Protocol (n = 84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Thailand	1	(1%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)
Zimbabwe	1	(1%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)
Chile	0	(0%)	0	(0%)	0	(0%)	2	(2%)	0	(0%)	2	(2%)
Indonesia	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Italy	0	(0%)	0	(0%)	0	(0%)	3	(3%)	0	(0%)	3	(4%)
Sri Lanka	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Switzerland	0	(0%)	0	(0%)	0	(0%)	2	(2%)	1	(3%)	1	(1%)
Uganda	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Funder												
Industry	4	(3%)	2	(5%)	2	(2%)	1	(1%)	0	(0%)	1	(1%)
Non-industry	147	(92%)	32	(86%)	115	(94%)	108	(92%)	31	(91%)	77	(92%)
A combination	5	(3%)	1	(3%)	4	(3%)	6	(5%)	1	(3%)	5	(6%)
Unknown	3	(2%)	2	(5%)	1	(1%)	3	(3%)	2	(6%)	1	(1%)
Trial did not receive funding	1	(1%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)
Therapeutic area**												
Psychiatry/Psychology	21	(13%)	2	(5%)	19	(15%)	18	(15%)	0	(0%)	18	(21%)
Public Health	17	(11%)	2	(5%)	15	(12%)	11	(9%)	6	(18%)	5	(6%)
Neurology	15	(9%)	3	(8%)	12	(10%)	13	(11%)	6	(18%)	7	(8%)
Oncology	11	(7%)	4	(11%)	7	(6%)	12	(10%)	1	(3%)	11	(13%)
Surgery	11	(7%)	3	(8%)	8	(7%)	4	(3%)	2	(6%)	2	(2%)
Musculoskeletal	10	(6%)	6	(16%)	4	(3%)	2	(2%)	2	(6%)	0	(0%)
Trauma	9	(6%)	2	(5%)	7	(6%)	4	(3%)	1	(3%)	3	(4%)
Critical Care	8	(5%)	1	(3%)	7	(6%)	0	(0%)	0	(0%)	0	(0%)

	Report progression criteria						Comparator subset*					
	Total (n = 160)		Completed (n = 37)		Protocol (n = 123)		Total (n = 118)		Completed (n = 34)		Protocol (n = 84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Obstetrics/Gynaecology	8	(5%)	2	(5%)	6	(5%)	4	(3%)	1	(3%)	3	(4%)
Endocrinology	6	(4%)	0	(0%)	6	(5%)	2	(2%)	2	(6%)	0	(0%)
Geriatrics	5	(3%)	1	(3%)	4	(3%)	10	(8%)	3	(9%)	7	(8%)
Paediatrics	5	(3%)	2	(5%)	3	(2%)	4	(3%)	1	(3%)	3	(4%)
Other	34	(21%)	9	(24%)	25	(20%)	34	(29%)	9	(26%)	25	(30%)
Intervention type												
Drug	13	(8%)	4	(11%)	9	(7%)	11	(9%)	1	(3%)	10	(12%)
Surgery/procedure	19	(12%)	6	(16%)	13	(11%)	7	(5%)	3	(9%)	4	(5%)
Counselling/lifestyle/physiotherapy	94	(59%)	22	(59%)	72	(59%)	59	(50%)	18	(53%)	41	(49%)
Equipment	9	(6%)	4	(11%)	5	(4%)	9	(7%)	3	(9%)	6	(7%)
Other	25	(16%)	1	(3%)	24	(20%)	32	(27%)	9	(26%)	23	(27%)
Sample size target* **												
Mean (SD)	217.3 (1074.9)		72.8 (62.5)		258.5 (1215.7)		87.5 (90.6)		64 (51.8)		97.0 (101.0)	
Median (IQR)	60 (40-100)		60 (32-90)		60 (40-100)		60 (40-100)		60 (30-80)		62 (44-116)	
Min-Max	6-12000		6-300		20-12000		10-700		10-300		12-700	
Cluster randomised pilot trials	***(n=21)***		***(n=3)***		***(n=18)***		***(n=14)***		***(n=7)***		***(n=7)***	
Mean number of clusters (SD)	*9.3 (10.7)*		*7.3 (2.3)*		*9.7 (11.6)*		*6.2 (3.8)*		*6.9 (4.6)*		*5.6 (2.9)*	
Median (IQR)	*6 (4-10)*		*6 (6-10)*		*6 (3-10)*		*6 (4-8)*		*6 (4-8)*		*6 (2-8)*	
Min-Max	*2-45*		*6-10*		*2-45*		*2-16*		*2-16*		*2-9*	
Number of arms												
2	143	(89%)	32	(86%)	111	(90%)	102	(86%)	28	(82%)	74	(88%)
>2	17	(11%)	5	(14%)	12	(10%)	16	(14%)	6	(18%)	10	(12%)

	Report progression criteria						Comparator subset*					
	Total (n = 160)		Completed (n = 37)		Protocol (n = 123)		Total (n = 118)		Completed (n = 34)		Protocol (n = 84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Number of centres												
Single centre	55	(34%)	19	(51%)	36	(29%)	40	(34%)	13	(38%)	27	(32%)
Multi-centre	102	(64%)	18	(49%)	84	(68%)	76	(64%)	20	(59%)	56	(67%)
Unclear	3	(2%)	0	(0%)	3	(2%)	2	(2%)	1	(3%)	1	(1%)
Feasibility objective/s explicitly described as primary												
Yes	71	(44%)	9	(24%)	62	(50%)	41	(35%)	8	(24%)	33	(39%)
No	89	(56%)	28	(76%)	61	(50%)	77	(65%)	26	(76%)	51	(61%)
Trial outcomes address trial objectives												
Yes	109	(68%)	18	(49%)	91	(74%)	61	(52%)	17	(50%)	44	(52%)
No	1	(1%)	0	(0%)	1	(1%)	2	(2%)	0	(0%)	2	(2%)
Somewhat****	50	(31%)	19	(51%)	31	(25%)	55	(47%)	17	(50%)	38	(45%)
Hypothesis testing												
Yes	18	(11%)	2	(5%)	16	(13%)	16	(14%)	2	(6%)	14	(17%)
Yes, exploratory/caution advised	61	(38%)	18	(49%)	43	(35%)	28	(24%)	12	(35%)	16	(19%)
No	81	(51%)	17	(46%)	64	(52%)	74	(63%)	20	(59%)	54	(64%)
Number of uncertainties reported												
One	1	(1%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)
Multiple	159	(99%)	37	(100%)	122	(99%)	118	(100%)	34	(100%)	84	(100%)

	Report progression criteria						Comparator subset*					
	Total (n = 160)		Completed (n = 37)		Protocol (n = 123)		Total (n = 118)		Completed (n = 34)		Protocol (n = 84)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Where uncertainties are first reported (excluding abstract)												
Introduction	1	(1%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)
Research question(s)	6	(4%)	2	(5%)	4	(3%)	3	(3%)	1	(3%)	2	(2%)
Aim(s)	21	(13%)	5	(14%)	16	(13%)	20	(17%)	8	(24%)	12	(14%)
Objective(s)	72	(45%)	10	(27%)	62	(50%)	39	(33%)	12	(35%)	27	(32%)
Outcome(s)	26	(16%)	9	(24%)	17	(14%)	30	(25%)	6	(18%)	24	(29%)
Outcome measure(s) or trial measure(s)	23	(14%)	7	(19%)	16	(13%)	15	(13%)	4	(12%)	11	(13%)
Analysis	2	(1%)	0	(0%)	2	(2%)	0	(0%)	0	(0%)	0	(0%)
Under a feasibility/uncertainty heading	3	(2%)	2	(5%)	1	(1%)	3	(3%)	0	(0%)	3	(4%)
Throughout the text, not in one specific area	6	(4%)	2	(5%)	4	(3%)	8	(7%)	3	(9%)	5	(6%)

Percentages might not add up to 100 due to rounding

*The comparator subset of publications do not report detailed progression criteria but do report prespecified targets relating to recruitment or sample size

**Therapeutic areas that were given in ≥ five publications (reporting progression criteria) are listed; all others are categorised in 'other'

***Where publications reported a sample size target range (e.g. 12-16 participants), the lower bound of the target is included. A sample size target was not reported in two publications (both reporting completed pilot trials and including the actual number of recruited participants).

****Reported objective was vague (e.g. to 'assess feasibility'), i.e. specific areas of feasibility uncertainty are not explicitly stated

2.3.3 Characteristics of progression criteria

Of the 160 publications which reported progression criteria, the characteristics of reported progression criteria are presented in Table B3. The reported progression criteria generally addressed some (99/160, 62%) or all (53/160, 33%) of the pilot trial's feasibility outcomes. The average number of progression criteria targets reported was 4 per publication (mean = 4.05, median = 3, range 0-10, IQR=3-5). The lower range was 0 since one study reported that their progression criteria were based on the ADePT framework, but did not explicitly report the specific indicators of feasibility that this included [104].

In total I identified 58 distinct areas of trial feasibility that contributed to progression criteria, which I grouped into four domains: process, resource, management and scientific, see Table B4. Most were process uncertainties (34/58, 59%), defined as those regarding the feasibility of processes that are key to the success of the future definitive RCT [15]. Recruitment (113/160, 71%) and retention (106/160, 66%) were the most common indicators of feasibility to inform progression criteria.

Although hypothesis testing in pilot trials is generally not recommended (as outlined in Chapter 1), four publications reported progression criteria that were based on detecting potential efficacy including determining non-inferiority of the intervention compared to comparator [105,106], determining superiority at follow-up [107] and finding a '*trend for difference*' between intervention and control groups on clinical outcomes [108].

Some reports described certain progression criteria as those that were 'primary' or 'key' [109–117], demonstrating a somewhat hierarchical approach to progression criteria by outlining those that are considered most important to indicate definitive RCT success.

Table B3 Characteristics of progression criteria reported

	Total (n = 160)		Completed (n = 37)		Protocol (n = 123)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Feasibility outcomes informing progression criteria						
All	53	(33%)	14	(38%)	39	(32%)
Some	99	(62%)	22	(59%)	77	(63%)
None	3	(2%)	1	(3%)	2	(2%)
Unclear*	5	(3%)	0	(0%)	5	(4%)
Reported process for establishing progression criteria						
Who decided on progression criteria						
Reported	12	(8%)	4	(11%)	8	(6%)
Not reported	148	(93%)	33	(89%)	115	(94%)
Rationale for progression criteria						
Reported for all progression criteria	28	(18%)	8	(22%)	20	(16%)
Reported for some progression criteria	16	(10%)	4	(11%)	12	(10%)
Not reported	116	(73%)	25	(68%)	91	(74%)
Progression criteria format						
Research method informing progression criteria						
Quantitative	125	(78%)	32	(86%)	93	(76%)
Quantitative and qualitative (mixed methods)	34	(21%)	5	(14%)	29	(24%)
Other**	1	(1%)	0	(0%)	1	(1%)
Qualitative research contribution						
Informs progression criteria	34	(21%)	5	(14%)	29	(24%)
Does not inform progression criteria	74	(46%)	14	(38%)	60	(49%)
Qualitative research not conducted	52	(33%)	18	(49%)	34	(28%)
Quantitative progression criteria target format						
Distinct threshold	133	(83%)	34	(92%)	99	(80%)
Traffic light system	20	(13%)	2	(5%)	18	(15%)
Other	7	(4%)	1	(3%)	6	(5%)
Reported process for assessing progression criteria to inform the progression decision						
Process for progression decision making						
Reported	74	(46%)	16	(43%)	58	(47%)
Not reported	86	(54%)	21	(57%)	65	(53%)
Who is involved in assessing progression criteria						
Reported	35	(22%)	5	(14%)	30	(24%)
Not reported	125	(78%)	32	(86%)	93	(76%)

*Feasibility uncertainties are not completely defined in the objectives and outcomes

**One report stated that progression criteria are based on the ADePT framework [104]

Table B4 Indicator of feasibility contributing to progression criteria

Domain	Indicator of feasibility contributing to progression criteria	Frequency
Management	Data completion or missing data	38
	Barriers or challenges to intervention implementation	7
	Develop or test training materials	4
	Protocol components work together	2
	Data analysis	2
	Data collection methods are suitable/fit for purpose	1
	Data management	1
	Time to Ethics approvals at each site	1
	Time to readiness to initiate the clinical trial	1
Process	Recruitment rates	113
	Retention or attrition rate	106
	Non(compliance) or adherence rate (participants)	66
	Intervention acceptability or evaluation (patients)	33
	Withdrawal or completion rate (trial or intervention)	22
	Intervention acceptability or evaluation (non-patients)	17
	Consent or refusal rate	16
	Randomisation acceptability or rate	15
	Intervention fidelity	15
	Understanding or acceptability of data collection tools	14
	Non(compliance) or adherence rates (non-participants)	12
	Participant identification or screening	10
	Eligibility rate	9
	Trial acceptability or evaluation (patients)	8
	Characteristics or properties of trial outcome measures	7
	Randomisation adequacy	5
	Crossover or contamination between arms	4
	Enrolment rate	5
	Uptake or engagement rate	3
	Definitive study sample size is achievable	3
	Trial acceptability or evaluation (non-patients)	2
	Success or failure rate	2
	Understanding or acceptability of study instructions	2
	Describe control group	2
	Recruitment process	2
	Blinding procedures	1
	Eligibility criteria	1
	Understanding or acceptability of study information	1
	Allocation concealment	1
	Intervention credibility	1
	Intervention suitability	1
	Completeness of biological sample collection	1
	Interest in using the intervention post-study	1
	Positive expected net gain of sampling from a definitive trial	1
Resources	Centre or investigator recruitment, willingness or capacity	21
	Determining process time	7
	Collection of outcomes relevant to future economic evaluation	4
	Equipment or resource reliability	2
	Venue, location or setting appropriate	1
	Determining capacity	1
	Intervention agreement between methods	1

Domain	Indicator of feasibility contributing to progression criteria	Frequency
Scientific	Safety, adverse events, unintended consequences or harms	25
	Estimate of treatment effect	11
	Estimate of variance of treatment effect	6
	Patient response	5
	Signal of efficacy	4
	Estimate intracluster correlation coefficient	1
	Context and mechanisms of action	1
	Intervention tolerability	1

Two protocols reported multiple progression criteria for individual feasibility indicators [118,119], for example providing both an overall recruitment target and a target number of participants to be recruited within a given timeframe (example provided below in Figure B2). Of these, one protocol publication stipulated that all criteria would need to be met or met within reasonable limits (within the green or amber traffic light domain) to progress to a future definitive trial without major study re-design. It was unclear in the other protocol publication (presented in Figure B2) whether meeting one criterion for each indicator of feasibility was sufficient justification for progression.

Table 3 A priori success criteria to assess trial feasibility

	Success criteria I	Success criteria II
Recruitment	2–3 participants/ month recruited over 12 months (for target sample size n=30).	≥10% recruitment response rate achieved (min. feasible RCT response rate).
Attrition	85% participants successfully complete study (ie, complete T1 and T4 evaluations).	75% participants complete all assessments (ie, protocol adherence).
Adherence	Successful completers participate in ≥75% meetings with coach.	75% of the participants complete evaluations in ≤2 hours (to assess burden).
Stratification	Intervention/control groups similar for age and gender.	Intervention/control groups comparable on diagnosis and functional mobility.
Fidelity	High intervention fidelity (>8/10 on the Solution-Focused Fidelity Instrument).	Challenges/ease of remote coaching (coach, child, family report).

RCT, randomised controlled trial.

Figure B2 Multiple progression criteria example

Reproduced from Table 3 McPherson et al (2019) *BMJ Open* **9**:e025119, published CC-BY-NC 4.0

2.3.3.1 Progression criteria and quantitative indicators of feasibility

Of the 160 publications which reported progression criteria, all reported using quantitative indicators of trial feasibility (e.g. rate of recruitment and amount of missing data) to inform at least one of the trial's progression criteria, with 78% (125/160) basing all progression criteria on quantitative indicators.

All but seven publications reported quantifiable numerical targets (or thresholds) that were, or would be, used to assess progression criteria. Six trials did not set specific numerical thresholds but did detail how the progression decision would be made, and upon which feasibility indicators this would be based (such as rate of recruitment, amount of missing data) [120–125]. One publication reported that progression criteria and the progression decision would be based on the ADePT framework [82,104], which has been described in detail in Chapter 1.

Quantifiable numerical targets for progression criteria were most often reported as a distinct threshold (e.g. achieving a specified rate of recruitment, retention or a minimum amount of data completion) (133/160, 83%). This was followed by a traffic light approach to reporting progression criteria (20/160, 13%) with thresholds correlating to different domains (e.g. above a higher threshold (green) indicating the definitive trial is feasible/proceed, within a mid/acceptable threshold (amber) indicating that changes to definitive trial are required, and below a lower threshold (red) indicating that the definitive trial is not feasible/not proceed).

2.3.3.2 Progression criteria and qualitative indicators of feasibility

Of the 160 publications which reported progression criteria, many reported planned or completed qualitative research as part of the randomised pilot trial (108/160, 68%). Although the findings from qualitative research conducted as part of a pilot trial are often reported in a separate publication, the intention to conduct qualitative research as part of a pilot trial should be made explicit before the pilot trial commences and reported in the pilot trial protocol [126]. The intention to conduct qualitative research was reported in protocols (89/123, 72%) more often than the qualitative research findings were reported in pilot trial result publications (19/37, 51%). However, qualitative indicators of trial feasibility, such as participants' or researchers' views of the acceptability of the trial or intervention (e.g. collected using interviews or focus groups), only informed progression criteria in 34 of the 108 (31%) publications that reported planned or completed qualitative research.

2.3.3.3 Reported processes for developing progression criteria

Only 12 (4 completed; 8 protocol) of the 160 (12/160, 8%) publications explicitly reported who had developed or agreed the progression criteria (text extracts presented in Table B5), with most involving a trial steering (or oversight) committee (10/12, 83%; five having patient or public representation), funders (3/12, 25%) and a trial management group (5/12, 42%; two having patient or public representation). Other stakeholders reported to be involved included study physicians or those with relevant clinical experience (2/12, 17%) and a data monitoring and ethics committee (1/12, 8%; also had patient or public representation).

Sixteen of the 160 publications (16/160, 10%) reported rationale or justification for at least one progression criterion, and 28 (28/160, 18%) reported rationale or justification

for all progression criteria. For 29 publications the stated justification was previous related research, with 25 providing references to previous studies. Thirteen publications referenced various sources of guidance or methodological research [24,55,56,58,65,82,127–132], including three references to published guidance for internal pilot trials [22]. Four publications reported that definitive trial contextual considerations had informed progression criteria, such as what would be an achievable recruitment rate, or intervention timeframe in the definitive trial. Three reported that clinical considerations had informed progression criteria, including medical chart reviews, clinical advice, and the nature of the population. Most of the pilot trial publications (116/160, 73%) did not report any rationale or justification for their progression criteria.

Table B5 Reported processes for establishing progression criteria

Reference	Stakeholder input, as reported	PPI input
Bryant (2018)	*Progression criteria have been approved by the steering committee*	A member of the parent advisory group sits on the Trial Steering Committee
Forster (2018)	*The criteria are to be agreed by the independent PSC* [Programme Steering Committee] *and funder*	The Programme Steering Committee has patient and public involvement representation
Golla (2018)	*Target recruitment level: The expected sample size was predefined in collaboration with the physicians in the study centres**	None reported
Griffin (2019)	*Progression criteria* [were] *agreed on by the funding panel and the Study Steering Committee*	PPI representative acknowledged as a member of the Study Steering Committee
Jones (2019)	*At the outset of the feasibility trial, the Trial Management Group (TMG), including the PPI representatives, specified progression criteria* […] *to be met within reasonable limits. These progression criteria were agreed upon by the Trial Steering Committee (TSC)*	People with experience of hip fracture, as patients or carers, were recruited to the Trial Management Group and Trial Steering Committee.
Logan (2018)	*These criteria will be finalised in discussion with the Trial Steering Committee*	Trial Steering Committee includes patients and members of the public
Meiksin (2019)	*Pre-specified progression criteria* […] *have been agreed and will be monitored by the SIG* [Study Investigators Group] *and SSC* [Study Steering Committee]	None reported
O'Connor (2019)	*These criteria have been developed by our Trial Management Group and approved by our TSC*	One of the study co-investigators (and co-author) is a service user
Ponsford (2018)	*Pre-specified progression* criteria […] will *be agreed and monitored by the TIG* [Trial Investigators Group] *and SSC* [Study Steering Committee]	None reported
Pyle (2019)	*We have specific red/amber/green progression criteria that have been agreed with our iDMC* [independent Data Monitoring and Ethics Committee], *TSC* [Trial Steering Committee] *and funder*	independent Data Monitoring and Ethics Committee includes a service user; Trial Steering Committee includes a service user

Reference	Stakeholder input, as reported	PPI input
Quraishi (2019)	*This threshold will be agreed after discussions by the Trial Management Group and the IOCI* [Independent Oversight Committee]*	None reported
Wurz (2019)	*A priori targets for each feasibility outcome were set using relevant literature and the authors' own clinical experience*	None reported

PPI; Patient and Public Involvement

*Relates to one specific progression criteria (e.g. site recruitment target), rather than the development of progression criteria more generally

2.3.3.4 Reported process for assessing progression criteria to inform the progression decision

Of the 160 publications which reported progression criteria, nearly half (74/160, 46%) reported how progression criteria had or would inform the decision to progress to a future definitive RCT. This included whether changes to definitive RCT design would be considered if criteria were not strictly met but were met within reasonable limits or the aforementioned 'amber' traffic light range, or who had (or would) be involved when assessing progression criteria. Three trials that reported criteria in a distinct threshold (or stop-go) format (i.e. with one target to meet) also reported the intention to take a flexible approach to pilot trial progression, allowing for flexibility where targets had not strictly been met but changes to the definitive RCT design could be made [133–135].

One publication reported a two-stage decision making process with different criteria assessed at each stage. Stage 1 was to decide on the best intervention route, and stage 2 was to decide whether to take the optimal intervention route forward to a definitive RCT [136]. Another publication described the intention to hold a consensus conference of key stakeholders (patients, surgeons, public representatives and researchers) to agree whether a definitive RCT was feasible [125]. Four pilot trials referred to the ADePT framework [82] to facilitate progression decision-making [104,120,123,137]. Of these, one publication described the intention to also use PRECIS-2 (a tool to help trialists design their trials to be consistent with trial purpose [138]) alongside ADePT to inform the progression decision [104].

Nearly a quarter of publications reported who would be involved in assessing progression criteria (35/160, 22%). This was more often reported in publications of trial protocols compared to completed trials (24%, 30/123 versus 14%, 5/37 respectively) and most

often involved an independent trial steering committee (26/35, 74%). Other reported parties included the research team or trial management group (13/35, 37%), data monitoring committee (7/35, 20%), trial sponsor (2/35, 6%), funder (1/35 3%), independent statistician (1/35, 3%), and other stakeholders, such as patients, clinicians and public representatives (3/35, 9%).

2.3.4 Progression intentions reported in completed pilot trial publications

Thirty-seven of the 160 publications which reported progression criteria were for completed pilot trials. Most reported that a future RCT would be feasible or the intention to proceed (30/37, 81%), including the seventeen completed pilot trials which met all their progression criteria (Table B6). Thirteen publications reported pilot trials that met some of their progression criteria, of these nine reported that a future RCT would be feasible, two reported that they would not proceed to a definitive RCT and two reported the intention to conduct further feasibility assessment. Four publications reported pilot trials that did not meet their progression criteria, of which three reported that a future RCT would still be feasible with changes to study design. The extent to which progression criteria was met was unclear for three published trials, of these two publications reported the intention to conduct further feasibility assessment, and one reported that a future RCT would be feasible.

Table B6 Intentions reported in completed pilot trial publications

	Completed (n = 37) n	(%)				
Progression criteria met						
All	17	(46%)				
Some	13	(35%)				
None	4	(11%)				
Unclear	3	(8%)				
Progression decision						
Proceed/future RCT is feasible	30	(81%)				
With intended design			*0*	*(0%)*		
With amendments			*28*	*(93%)*		
Not reported whether changes will be made			*2*	*(7%)*		
Funding intentions						
Funding for definitive RCT identified			*4*	*(13%)*		
Non-industry					*3*	*(75%)*
Unclear					*1*	*(25%)*
Expected funding for definitive RCT not reported			*26*	*(87%)*		
Timing intentions						
Time frame of expected progression reported			*1*	*(3%)*		
Time frame for expected progression not reported			*29*	*(97%)*		
Conduct further pilot/feasibility work	4	(11%)				
Not proceed/future RCT is not feasible	3	(8%)				
Justification reported for the progression decision reported						
Yes	36	(97%)				
No	1	(3%)				
Comment on data quality (e.g. proportion of missing/incomplete data from questionnaires or results)						
Yes	27	(73%)				
No	10	(27%)				
Comment on refinement of hypotheses						
Yes	1	(3%)				
No	36	(97%)				

Percentages may not sum up to 100 due to rounding

All but two of the 30 completed pilot trial publications reporting that a future RCT would be feasible planned to make changes to their definitive RCT design (28/30, 93%). Of these, four reported the implications of the pilot trial findings in a table format, alongside whether progression criteria had or had not been met [139–142]. There is no standard approach to reporting the implications of pilot trial findings. The examples identified report the challenges faced during the external pilot, and the suggested solutions, recommendations or considerations for the definitive RCT design, an example is given in Figure B3 [141]. Proposed changes to the definitive RCT that were reported include altering eligibility criteria, recruitment strategies (e.g. number of sites, recruitment materials and recruitment setting), randomisation design, blinding, outcome measures, follow up schedules and duration, and seeking additional research team support (such as a dedicated trial manager, research coordinator and administrative team). It was unclear for two pilot trials whether changes to the definitive trial design would be made.

Four of the 30 completed pilot trial publications reporting that a future RCT would be feasible also reported definitive RCT funding intentions: Two NIHR Health Technology Assessment, one European and Developing Countries Clinical Trials Partnership, and one reported that a funding application had been prepared and submitted but did not specify the funder. One publication reported an anticipated progression timeframe, specifying a recruitment start year for the definitive RCT [143]. All but one publication reported some justification for their decision. Twenty-seven (73%) of the 37 completed pilot trial publications commented on data quality i.e. the extent of missing data, and one reported a refinement of their trial hypothesis based on their pilot trial findings.

Table 3 Were the feasibility criteria met?

Criteria	Feasibility criteria met?	Recommendations for full trial
Blinding of assessor	Yes	Treatment providers should try to keep the treatment duration close to or equal to 1 hour to avoid any guesses of group allocation between the treatment groups.
Recruitment rate	Yes	Incorporating advertisement to recruit the patients was a good idea, which should be considered in the full trial.
Attrition rate (in both arms)	Yes	Phone call reminders for the follow-up assessment helped reduce the drop-outs and which should be considered in the future trial.
Feasibility of outcome assessment	Yes	1. Practice administration of the outcome measures on real patients who are older and have lesser education before the actual recruitment by learning ways to keep patients focused on the questions being asked. 2. Keep the relatives and friends of the patients separate from the participant during screening and assessment. 3. Self-administration of the questionnaires for participants who can read and write could improve the efficiency of completing the screening and data collection forms. 4. Separate the pain-related questionnaires and general questionnaires during administration.
Contamination of intervention	Yes	Having an appointment time for follow-up helps avoid contamination.
Credibility of treatment	Yes	The credibility scores of the two treatment conditions were within 0.50 SD of each other; therefore, no changes in the treatment conditions are required.
Adherence to treatment	Yes	Not many patients read the handbook provided to them. Creating interesting short audios or videos with the key messages may be helpful for improving the adherence to home advice.
Difficulty level of the intervention	No	A large proportion of patients reported the interventions to be 'easy'. The complexity of the pain education content may be increased by providing more complex neurophysiological knowledge to the patients. However, this may demand longer duration of treatment time, and/or compromise the effectiveness of the intervention, and may require pretesting of the changed intervention before using it in the full trial.

Figure B3 Example table reporting the assessment of progression criteria

2.3.5 Assessment of a priori progression criteria reporting

Published protocols were available for 16 of the 37 (43%) completed randomised pilot trial publications which reported progression criteria, see Table B7. Trial registrations were identified for an additional 20 pilot trials. I was unable to identify a published protocol or trial registration for the one remaining completed pilot trial.

Table B7 Assessment of a priori progression criteria reporting

	Completed (n = 37)			
	n	**(%)**		
Published protocol available				
Yes	16	(43%)		
Alternative available e.g. trial registration or REC submission	20	(54%)		
No	1	(3%)		
Progression criteria in earlier trial record (protocol or registration)				
No change	10	(28%)		
Yes changed	26	(72%)		
Reasons for change reported			*1*	*(4%)*
No reason for change reported			*3*	*(12%)*
Progression criteria were not reported in the earlier trial record			*22*	*(85%)*

Percentages may not sum up to 100 due to rounding

Twenty-six published protocols or trial registrations identified either reported different progression criteria to the completed pilot trial (26/36, 72%), or did not report progression criteria at all. An additional four protocols or trial registrations reported different progression criteria to the pilot trial result publication. Only one completed trial publication explained why the progression criteria had changed from the protocol: as the qualitative findings were reported in a separate publication, the progression criteria associated with acceptability were not included in the completed pilot trial result publication. For one trial progression criteria were reported in more detail in the trial protocol publication which was referenced in the completed trial report for further detail on the progression criteria [141,144].

2.3.6 Progression criteria in prepublication peer reviewer reports

Prepublication peer review reports were available for 153 of the 160 (96%) publications which reported progression criteria. Peer reviewer reports were not publicly available for the three *PLoS One* publications and peer review was not commissioned for four of the pilot trial protocols published in *BMJ Open*. Over half of the prepublication peer reviewer reports commented on progression criteria (86/153, 56%), see Table B8.

Table B8 Analysis of peer reviewer reports

Progression criteria mentioned in peer reviewer reports	**Total (n=160)**		**Completed (n=37)**		**Protocol (n=123)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Yes	86	(54%)	19	(51%)	67	(54%)
Context of peer reviewer comment						
Progression criteria were not specified	*35*	*(41%)*	*6*	*(32%)*	*29*	*(44%)*
Unlikely progression criteria were specified	*5*	*(6%)*	*1*	*(5%)*	*4*	*(6%)*
Rationale or justification queried	*20*	*(23%)*	*5*	*(26%)*	*15*	*(22%)*
Other	*26*	*(30%)*	*7*	*(37%)*	*19*	*(29%)*
No	67	(42%)	15	(41%)	52	(42%)
Peer reviewer report unavailable	7	(4%)	3	(8%)	4	(3%)

Percentages may not sum up to 100 due to rounding

Of the 86 peer reviewer reports that mentioned progression criteria, 35 (41%) (6 completed; 29 protocol) indicated that progression criteria were not reported in the submitted prepublication manuscript. This is demonstrated in the following text extracts taken from the peer reviewer reports for one pilot trial publication:

> *Peer reviewer 1: How will the authors judge the feasibility of conducting a definitive trial on the basis of the current protocol e.g. >80% of recruited participants retained to final follow-up?*

> *Peer reviewer 2: There are no criteria specified which will determine whether succession to a main trial should be considered. Given that recruitment, retention and safety are all being monitored as feasibility outcomes, these outcomes should have some criteria around them which would then allow informed decisions to be made on the design of a future trial.*

The progression criteria for recruitment and retention rates that were reported in this publication had a distinct threshold target of >80%, the same threshold that peer reviewer 1 suggested [109]. Since no justification was reported for this progression criteria target, it is unclear whether the author based this on the example provided by the peer reviewer.

Whether progression criteria were reported in the submitted prepublication manuscript was unclear for five publications (6%) (1 completed; 4 protocol) due to ambiguity of peer reviewer comments.

Twenty of the 86 peer reviewer reports that mentioned progression criteria (23%) (5 completed; 15 protocol) referred to the rationale or justification given for progression criteria. For example, they asked why a specific progression criterion was set, why progression criteria were given for specific outcomes, how the progression criteria were decided on, and how the progression decision was or will be made.

A further 26 of the 86 peer reviewer reports that mentioned progression criteria (30%) (7 completed; 19 protocol) mentioned other aspects of progression criteria. For example, they mentioned changing where the progression criteria were reported in the manuscript (such as including the progression criteria in the publication abstract and not solely within a supplementary file), clarifying ambiguous wording, adding percentages in brackets for clarity, correcting inconsistencies in the manuscript, and clarifying how specific criteria will be assessed. Peer reviewers also complimented authors for describing progression criteria well.

Not every author opted to update or add progression criteria to their manuscript after prepublication peer review. In their response to peer reviewer comments, the authors of one trial protocol publication argued that they could not alter progression criteria following peer review since it had already been agreed by the trial management group, trial steering committee, and approved by their research ethics committee [135]. Other reasons for not reporting quantifiable numerical targets for progression criteria that authors stated in response to peer reviewer comments include: they were not set during trial design; strict thresholds might be influenced by contextual variations that may not affect a future trial; progression criteria are best viewed as guidelines in line with the CONSORT extension for PAFS; different perspectives could not be successfully captured by a set of criteria, and the trial is not an internal pilot:

> *Strict thresholds for progression have not been set as these factors can be influenced by contextual variations that may not impact on a future trial* [120]

> *According to the CONSORT 2010 extension statement for pilot and feasibility trials, even when such targets are set, they may be best viewed as guidelines rather than thresholds for progression* [123]

The study features a variety of data types to explore the acceptability of the intervention, the feasibility of trial procedures and to identify potential changes to make prior to a full trial. This includes qualitative interviews, app usage data and the assessment of recruitment and retention rates. We felt that these different perspectives could not be all successfully captured by a set of criteria, and as the study is not an internal pilot specific thresholds have not been set to determine the success of the trial and its procedures [122]

2.3.7 Trial characteristics associated with progression criteria reporting

I conducted a logistic regression to compare the sample of included publications to the secondary comparator subset of publications (that did not report detailed progression criteria but did report a prespecified sample or recruitment target for progression; see Figure B1), to determine whether progression criteria reporting is associated with certain trial characteristics in this sample. The trial characteristics included in the logistic regression have been previously associated with progression criteria reporting (journal and region of publication) [69], or have been associated with study design or reporting standard of clinical trials more generally (year, funding source, sample size, number of centres, and intervention type) [90].

In this section of the thesis I will present the characteristics of publications included in the comparator subset (see Figure B1; n=118) and the results of the logistic regression.

2.3.7.1 Characteristics of publications reporting recruitment or sample size target for progression only

Of the 278 eligible publications (see Figure B1), 118 publications did not report detailed progression criteria but instead only reported a pre-specified sample or recruitment target for progression. These 118 publications had similar characteristics to the 160 publications which did report progression criteria (main study sample), see Table B2: most reported protocols (84/118, 71%) rather than completed trials (34/118, 29%) and described two-arm (102/118, 86%), multicentre (76/118, 64%), non-industry funded (108/118, 92%) trials of counselling, lifestyle or physiotherapy interventions (59/118, 50%). Publications covered 25 therapeutic areas and 19 countries, mostly from the UK (66/118, 56%). Compared to the main sample of publications that reported progression criteria, most of the publications were published in *BMJ Open* (46/118, 39%).

Primary feasibility objectives were explicitly stated in 41/118 (35%) publications and were more often stated in protocols than completed trial reports (39%, 33/84 versus 24%, 8/34 respectively). Compared to the main sample of publications that reported progression criteria, fewer reported feasibility outcomes in the methods that addressed all the stated feasibility objectives (52%, 61/118 versus 68%, 109/160 respectively). Again, most of the trial publications that reported the intention to conduct hypothesis testing advised caution in interpretation. The place in the publication where the specific uncertainties related to trial feasibility were first reported again varied, but most often this was also within the pilot trial feasibility objectives (39/118, 33%) or the data collection section describing the feasibility outcomes (30/118, 25%).

Characteristics of the prespecified sample or recruitment targets reported in the 118 publications which did not report detailed progression criteria are presented in Table B9.

Table B9 Characteristics of recruitment or sample size targets reported in comparator subset publications

	Total (n = 118)		Completed (n = 34)		Protocol (n = 84)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Total trial target or site-specific target						
Overall target	109	(92%)	32	(94%)	77	(92%)
Site-specific target	9	(8%)	2	(6%)	7	(8%)
Target format						
Distinct threshold	118	(100%)	34	(100%)	84	(100%)
Rationale/justification given for target						
Yes	91	(77%)	21	(62%)	70	(83%)
No	27	(23%)	13	(38%)	14	(17%)
Other uncertainties (aside from recruitment) reported						
Yes	118	(100%)	34	(100%)	84	(100%)

Most publications reported an overall pilot trial target (109/118, 92%) as opposed to site specific targets (9/109, 8%), with all targets reported in a distinct threshold format. Most publications provided rationale or justification for their prespecified sample or recruitment target (91/118, 77%). This was more often reported in protocol than completed trial publications (83%, 70/84 versus 62%, 21/34 respectively). Rationale provided included prior studies, pragmatic or practical considerations, power calculations, a target deemed to be sufficient to provide estimates of key parameters for the definitive trial, and sources of guidance relating to sample size calculations for pilot trials. Guidance for pilot trial sample size referenced included various publications [13,42,48–51,54,55,145–148], NIHR Research Design Service guidance [149], an introductory handbook to randomised trials in education (unable to locate reference online), and online guidance published by the Nielsen Norman Group, an American computer user interface and user experience consulting firm [150].

Of the 34 completed trials, 22 (65%) met their sample size target, one required an extension in order to meet their target, and 11 (32%) did not meet their target.

2.3.7.2 Logistic regression results

Logistic regression was conducted to determine whether progression criteria reporting is associated with certain trial characteristics in this sample.

Since some countries were infrequently represented or only represented in one group (see Table B2), I grouped countries into the following categories based on geographical region to facilitate analysis: UK, Canada, USA, Oceania (Australia and New Zealand), Europe excluding UK (Republic of Ireland, Germany, Sweden, The Netherlands, Denmark, Norway, Italy, Switzerland), Asia (China, Nepal, Korea, Thailand, Indonesia, Sri Lanka) and other (Brazil, Tanzania, Zimbabwe, Chile, Uganda).

In the univariate model four variables–journal, region, intervention type and sample size–were identified to be associated with reporting of more detailed progression criteria based on a relaxed p-value of ≤0.25. Trial type, year, funder, and number of centres were not identified to be associated with reporting detailed progression criteria, see Table B10.

Journal, region, intervention type and sample size were included in the first multivariate model, see Table B10. In this model, journal and region were associated with progression criteria reporting at a p-value of ≤0.05. Pilot trial publications in *BMJ Open* (multivariate OR 0.40; 95% CI 0.21 - 0.73; p-value 0.003) and *Trials* (multivariate OR 0.50; 95% CI 0.26 - 0.94; p-value 0.033) were associated with lower odds of reporting progression criteria compared to those published in *Pilot and Feasibility Studies.* Publications of trials from Canada (multivariate OR 4.39; 95% CI 1.34 - 14.40; p-value 0.015) were associated with higher odds of reporting progression criteria compared to those from the UK.

Table B10 Logistic regression results

Characteristic	Univariate p-value	Multivariate (AIC = 1.36) Odds ratio	95% CI	p-value
Trial type	0.284	Not included		
Completed				
Protocol				
Year	0.794	Not included		
2018				
2019				
Journal	**0.019*** **			
Pilot and Feasibility Studies (PAFS)		1 (reference)		
British Medical Journal (BMJ) Open		0.40	0.21 - 0.73	**0.003*** **
Public Library of Science (PLoS) One		1.08	0.10 - 11.62	0.949
Trials		0.50	0.26 - 0.94	**0.033*** **
Region	**0.068** **			
UK		1 (reference)		
Canada		4.39	1.34 - 14.40	**0.015*** **
USA		1.21	0.46 - 3.21	0.700
Oceania		0.73	0.31 - 1.72	0.473
Europe excluding UK		0.61	0.26 - 1.42	**0.249***
Asia		1.56	0.47 - 5.16	0.469
Other		0.49	0.10 - 2.40	0.382
Funder	0.590	Not included		
Non-industry				
A combination				
Industry				
Trial did not receive funding				
Unknown				
Number of centres	0.989	Not included		
Multi-centre				
Single centre				
Unclear				
Intervention type	**0.075** **			
Counselling/lifestyle/physiotherapy		1 (reference)		
Drug		0.59	0.23 - 1.52	0.278
Equipment		0.74	0.26 - 2.10	0.575
Other		0.57	0.29 - 1.08	**0.086** **
Surgery/procedure		1.91	0.73 - 5.00	**0.191***
Sample size	**0.247***			
Small (0-60)		1 (reference)		
Large (61+)		0.81	0.42 - 1.61	0.553

*p<0.25, **p<0.1, ***p<0.05; Categories compared to reference category indicated

I produced a second multivariate model that only included variables with p-value ≤0.05 in the full multivariate model (i.e. journal and region), see Table B11. Journal and region were also associated with progression criteria reporting at a p-value of ≤0.05 in this reduced multivariate model. Pilot trial publications in *BMJ Open* (multivariate OR 0.40; 95% CI 0.22 - 0.73; p-value 0.003) and *Trials* (multivariate OR 0.48; 95% CI 0.26 - 0.91; p-value 0.025) were associated with lower odds of reporting progression criteria compared to those published in *Pilot and Feasibility Studies.* Publications of trials from Canada (multivariate OR 4.16; 95% CI 1.32 - 13.17; p-value 0.015) were associated with higher odds of reporting progression criteria compared to those from the UK.

Table B11 Reduced multivariate logistic regression results

	Multivariate (AIC = 1.35)		
Characteristic	**Odds ratio**	**95% CI**	**p-value**
Journal			
Pilot and Feasibility Studies (PAFS)	1 (reference)		
British Medical Journal (BMJ) Open	0.40	0.22 - 0.73	**0.003***
Public Library of Science (PLoS) One	1.21	0.11 - 13.25	0.879
Trials	0.48	0.26 - 0.91	**0.025***
Region			
UK	1 (reference)		
Canada	4.16	1.32 - 13.17	**0.015***
USA	1.29	0.50 - 3.31	0.603
Oceania	0.73	0.32 - 1.69	0.463
Europe excluding UK	0.56	0.25 - 1.27	0.167
Asia	1.59	0.49 - 5.11	0.436
Other	0.54	0.11 - 2.57	0.436

*p<0.05; Categories compared to reference category indicated

2.4 Discussion

2.4.1 Summary of findings

This chapter presents a methodological review of 160 pilot trial publications (37 completed; 123 protocol) that reported progression criteria and were published in four key journals between January 2018 and December 2019. The findings suggest that there is heterogeneity in the application and reporting of progression criteria in current practice. It is often unclear in pilot trial publications how progression criteria were established, upon what justification or rationale they were based, how they will be assessed or analysed to inform the progression decision, and who is involved at each stage. Progression criteria also featured in many prepublication peer reviewer reports for both protocols and completed pilot trials, indicating that criteria might not have been established a priori as is recommended for good practice.

I identified an additional 118 publications (34 completed; 84 protocol) that reported only a recruitment or sample size target which were included in a comparator publication subset for logistic regression analysis. Two trial characteristics, journal and region, were identified to be associated with progression criteria reporting.

2.4.2 Findings in context

Previous research has highlighted that many RCTs with internal pilot phases do not specify progression criteria in their pilot trial protocols, and where specified, rationale for choice of progression criteria is not often reported [151,152]. The findings of this study, which highlight inconsistent progression criteria reporting across included publications, suggest that this is also true for external randomised pilot trials. Publications did not often

report how criteria had been developed, who was involved and what rationale they were based on. However, my findings might indicate that progression criteria reporting in external randomised pilot trial publications is improving. At full text screening I identified and included 160 external randomised pilot trial publications that reported progression criteria, and 118 that reported a recruitment or sample size target to inform progression. I excluded 251 publications where I was unable to identify any reported progression criteria. This would suggest that just over 30% of the external randomised pilot trial publications assessed report clear progression criteria (160/529; 30%), which is an improvement on a previous estimate that 20% of pilot trial protocol publications, published in *BMJ Open*, *Trials*, and *PAFS* between 2013 and 2017, report clear progression criteria [69]. This improvement in progression criteria reporting over time between the two estimates is likely due to publication and dissemination of the 2016 CONSORT extension for PAFS [24], which can also be used to guide pilot trial design. It is unclear whether this improvement is reflected across all clinical areas. A more recent review of 111 PAFS submitted to top dental journals between 2017 and 2020 found that none reported progression criteria [37], which might suggest that there is variation in uptake of reporting guidelines across different medical specialities.

It is recommended that PAFS should clearly describe the criteria for assessing success of feasibility (i.e. progression criteria), and that these criteria should be based on the feasibility objectives [15]. However, many of the studied publications reported a broad overarching feasibility objective, *e.g. to investigate feasibility of the trial/intervention*, with specific feasibility uncertainties (e.g. recruitment, data completeness, adherence) reported elsewhere. Recruitment and retention rates were the most common feasibility uncertainties to contribute towards progression criteria compared to other feasibility indicators. This is supported by a recent review which identified recruitment to be the

most common uncertainty evaluated in surgical PAFS [32], and is unsurprising considering that recruiting to target is a common challenge for many RCTs [8]. Fairhurst et al. suggested that researchers might focus on feasibility uncertainties that they perceived to be most important to funders, for example recruitment [32], with less awareness of other potential uncertainties that can compromise an RCT [32]. In support of this suggestion, I identified that other feasibility uncertainties that are equally as important to trial success, such as intervention acceptability, contributed to progression criteria much less often.

The role of qualitative research in enhancing feasibility assessment has been previously described [84,85], and many of the studied pilot trial publications included qualitative research. However, it was often unclear whether, or how, qualitative findings informed progression criteria. This suggests that although many researchers might see value in doing qualitative research within or alongside their pilot trial, many opt to base progression criteria on 'quantitative benchmarks' to indicate feasibility [72]. It was also unclear how feasibility is interpreted where trials report multiple progression criteria for one feasibility outcome: should all progression criteria be met or is meeting one target for each progression criterion considered sufficient justification for progression.

My findings highlight that peer reviewers improved pilot trial reporting, for example, by prompting authors to explain their progression criteria and rationale. I also identified instances where new progression criteria were likely added as a result of peer review, in both pilot trial protocol and result manuscripts. Adding post hoc progression criteria to results manuscripts could introduce bias since progression criteria might be based on targets that have been met or exceeded to justify progression to a definitive RCT. This highlights the need for clearer guidance for establishing progression criteria a priori, and

adequate reporting in external randomised pilot trial protocols [69]. This is particularly timely considering the extensive sample of recently published pilot trial protocols identified for inclusion in the study (207 in total) indicating increased pilot trial protocol publication.

I identified that publications in *Trials* and *BMJ Open* were associated with lower odds of reporting progression criteria compared to those published in *Pilot and Feasibility Studies (PAFS)*. One potential explanation for this is that the *PAFS* journal guides authors directly to the CONSORT extension for PAFS [24], where progression criteria is a reporting item. Region was also associated with progression criteria reporting, with publications of pilot trials from Canada associated with higher odds of reporting progression criteria compared to the UK. This supports previous research which also identified that protocols of pilot trial from North America are associated with higher odds of reporting progression criteria [69], and indicates that there might be regional differences in approaches to external randomised pilot trials. One potential explanation for this finding is that regional research funders have different stipulations for applicants to follow. Upon reflection, this could have been investigated further if more granular data about trial funding source was extracted from publications (e.g. specific funding source rather than the broader industry versus non-industry categories used).

2.4.3 Strengths and limitations

The strength of this review is the inclusion of an extensive and recent sample of 278 randomised pilot trial publications (160 reporting progression criteria and 118 comparator publications) between January 2018 and December 2019 spanning four key journals that publish randomised pilot trial reports. Reporting quality of clinical trials has previously been shown to be better where publications are written in English [153] and

are published in journals with higher impact factors [154] or those that endorse the CONSORT statement [155]. Since I only included key journals that are known to publish pilot trials, it is unclear whether publication standard of the included sample is an over estimation of current practice compared to other journals that publish pilot trial protocol and results publications. However, these journals were specifically selected because they had the most PubMed indexed publications that included the terms '*pilot'* or '*feasibility'* (and) '*trial'* or '*protocol'* in their title between January 2018 and December 2019 and were therefore considered to be a good representation of current practice. This bias might be further exacerbated by historical inadequacies in PAFS reporting. A previous study that investigated the reporting of pilot studies published in six anaesthesia journals between 2007 and 2017 estimated that only 13% of studies claiming to be a pilot or feasibility study were correctly described as such [38]. This highlights that some researchers might still use incorrect and inconsistent terms to describe PAFS, and journal editors and peer reviewers might not always pick up on these misdescribed studies. Therefore it is possible that eligible pilot trials might have been missed simply because they were not described using standard terminology used throughout this thesis [11]. It is also likely that correctly described PAFS, like those included in this review, are of higher methodological quality and potentially more likely to include progression criteria. In addition, the inclusion of only journals that publish in English might have introduced potential language bias [156].

The main limitation of this review is that single screening was used, which may have missed eligible publications. Double data extraction was only conducted for 25% of the included publications that reported progression criteria, which might have also led to errors in data extraction [157]. This was a pragmatic decision: double data extraction for all included publications was not feasible given the timeframe of this DPhil and the

resource availability. Furthermore, data extraction differences were minimal and were all resolved through discussion to reach consensus, therefore conducting only 25% data extraction was considered sufficient.

In addition, aspects of this review were subject to interpretation. For example, peer-review is considered to be a subjective process [158] therefore my review of peer reviewer reports was also subject to interpretation. Prepublication peer reviewer reports were also not available for all included publications: PLoS One allows authors to opt in to publish peer reviewer reports, and peer review was not commissioned for four pilot trial protocols published in *BMJ Open* that had already been peer reviewed for ethical and funding approval before journal manuscript submission. Progression criteria might also have been added or altered based on earlier editorial manuscript review. Unlike peer review, it is not common practice to make editorial reviewer reports publicly available.

Finally, although the logistic regression findings are consistent with previous research [69] and publication characteristics between the two groups were quite balanced, the publications included in this study were predominated by UK based research groups and the inclusion of more pilot trials from different regions might have led to increased precision (i.e. narrower confidence intervals) around the findings.

2.4.4 Chapter summary

This chapter presented the methods and findings of a methodological study of the characteristics of progression criteria, where reported, in pilot trial publications.

I identified a large cohort of pilot trial publications that reported progression criteria. However, many did not report how progression criteria were established or how criteria subsequently guide feasibility assessment and progression decision making. This

highlights the need to conduct further research to examine progression criteria in different pilot trial documents e.g. pilot trial funding applications (presented in Chapter 3), and to use qualitative research methods to explore how researchers develop and use progression criteria in practice (presented in Chapter 4).

My findings also support previous research that investigated the use of progression criteria in internal pilot trials [151] highlighting that many pilot trials proceed to definitive trials even if they have not strictly met all progression criteria. However, the included sample of pilot trial result publications reporting progression criteria was small (n=37). Therefore, I have prospectively followed up the pilot trial protocols that were included in this review (presented in Chapter 5), for a more comprehensive understanding of how progression criteria inform feasibility assessment and subsequent progression decision making.

Chapter 3 A cross-sectional study of progression criteria stipulated in NIHR Research for Patient Benefit external randomised pilot trial funding applications

Associated research outputs:

The protocol for this chapter is registered on the *Open Science Framework* [1] and the results are published in *Trials* [2]. I presented the findings from this study at the *Society for Clinical Trials* conference (2022, San Diego), where I received the best poster presentation award.

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[1] Mellor K, Hejdenberg J, Morgan B, Hopewell S. Progression criteria in external randomised pilot trials: Protocol for a review of Research for Patient Benefit funding applications. *OSF* 2021. doi:10.17605/OSF.IO/89AP7

[2] Mellor K, Harwood J, Hejdenberg J, et al. Inclusion of progression criteria in external randomised pilot trials: a cross sectional study of funding applications submitted to the NIHR Research for Patient Benefit Programme. *Trials* 2022;**23**:931. doi.org/10.1186/s13063-022-06868-8

3.1 Chapter introduction

3.1.1 Rationale for study

As presented in Chapter 1, NIHR guidance for RDS advisors recommends that progression criteria are agreed early to ensure effective monitoring so that pilot trials can be adapted in an efficient and timely manner where required to improve the success of feasibility assessment [57]. It has also been advised that progression criteria for internal pilot trials are agreed in advance with research funders [22], however the findings from the methodological review, presented in Chapter 2, highlighted that researchers do not consistently report who had agreed progression criteria for external randomised pilot trials. Although a priori progression criteria reporting in external pilot trial protocols has been previously explored [69], whether researchers stipulate progression criteria in their pilot trial funding applications has not been studied. It is therefore unclear how researchers submitting funding applications for external pilot trials plan to determine whether their pilot trial is feasible.

One of the largest funders of PAFS in the UK is the NIHR Research for Patient Benefit (RfPB) funding stream. The NIHR RfPB programme published guidance in 2017 (v1.0, July 2017) to stipulate that applications for feasibility studies should include clear progression criteria [17]. This was updated in 2021 (v2.0, February 2021) to cover all types of preparatory studies and include the expectation that the application would include progression criteria and set out the pathway to definitive RCT in the research plan [159]. In this chapter I present the methods and findings of a cross-sectional study of progression criteria, where stipulated, in pilot trial funding applications submitted to the NIHR RfPB funding stream.

3.1.2 Aim and objectives

I aimed to examine the progression criteria stipulated in the research plans of NIHR RfPB funding applications to identify how researchers conducting randomised pilot and feasibility trials plan to determine the feasibility of a future definitive RCT in current practice.

The primary objective was to examine how researchers report and plan to assess progression criteria in external pilot trial funding applications submitted to NIHR RfPB.

The secondary objectives were to:

- determine which indicators of feasibility inform progression criteria
- document and describe any rationale provided for stated progression criteria
- review RfPB funding panel committee feedback, to determine the extent and context in which progression criteria are mentioned
- determine whether applications for external pilot trials that stipulate progression criteria are more likely to obtain funding, continue to completion, proceed to a further funding application, and be published

3.2 Methods

3.2.1 Protocol and registration

I published a protocol for this study on the Open Science Framework (osf.io/89ap7) [160]. I received ethical approval for this research from The University of Oxford Medical Sciences Interdivisional Research Ethics Committee (MS IDREC), a sub-committee of the Central University Research Ethics Committee (CUREC), reference R74410/RE001. My reporting in this chapter follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) 2007 checklist of items that should be included in reports of cross-sectional studies [161,162] presented in Appendix C1.

3.2.2 Data Sharing Agreement

A Data Sharing Agreement (DSA) between the Secretary of State for Health and Social Care (the data provider) and the Chancellor, Masters and Scholars of the University of Oxford (the data recipient) was produced and signed off before this research started. The DSA outlined the data that would be provided (or shared), the purpose of sharing that data (i.e. to conduct this specific research study), and the agreed terms and conditions in relation to how the data was used. The agreed data to be shared as per Schedule 2 of the DSA included:

1. application research plan
2. project specific feedback from the relevant funding panel/committee
3. whether the application was funded
4. whether a pilot trials results report was published

5. whether any funded applications progressed to further research funding e.g. for a definitive clinical trial

All data received was treated as confidential. Funding applications were only included where the lead applicant had given approval (via email) for their application to be shared for the purpose of research. To maintain applicant anonymity, only the research plan section of each application was shared, with any identifiable information (e.g. names, locations, institutions and trial acronyms) redacted before sharing. The process of obtaining approval and data sharing was coordinated by NIHR RfPB Programme Managers and is described in detail in section 3.2.4.

3.2.3 Sample of eligible applications

Stage 1 applications submitted to the RfPB funding committee for external randomised pilot trials, with a funding decision between July 2017 and July 2019, were eligible for inclusion irrespective of application outcome at Stage 1 (i.e. proceed to Stage 2 or unsuccessful) or Stage 2, if applicable (i.e. awarded funding or unsuccessful). Applications from July 2017 were included because guidance to stipulate that clear progression criteria should be included in RfPB applications was first published in July 2017. Where the Stage 1 application outline had been invited to the full Stage 2 application, the corresponding full Stage 2 application was also included along with the funding committee feedback.

3.2.4 Retrieval of applications and data management

The RfPB database was searched by Jennie Hejdenberg, Senior Programme Manager at NIHR RfPB, to identify all Stage 1 applications from Competition 31 (awarded July 2017) to 37 (awarded July 2019). Application titles and the plain English summaries were

searched for the keyword's 'pilot', 'feasibility' or 'feasible'. A second keyword search for random* in the title or plain English summary was used to identify applications with a randomised design. To ensure all randomised pilot trials had been included, application summaries were also searched for the terms 'random', or 'control'.

The NIHR RfPB Senior Programme Manager then emailed all lead applicants of identified applications to request their approval for the research plan of their application to be shared with the research team at the University of Oxford. Email wording that was sent by NIHR RfPB to each applicant is detailed in Appendix C1. Once approval had been given, the NIHR RfPB Senior Programme Manager coordinated the redaction of application research plans to remove any identifiable information, providing each redacted application with a unique ID which was maintained throughout data collection.

The NIHR RfPB Senior Programme Manager shared the applications in nine small batches over a period of five months by secure encrypted transfer. Upon receipt, I reviewed each Stage 1 application research plan to provide a second confirmation that they described an external randomised pilot trial. All applications were saved to my personal password protected server (H: drive) in accordance with the University of Oxford data protection policies. A shared MSD drive was requested from the university so that a random 25% sample of applications could be shared with James Harwood, a DPhil researcher based at the University of Oxford, for double data extraction.

3.2.5 Data extraction

All data were collected into a REDCap (REsearch Data Capture) database that I had produced for this study. The data dictionary codebook is presented in Appendix C3. Data was collected to describe characteristics of the application including the pilot trial design,

sample size, number of treatment groups, therapeutic area, intervention, feasibility objectives and outcomes, and whether qualitative research had been conducted. I collected the application outcome at both Stage 1 (i.e. proceed to Stage 2 or unsuccessful) and Stage 2, if applicable (i.e. awarded funding or unsuccessful).

I collected whether progression criteria were included, and the areas of trial design that progression criteria related to e.g. recruitment, retention, adherence etc. I documented the format of the progression criteria e.g. stop-go (distinct threshold) vs stop-amend-go (traffic light system). I recorded any justification or rationale for progression criteria and whether it was reported who had been involved in establishing progression criteria.

I reviewed RfPB committee feedback to identify any instances where progression criteria were mentioned. For applications that proceeded to Stage 2, I documented whether there had been any changes relating to progression criteria between Stage 1 and 2 and noted where changes had been made to address committee feedback.

As part of RfPB routine post close monitoring, investigators are followed up post funding award to collect routine follow up data. From this data, I documented whether the external pilot trial had completed, whether a future definitive trial was considered feasible, whether funding for a future trial was applied for and if so, whether it had been awarded.

Double data extraction was conducted for 25% of included applications. Again, the decision to conduct double data extraction for 25%, rather than all included applications, was based on time and resource constraints. The second data extractor was blinded to the date of the funding call to which the application was submitted (either pre- or post-2017). The second data extractor also extracted data directly into REDCap, and I provided guidance notes, training and a database demonstration to facilitate this. I compared REDCap data entries (i.e. my and the second data extractors REDCap entry for the same

application) in rolling batches of five applications for any discrepancies. Discrepancies were discussed at regular virtual meetings with the second data extractor until consensus was reached.

Throughout data extraction the NIHR RfPB Senior Programme Manager was also available and willing to respond to any queries over email e.g. where applications were incomplete (pages missing), or to answer any questions that I had about funding panel feedback.

3.2.6 Data analysis

I produced descriptive statistics (including proportions and median and IQR for sample size) using Stata (version. 16.0; StataCorp) to describe the funding applications, any progression criteria that were stipulated and the application outcomes. I compared the characteristics of stipulated progression criteria by funding application stage (Stage 1 and Stage 2), and by funding outcome at each stage.

I conducted an additional post hoc analysis to compare whether applications with Stage 1 outline submitted to funding calls launched after July 2017 (the date funder guidance to include progression criteria was first published) were more likely to include progression criteria compared to those submitted to funding calls launched before July 2017.

3.3 Results

3.3.1 Screening and inclusion of applications

In total 918 Stage 1 application outlines with a funding decision made between July 2017 and July 2019 were identified in the RfPB database. Of these, 341 had the terms ‘pilot’, ‘feasibility’ or ‘feasible’ in their title or plain English summary. 269 included the term ‘random*’ in their title or plain English summary or were considered randomised in design based on initial review of their research plan. The 236 lead applicants of the 269 applications were contacted and invited to provide consent for their application to be included in the review. Eighty-nine lead applicants gave approval for 100 applications to be included, 14 applicants (lead applicants for 20 applications) responded but did not give approval, and 133 applicants (lead applicants for 149 applications) did not respond. In total, the NIHR RfPB Senior Programme Manager shared the research plans and committee feedback of 100 redacted applications. This is summarised in Figure C1.

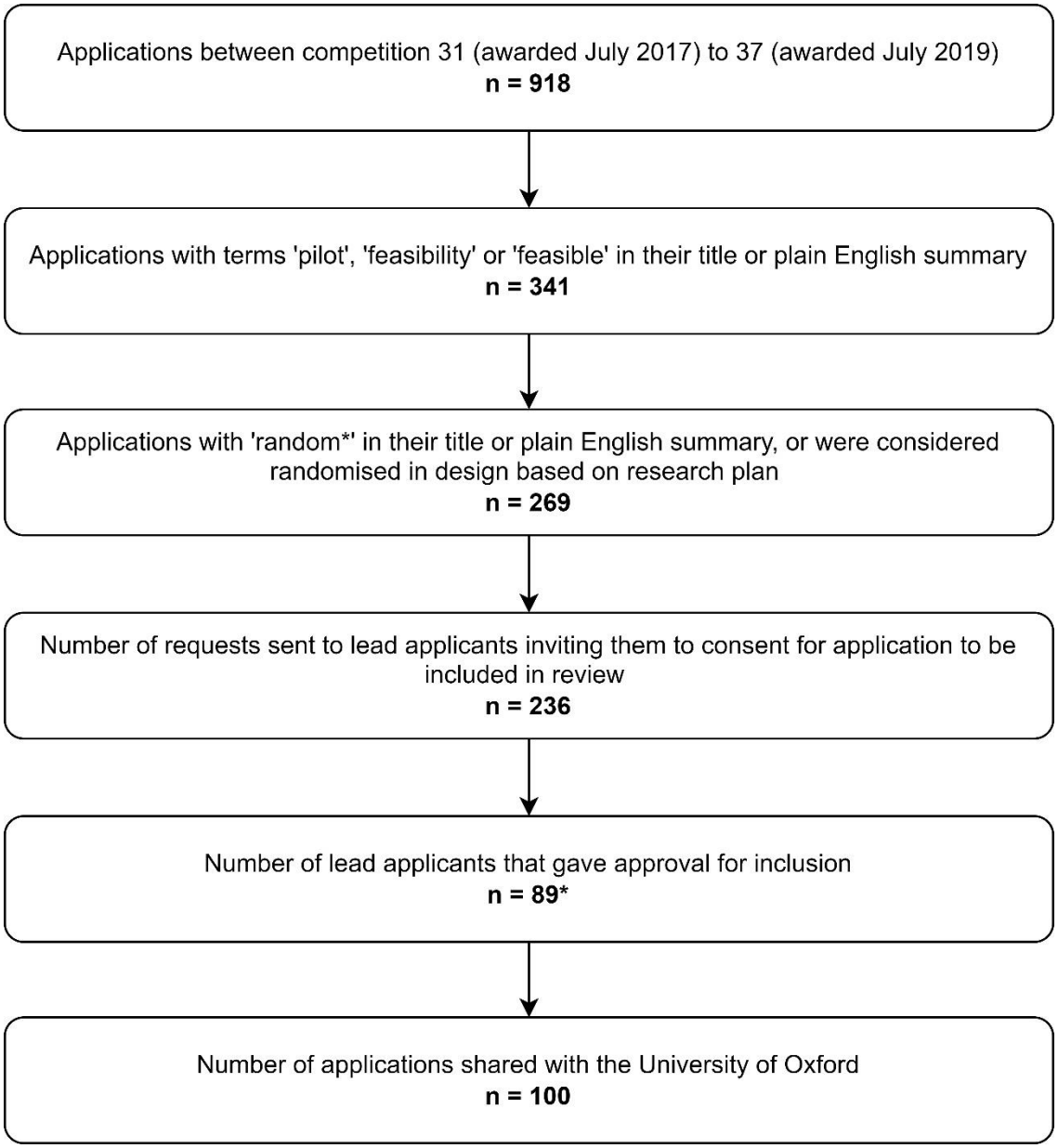

Figure C1 Flow chart to present identification and screening of applications

*Some applicants were lead applicants for more than one application

3.3.2 Characteristics of included applications

Of the 100 applications included in the original sample, five (5/100, 5%) were determined to be ineligible at Stage 1 as they were single arm studies and not randomised trials. Of the 95 applications that were eligible at Stage 1 (outline stage), 52 (52/95, 55%) were invited to Stage 2 (full application) and 43 (43/95, 45%) were rejected at Stage 1. Three applications (3/52, 6%) were subsequently ineligible at Stage 2 because the randomisation component had been dropped from the application, i.e. the full Stage 2 application was for a non-randomised or single arm feasibility study. Of the 49 applications that were eligible at full Stage 2 application, 35 (35/49, 71%) were awarded funding and 14 (14/49, 29%) were unsuccessful. Of the 35 that were awarded funding, at the time of data analysis nine had completed (9/35, 26%). Of these, four had been published (4/9, 44%), one had led to a definitive trial funding award (1/9, 11%) and a funding application was being prepared for another (1/9, 11%), see Figure C2.

Table C1 details the characteristics of included applications. Included applications assessed 23 therapeutic areas and six types of intervention. Of the 95 Stage 1 outline applications most were for multi-centre (69/95, 73%), two-arm (84/95, 88%) parallel randomised (84/95, 88%) pilot trials. All but four Stage 1 application outlines provided a clear sample size, ranging from 20-250, with a median of N=60 (IQR 50-90). Most of the 49 eligible Stage 2 full applications were again for multi-centre (36/49, 73%), two arm (44/49, 90%) parallel randomised (45/49, 92%) pilot trials, assessing 21 different therapeutic areas and six types of intervention. The median sample size was again N=60 (range 25-800, IQR 50-80). At Stage 1, 80 applications (80/95, 84%) included plans to do qualitative research within or alongside the pilot trial. At Stage 2, 44 applications included a qualitative research component (44/49, 90%).

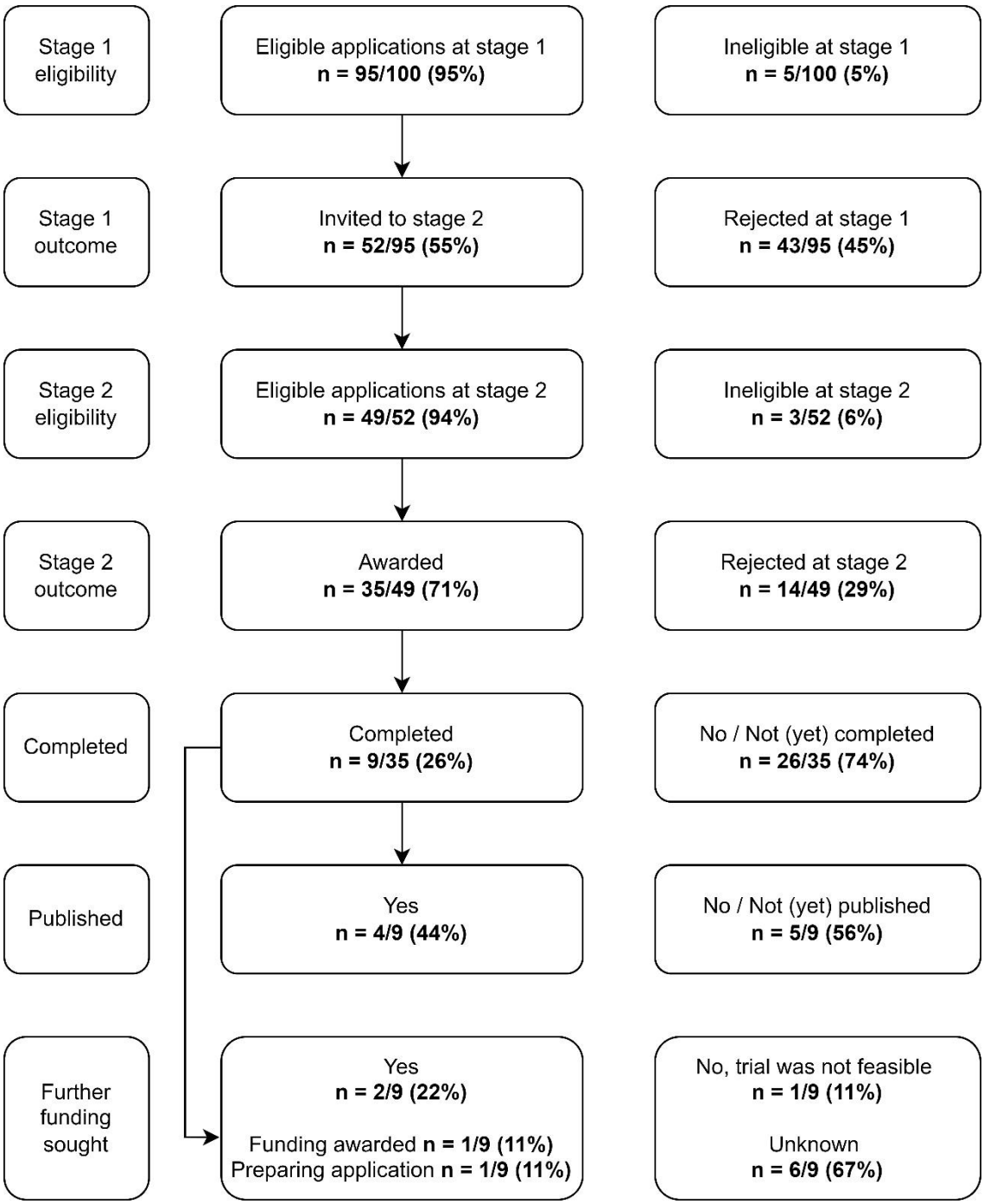

Figure C2 Flow chart to present funding outcomes of included applications

Table C1 Characteristics of included applications

	STAGE 1 (n = 95)		STAGE 2 (n = 49)	
	n	**(%)**	**n**	**(%)**
Therapeutic areas*				
Oncology	12	(13%)	5	(10%)
Psychiatry/Psychology	12	(13%)	7	(14%)
Paediatrics	10	(11%)	7	(14%)
Respiratory	7	(7%)	4	(8%)
Primary care	7	(7%)	1	(2%)
Gastroenterology/Hepatology	6	(6%)	3	(6%)
Trauma	5	(5%)	4	(8%)
Other	36	(38%)	18	(37%)
Intervention type				
Drug	9	(9%)	4	(8%)
Surgery or procedure	15	(16%)	8	(16%)
Counselling, lifestyle or physiotherapy	55	(58%)	28	(57%)
Equipment	4	(4%)	3	(6%)
Medical Device	1	(1%)	1	(2%)
Other	11	(12%)	5	(10%)
Randomisation design				
Parallel	84	(88%)	45	(92%)
Parallel + patient preference arms	2	(2%)	0	(0%)
Cluster	9	(9%)	4	(8%)
Sample size				
Sample size unclear in funding application	4		0	
Min-max	20-250		25-800	
Median	60		60	
IQR	50-90		50-80	
Single/multi centre				
Single	19	(20%)	10	(20%)
Multi	69	(73%)	36	(73%)
Unclear	7	(7%)	3	(6%)
Number of arms				
2	84	(88%)	44	(90%)
>2	11	(12%)	5	(10%)
Primary focus is feasibility (based on stated objectives and outcomes)				
Yes	94	(99%)	49	(100%)
No**	1	(1%)	0	(0%)

	STAGE 1 (n = 95)		STAGE 2 (n = 49)	
	n	**(%)**	**n**	**(%)**
Qualitative research conducted				
Yes	80	(84%)	44	(90%)
No	15	(16%)	5	(10%)

Percentages might not add up to 100 due to rounding

*Therapeutic areas that were given in ≥ five Stage 1 application outlines are listed; all others are categorised in 'other'

**The primary focus of one study was only on safety rather than feasibility, this study was redesigned at Stage 2 as single arm proof of concept study (ineligible at Stage 2)

3.3.3 Inclusion of progression criteria in applications

Table C2 describes the inclusion of progression criteria in funding applications. Just over half (48/95, 51%) of Stage 1 applications stipulated what their criteria for progression to a future definitive RCT would be. Of these, half (24/48, 50%) were invited to Stage 2 and half (24/48, 50%) were rejected. Of the 47 Stage 1 applications that did not stipulate progression criteria (47/95, 49%), 60% (28/47) were invited to Stage 2, and 40% (19/47) were rejected.

Three applications that were invited following Stage 1 were subsequently ineligible at Stage 2, one of these applications had stipulated progression criteria at Stage 1.

A larger proportion of Stage 2 applications stipulated progression criteria (73%, 36/49). Of these, 72% (26/36) were subsequently funded and 28% (10/36) were rejected. Of the 13 Stage 2 applications that did not stipulate progression criteria (13/49, 27%), nine were subsequently funded (9/13, 69%) and four were rejected (4/13, 31%).

Twenty-three applications assessed at Stage 2 (23/49, 47%) included progression criteria in both Stages 1 and 2, and 13 applications that did not include progression criteria at Stage 1 did in the corresponding Stage 2 application (13/49, 27%). Of the applications

that stipulated progression criteria at both stages, over half (13/23, 57%) made changes to their progression criteria between stages one and two, for example altering or adding specific numerical targets, or providing additional criteria.

There was little difference between progression criteria reporting and application outcome at each stage. At Stage 1, 46% (24/52) of invited applications included progression criteria, compared to 56% (24/43) of rejected applications. These proportions were more similar at Stage 2, with 74% (26/35) of awarded applications including progression criteria compared to 71% (10/14) rejected applications.

Table C2 Inclusion of progression criteria by application stage and outcome

Progression criteria stipulated in application	STAGE 1						STAGE 2					
	Total (n = 95)		Invited (n = 52)*		Rejected (n = 43)		Total (n = 49)*		Awarded (n = 35)		Rejected (n = 14)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Yes	48	(51%)	24	(46%)**	24	(56%)	36	(73%)	26	(74%)	10	(71%)
Stipulated in Stage 1 and Stage 2	N/A		N/A		N/A		*23*	*(65%)***	*17*	*(65%)*	*6*	*(60%)*
Stipulated in stage two only	N/A		N/A		N/A		*13*	*(36%)*	*9*	*(35%)*	*4*	*(40%)*
No	47	(49%)	28	(54%)	19	(44%)	13	(27%)	9	(26%)	4	(29%)

Percentages might not add up to 100 due to rounding

*Three applications that were invited following Stage 1 were subsequently ineligible at Stage 2

**One of the three applications that was ineligible at Stage 2, and so not included in the Stage 2 analysis, did include progression criteria at Stage 1

3.3.4 Characteristics of included progression criteria

Table C3 describes the characteristics of the included progression criteria. Most applications, at Stage 1 and 2, provided progression criteria in a stop-go format where distinct thresholds were given against which feasibility would be assessed (Stage 1 33/48, 69% and Stage 2 21/36, 58%). In both instances, around half also reported additional considerations, often non-numerical, that would inform the interpretation of pilot trial findings (denoted in the table as 'distinct threshold/STOP-GO +', Stage 1 15/33, 45% and Stage 2 11/21, 52%). A larger proportion of applications at Stage 2 reported progression criteria in a 'traffic light system/STOP-AMEND-GO' format, with or without additional considerations, compared to applications at Stage 1 (Stage 1 9/48, 19% and Stage 2 13/36, 36%).

In most applications, progression criteria were given within the text rather than within a table (Stage 1 45/48, 94% and Stage 2 32/36, 89%). At both Stages 1 and 2 some applications opted to stipulate progression criteria in a wholly non-numerical format (Stage 1 6/48, 13% and Stage 2 2/36, 6%), for example: *'progression to a future randomised trial will be informed by the observed recruitment rate and the number of patients that have been retained at 12-months'.* In one application researchers provided justification for why they had decided against pre-determining progression criteria and how they would instead determine feasibility. They stated that instead they plan to report their findings against their study objectives and would consider other factors alongside their feasibility outcomes such as point estimates. They described the intention to engage in discussion between the research team, independent steering committee and PPI advisory group to discuss achievable modifications to the protocol to overcome any identified challenges to optimally inform decisions about the feasibility of the full trial.

I identified various uncertainties about feasibility that informed progression criteria. The most common areas included recruitment (Stage 1 41/48, 85% and Stage 2 31/36, 86%), retention (Stage 1 27/48, 56% and Stage 2 24/36, 67%) and acceptability of the trial or intervention to participants (Stage 1 19/48, 40% and Stage 2 15/36, 42%). Participant noncompliance (adherence) (Stage 1 13/48, 27% and Stage 2 13/36, 36%), and data completion (Stage 1 16/48, 33% and Stage 2 11/36, 31%) also often contributed to progression criteria. Areas of uncertainty that contribute to progression criteria were generally similar between application stages and outcomes.

The progression criteria in 20 applications at Stage 1 was informed by the findings of qualitative research (20/48, 42%) with half of these invited to Stage 2 (10/20, 50%) and the other half rejected (10/20, 50%). Of the applications assessed at Stage 2, a higher proportion included progression criteria that would be informed by qualitative research (18/36, 50%). Of these 12 were awarded (12/18, 66%) and six were rejected (6/18, 33%).

One-third of applications reported justification or rationale for choice of all or some of the specified progression criteria (Stage 1 16/48, 33% and Stage 2 12/36, 33%). At Stage 1 half of the applications that provided some rationale or justification for either all or some of their progression criteria were rejected (8/16, 50%) and half were invited to Stage 2 (8/16, 50%). Of the 12 applications that provided some rationale or justification at Stage 2, nine (9/12, 75%) were funded and three (3/12, 25%) were rejected.

Only one application at each stage explicitly detailed who had decided on progression criteria (Stage 1 1/48, 2% and Stage 2 1/36, 3%). One Stage 1 application described that the Trial Management Group had proposed progression criteria, which would be subsequently approved by the Trial Steering Committee, and one Stage 2 application described that progression criteria had been guided by clinician experience. Although

very few applications provided this detail, some described how they had sought advice of a RDS or CTU on their trial design although they did not explicitly suggest that these stakeholders had helped develop their progression criteria.

Eight applications at Stage 1 and nine at Stage 2 detailed who would be involved in assessing progression criteria (Stage 1 8/48, 17% and Stage 2 9/36, 27%). In all instances, a Trial Steering Committee would be involved (Stage 1 8/8, 100% and Stage 2 9/9, 100%). Other parties included the Trial Management Group (Stage 1 2/8, 20% and Stage 2 3/9, 33%), PPI Representatives (Stage 1 1/8 13%), and a Data Monitoring Committee (Stage 2 1/9, 11%).

Table C3 Characteristics of progression criteria by application stage and outcome

	STAGE 1						STAGE 2					
	Total (n = 48)		Invited (n = 24)		Rejected (n = 24)		Total (n = 36)		Awarded (n = 26)		Rejected (n = 10)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Format												
Distinct threshold / STOP-GO	18	(38%)	8	(33%)	10	(42%)	10	(27%)	9	(35%)	1	(10%)
Distinct threshold / STOP-GO +*	15	(31%)	8	(33%)	7	(29%)	11	(31%)	9	(35%)	2	(20%)
Traffic light system / STOP-AMEND-GO	5	(10%)	3	(13%)	2	(8%)	8	(22%)	3	(12%)	5	(50%)
Traffic light system / STOP-AMEND-GO +*	4	(8%)	2	(8%)	2	(8%)	5	(14%)	3	(12%)	2	(20%)
Non-numerical	6	(13%)	3	(13%)	3	(13%)	2	(6%)	2	(8%)	0	(0%)
Presentation												
Text	45	(94%)	23	(96%)	22	(92%)	32	(89%)	23	(88%)	9	(90%)
Table	3	(6%)	1	(4%)	2	(8%)	4	(11%)	3	(12%)	1	(10%)
Areas of feasibility informing progression criteria												
Recruitment	41	(85%)	22	(92%)	19	(79%)	31	(86%)	21	(81%)	10	(100%)
Retention	27	(56%)	13	(54%)	14	(58%)	24	(67%)	16	(62%)	8	(80%)
Acceptability of intervention or trial (participants)	19	(40%)	9	(38%)	10	(42%)	15	(42%)	10	(38%)	5	(50%)
Data completion or missing data	16	(33%)	7	(29%)	9	(38%)	11	(31%)	7	(27%)	4	(40%)
Non/compliance or adherence (participants)	13	(27%)	4	(17%)	9	(38%)	13	(36%)	11	(42%)	2	(20%)
Consent or refusal rate	9	(19%)	4	(17%)	5	(21%)	6	(17%)	6	(23%)	0	(0%)
Acceptability of intervention or trial (non-participants)	8	(17%)	5	(21%)	3	(13%)	11	(31%)	8	(31%)	3	(30%)
Intervention fidelity	7	(15%)	1	(4%)	6	(25%)	9	(25%)	7	(27%)	2	(20%)
Safety or adverse events	6	(13%)	5	(21%)	1	(4%)	7	(19%)	6	(23%)	1	(10%)

	STAGE 1						STAGE 2					
	Total (n = 48)		Invited (n = 24)		Rejected (n = 24)		Total (n = 36)		Awarded (n = 26)		Rejected (n = 10)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Determine/estimate definitive trial sample size	6	(13%)	4	(17%)	2	(8%)	4	(11%)	4	(15%)	0	(0%)
Completion or withdrawal	5	(10%)	2	(8%)	3	(13%)	4	(11%)	4	(15%)	0	(0%)
Randomisation	5	(10%)	1	(4%)	4	(17%)	3	(8%)	2	(8%)	1	(10%)
Eligibility	4	(8%)	2	(8%)	2	(8%)	2	(6%)	2	(8%)	0	(0%)
Centre or investigator recruitment, willingness or capacity	3	(6%)	2	(8%)	1	(4%)	2	(6%)	2	(8%)	0	(0%)
Data collection tools, measures or assessments	3	(6%)	0	(0%)	3	(13%)	3	(8%)	2	(8%)	1	(10%)
Non/compliance or adherence (non-participants)	2	(4%)	2	(8%)	0	(0%)	3	(8%)	3	(12%)	0	(0%)
Characteristics of clinical outcomes/decide on primary outcome	2	(4%)	1	(4%)	1	(4%)	3	(8%)	1	(4%)	2	(20%)
Barriers or challenges to intervention implementation	1	(2%)	0	(0%)	1	(4%)	0	(0%)	0	(0%)	0	(0%)
Screening	1	(2%)	0	(0%)	1	(4%)	0	(0%)	0	(0%)	0	(0%)
Pilot collection of health economic outcomes	0	(0%)	0	(0%)	0	(0%)	1	(3%)	0	(0%)	1	(10%)
Other	19	(40%)	11	(46%)	8	(33%)	17	(47%)	13	(50%)	4	(40%)
Qualitative research informs progression criteria												
Yes	20	(42%)	10	(42%)	10	(42%)	18	(50%)	12	(46%)	6	(60%)
No	18	(38%)	8	(33%)	10	(42%)	14	(39%)	11	(42%)	3	(30%)
No qualitative research conducted	10	(21%)	6	(25%)	4	(17%)	4	(11%)	3	(12%)	1	(1%)
Justification or rationale for progression criteria given												
Yes	9	(19%)	3	(13%)	6	(25%)	7	(19%)	5	(19%)	2	(20%)
For some criteria	7	(15%)	5	(21%)	2	(9%)	5	(14%)	4	(15%)	1	(10%)
No	32	(67%)	16	(67%)	16	(67%)	24	(67%)	17	(65%)	7	(70%)

	STAGE 1						STAGE 2					
	Total (n = 48)		Invited (n = 24)		Rejected (n = 24)		Total (n = 36)		Awarded (n = 26)		Rejected (n = 10)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Application details who decided on progression criteria												
Yes	1	(2%)	0	(0%)	1	(4%)	1	(3%)	0	(0%)	1	(10%)
No	47	(98%)	24	(100%)	23	(96%)	35	(97%)	26	(100%)	9	(90%)
Application details who will assess progression criteria												
Yes	8	(17%)	3	(13%)	5	(21%)	9	(25%)	6	(23%)	3	(30%)
No	40	(83%)	21	(88%)	19	(79%)	27	(75%)	20	(77%)	7	(70%)

Percentages might not add up to 100 due to rounding

*+ indicates additional considerations specified that are not in a STOP-GO or STOP-AMEND-GO format

3.3.5 RfPB committee feedback for included applications

Table C4 presents funding committee feedback in relation to progression criteria. At both Stage 1 and Stage 2, over 20% of committee feedback explicitly mentioned progression criteria (Stage 1 22/95, 23% and Stage 2 11/49, 22%). At Stage 1, most often feedback implied that progression criteria were not stipulated in the funding application (Stage 1 11/22, 50%), this proportion was lower at Stage 2 (4/11, 36%). Committee feedback for a further eight Stage 1 and three Stage 2 applications requested further detail or clarity for progression criteria, e.g. the committee requested the addition of numerical thresholds where these were not given or for progression criteria to be expanded (Stage 1 8/22, 36% and Stage 2 3/11, 27%). There were also instances where committee feedback queried rationale or justification for stated progression criteria, e.g. they questioned why a certain target had been set (Stage 1 3/22, 14% and Stage 2 4/11, 36%).

The assessment of funding committee feedback was subjective, and it was sometimes difficult to determine whether funding panellists were or were not requesting the addition of progression criteria. Consider the following anonymised excerpt of funding committee feedback for a Stage 1 application:

> *The Panel requested that the feasibility outcomes should be more clearly presented in the Stage 2 application. Further clarification was sought on how the data would be collectively integrated to make a judgement on feasibility and design of future trial.*

In this instance, the committee did not explicitly mention progression criteria, however the addition of progression criteria would adequately address this feedback and provide ‘further clarity’ for how feasibility would be assessed or ‘judged’.

Where the committee did explicitly mention progression criteria, the feedback was sometimes ambiguous and it was unclear whether the committee were requesting that progression criteria were added altogether, or whether existing criteria should be more detailed. In the following anonymised example, the committee stated that the application 'lacked detail' about the progression criteria.

> *The Panel was of the opinion that the application lacked detail about the progression criteria from feasibility to a full trial.*

This could be interpreted to mean that the progression criteria were vague, or that there were no progression criteria altogether at Stage 1. In this particular instance the Stage 1 application included some non-numerical progression criteria, so I deduced that the panellists were likely requesting more detail e.g. numerical thresholds instead of broader statements about demonstrating '*ability to recruit to time and target*' and '*acceptable attrition rates*'. In general, whenever funding committee feedback requested further detail, I did not assume that this implied that progression criteria were not present and checked the application to help interpret committee feedback.

At Stage 1 there were 35 applications where progression criteria were not stipulated, and funding committee feedback did not mention progression criteria (35/95, 37%). At Stage 2, nine of the applications assessed did not include progression criteria and funding committee feedback did not mention progression criteria (9/49, 18%).

Table C4 Analysis of funding committee feedback by application stage and outcome

Committee feedback explicitly mentions progression criteria	STAGE 1 Total (n = 95) n	(%)	Invited (n = 52) n	(%)	Rejected (n = 43) n	(%)	STAGE 2 Total (n = 49) n	(%)	Awarded (n = 35) n	(%)	Rejected (n = 14) n	(%)
Yes	22	(23%)	15	(29%)	7	(16%)	11	(22%)	9	(26%)	2	(14%)
Progression criteria stipulated	*10*	*(45%)*	*7*	*(47%)*	*3*	*(43%)*	*7*	*(64%)*	*5*	*(56%)*	*2*	*(100%)*
Progression criteria not stipulated	*12*	*(55%)*	*8*	*(53%)*	*4*	*(57%)*	*4*	*(36%)*	*4*	*(44%)*	*0*	*(0%)*
No	73	(77%)	37	(71%)	36	(84%)	38	(78%)	26	(74%)	12	(86%)
Progression criteria stipulated	*38*	*(52%)*	*17*	*(46%)*	*21*	*(58%)*	*29*	*(76%)*	*21*	*(81%)*	*8*	*(67%)*
Progression criteria not stipulated	*35*	*(48%)*	*20*	*(54%)*	*15*	*(42%)*	*9*	*(24%)*	*5*	*(19%)*	*4*	*(33%)*
Details of feedback where stipulated	**(n = 22) n**	**(%)**	**(n = 15) n**	**(%)**	**(n = 7) n**	**(%)**	**(n = 11) n**	**(%)**	**(n = 9) n**	**(%)**	**(n = 2) n**	**(%)**
Feedback implies progression criteria was not stipulated	11	(50%)	7	(47%)	4	(57%)	4	(36%)	4	(44%)	0	(0%)
Feedback requests further detail/clarity e.g. numerical thresholds	8	(36%)	5	(33%)	3	(43%)	3	(27%)	3	(33%)	0	(0%)
Feedback relates to rationale or justification for progression criteria	3	(14%)	3	(20%)	0	(0%)	4	(36%)	2	(22%)	2	(100%)

Percentages might not add up to 100 due to rounding

3.3.6 Examining the effect of funder guidance

The funding decision date for all included applications was after the publication of earliest guidance by NIHR RfPB to include progression criteria [17]. However, 49 of the 100 applications received were submitted to funding calls that were launched prior to July 2017. Table C5 presents a comparison of progression criteria inclusion in funding applications submitted to funding calls launched pre- and post-July 2017.

Of the 95 applications eligible at Stage 1, 47 (49%) were submitted to funding calls launched pre-July 2017, and 48 (51%) were submitted to funding calls launched after July 2017. The proportion of Stage 1 applications that included progression criteria increased following July 2017 (17/47, 36% to 31/48, 65% respectively).

Of the 49 applications eligible at Stage 2, 27 (55%) were submitted to funding calls launched pre-July 2017, and 22 (45%) were submitted to funding calls launched after July 2017. All the Stage 2 applications that were submitted to funding calls launched after July 2017 included progression criteria in their research plans (22/22, 100%), compared to just over half of those submitted before July 2017 (14/27, 52%).

Table C5 Inclusion of progression criteria by funding call submission date

Progression criteria stipulated	**STAGE 1**				**STAGE 2**			
	Pre-July 2017 (n = 47)		**Post-July 2017 (n = 48)**		**Pre-July 2017 (n = 27)**		**Post-July 2017 (n = 22)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Yes	17	(36%)	31	(65%)	14	(52%)	22	(100%)
No	30	(64%)	17	(35%)	13	(48%)	0	(0%)

3.4 Discussion

3.4.1 Summary of findings

This chapter presents the findings from a review of the research plans and committee feedback of 100 funding applications for randomised pilot trials submitted to the UK NIHR RfPB funding stream with a decision made between July 2017 and July 2019. Of the 100 Stage 1 application outlines reviewed, 95 were eligible, 52 were invited to full Stage 2 application (of which 49 were eligible at Stage 2), and 35 were awarded funding. In this sample, just over half of the applications assessed at Stage 1 outline (51%) and just under three quarters of those assessed at full Stage 2 application (73%) included progression criteria in their research plans. However, applications submitted to funding calls launched after July 2017 were much more likely to include progression criteria compared to those submitted to funding calls launched before July 2017. This suggests that many researchers and funding panellists do adopt research funder guidance and indicates that progression criteria inclusion in funding applications has likely increased in more recent applications submitted following those included in this sample.

3.4.2 Findings in context

In this sample, a higher proportion of full Stage 2 applications stipulated progression criteria compared to Stage 1 outlines. This might be expected given the tighter research plan word limit at Stage 1 [163]. I also found that the proportions of applications reporting progression criteria were similar between those that were invited or awarded, and those rejected at each stage. This might indicate that that although the reporting of progression criteria improved between Stage 1 and 2, inclusion of progression criteria did not necessarily mean that applications were more likely to be invited or awarded funding.

Instead, this improvement in reporting was more likely due to funding committee members requesting the inclusion of progression criteria where they were not stipulated. This finding might be surprising considering current NIHR RfPB guidance states that '*a clear route (e.g. progression criteria) should be included in the research plan*' of feasibility study funding applications [17]. The guidance also advises that '*RfPB committees consider the pathway to RCT as part of their assessment*', yet over one-third of Stage 1 application outlines submitted following publication of this guidance did not include progression criteria, suggesting that some researchers do not follow funder guidance.

Where stipulated, progression criteria most often followed a stop-go format, with many applications also stipulating additional factors that researchers would consider when determining feasibility. The stop-amend-go format, which is recommended for progression criteria in RCTs with internal pilot phases [22], was less often used. However, the proportion of applications that opted for a stop-amend-go format increased between Stage 1 and 2. I also identified several funding applications that included non-numerical progression criteria, however, this reduced between Stage 1 and 2, either because the application was rejected or following request of the funding committee for further detail or clarity around progression criteria, such as the addition of specific quantifiable thresholds.

In this sample of funding applications, recruitment was the most common indicator of feasibility to inform progression criteria, followed by retention. This mirrors the findings of the methodological review presented in Chapter 2, and supports previous research that identified recruitment uncertainties to be most commonly assessed in pilot trials [32]. Most applications did not stipulate justification or rationale for their progression criteria,

yet I identified only several instances where funding committee members queried choice of progression criteria, suggesting that how progression criteria have been developed (e.g. what rationale they are based on and who decided on them) might be less important to funding committee members when assessing funding applications. This information was also not often reported in the pilot trial publications studied in Chapter 2.

3.4.3 Strengths and limitations

This is the first study of its type to provide data on progression criteria for external randomised pilot trials submitted to a large research funder in the UK. This research also serves as an example of how researcher-funder collaboration can enhance trial methodology research. Although previous studies have investigated progression criteria stipulated in RCTs with internal pilot phases that were awarded NIHR Health Technology Assessment (HTA) funding [151,152], these studies were limited to include only applications for RCTs that were awarded. By collaborating with research funders directly I was able to study the research plans of all submitted funding applications, irrespective of funding outcome. The inclusion of funding applications that both were and were not successful adds significant value to this thesis. However, it is unclear whether these findings are generalisable to pilot trial funding applications submitted to different research funders such as charities and non-UK funding sources.

Collaboration with research funders was central to the process of obtaining consent from researchers to include their application in the review. However, the requirement for researchers to consent for their funding application to be shared outside of the NIHR may have introduced bias, with researchers who were awarded funding perhaps more likely to give consent than those who were not. This might explain why the success rate of included applications (35/95, 37%) was higher than previously observed overall success

rates across all RfPB funding applications assessed at Stage 1, typically around 20% [164].

A further limitation is that the shared research data was limited to the redacted research plan section of the funding application. Other aspects of the funding application, such as whether the application had been supported by a Clinical Trials Unit, a Research Design Service, or had Patient and Public Involvement, could not be accurately collected. Since applications were fully anonymised, I was also unable to account for potential biases where funding applications might have been submitted to different funding calls (for example resubmission of an application that was previously unsuccessful).

Although a strength of this study is the relatively recent sample of included funding applications, I was unable to fully investigate whether there was any correlation between the inclusion of progression criteria and post funding award outcomes for most of the included applications for a number of reasons. Many funded pilot trials might simply not have had enough time to proceed to completion, and many could have faced delays and/or pauses due to COVID-19. This limits any conclusions I can draw about whether applications with clearly defined progression criteria are more likely to lead to a future definitive trial. A longer term follow up of these applications to determine how many progressed to further research funding awards for definitive RCTs would add value to these findings. However, this was not considered feasible within the timeframe of this DPhil.

Finally, the main limitation of this chapter is that I obtained and included applications with a funding decision date following the publication of guidance to include progression criteria (July 2017) [17]. In hindsight, the eligibility criteria should have been instead based on the funding call launch date, rather than the funding decision date. Almost half

of the included applications were submitted to funding calls that were launched prior to July 2017. This has introduced bias as these applications were not required by research funders to stipulate progression criteria at the time of submission. Unfortunately upon realisation of this limitation, there was not sufficient remaining time to obtain further funding applications from NIHR RfPB. To assess the impact of this bias I conducted a post-hoc analysis, which was not originally protocolised, to compare the inclusion of progression criteria between applications submitted to funding calls launched pre- and post-July 2017. The findings of this analysis indicated that publication of funder guidance in July 2017 [17] has likely led to more applications including progression criteria. Therefore, the number of identified applications that stipulated progression criteria in this sample is likely to be an underestimate of current practice.

3.4.4 Chapter summary

This chapter presented the methods and findings of a cross-sectional study of progression criteria, where stipulated, in pilot trial funding applications submitted to the NIHR RfPB funding stream. The key findings were that half the applications assessed at Stage 1 and nearly three quarters of those assessed at Stage 2, included progression criteria which were most often specified in a stop-go format, with only one third of applications at each stage providing justification or rationale for any targets given. The number of applications that include progression criteria increased following feedback from funding committees, and in applications that were submitted after RfPB published guidance that advised applicants to stipulate progression criteria in their funding applications for pilot trials.

Chapter 4 A qualitative interview study and framework analysis to examine how researchers make progression decisions following external randomised pilot trials

Associated research outputs:

The protocol for this chapter is registered on the *Open Science Framework* [1] and the results have been published in *Trials* [2]. I presented the findings of this study at the *Australian Trials Methodology* conference (2021, virtual) and at the *Society for Clinical Trials* conference (2022, San Diego).

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[1] Mellor K, Albury C, Hopewell S. Using progression criteria to determine feasibility of external randomised pilot trials: protocol for a qualitative study of stakeholder views. *OSF* 2020. doi:10.17605/OSF.IO/5N2KZ

[2] Mellor K, Dutton S J, Hopewell S, et al. How are progression decisions made following external randomised pilot trials? A qualitative interview study and framework analysis. *Trials* 2022;**23**:132. doi:10.1186/s13063-022-06063-9

4.1 Chapter introduction

4.1.1 Rationale for qualitative research study

Chapter 2 examined progression criteria reporting in pilot trial publications, and Chapter 3 examined the inclusion of progression criteria in pilot trial funding applications. The findings of both chapters highlighted inconsistency in approaches to progression criteria and left unanswered questions around how criteria are developed in practice, a process that was often not stipulated in funding applications or publications.

As described in detail in Chapter 1, there is no formal guidance for who should be involved in deciding on progression criteria for external randomised pilot trials. There are, however, published case studies that describe processes for co-producing progression criteria with input from various stakeholders [79,81], and it has been suggested that investigators conducting RCTs with internal pilot trial phases agree progression criteria in advance with their funders [22].

To address this gap in knowledge, I generated first-hand evidence to understand *how* researchers come up with their progression criteria and *why* they choose the criteria that they set. I wanted to explore and understand the thoughts, experiences and perspectives of external randomised pilot trial stakeholders who make decisions about progression criteria. Qualitative research methods were best placed to provide this data.

The stakeholders I interviewed included researchers with previous or current experience of conducting external randomised pilot trials (including clinical investigators, trialists, statisticians), PPI representatives for pilot trials, and researchers conducting pilot or feasibility trial methodology research. These stakeholders are often affiliated to TMGs or

TSCs, which were identified in Chapter 2 as groups that can be involved in developing and/or reviewing progression criteria.

Qualitative research methods have previously been used to address important trial methodology research questions, such as exploring stakeholder perceptions and experiences of different trial designs, and how risks and benefits of trial participation are communicated to potential participants through informed consent materials [165–167]. In this chapter I present the methods and findings of a qualitative interview study to examine how progression decisions are made following external randomised pilot trials.

4.1.2 Aim and objectives

I aimed to explore the experiences of key stakeholders in relation to external randomised pilot trial progression decision making.

The primary objective was to explore key stakeholders' experiences of the development, application and assessment of progression criteria.

The secondary objectives were to explore:

- Who is involved in the development, application and assessment of progression criteria?
- What rationale underpins choice of progression criteria for key stakeholders?
- Any additional considerations important to stakeholders that inform the progression decision
- Any challenges stakeholders face when making progression decisions based on progression criteria in practice

4.2 Methods

4.2.1 Protocol and registration

I wrote a protocol for this study and published it on the Open Science Framework (osf.io/5n2kz) [168]. My reporting in this chapter is in line with established best-practice, and follows the Consolidated Criteria for Reporting Qualitative Research (COREQ) 2007 checklist [169] presented in Appendix D1. I received ethical approval for this research from The University of Oxford MS IDREC, reference R72039/RE001. The Information Governance Manager at Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS) helped me to produce a Data Protection Agreement (DPA) for this research. The DPA was approved by the Departmental Administrator and Senior Information Risk Owner to ensure that the data processing required was appropriately assessed for privacy by design. We reviewed the DPA at 6-monthly intervals throughout the study.

4.2.2 Research team and reflexivity

4.2.2.1 Personal Characteristics

This was my first experience leading a qualitative research study. I have previously worked on multi-centre clinical trials with embedded qualitative research studies, and throughout my DPhil I observed TMG meetings for an external randomised pilot trial that also had a qualitative research study embedded. I have a Master of Science degree in Clinical Research (2017), where I was trained in qualitative research methods and mixed methods research. I attended an Introduction to Qualitative Interviewing training course ran by the University of Oxford Nuffield Department of Primary Care Health Sciences

prior to data collection. Dr Charlotte Albury, an experienced qualitative researcher, was appointed as a DPhil supervisor to support me with the design, conduct, analysis and reporting of this study.

4.2.2.2 Relationship with participants

I was familiar with some of the participants through my previous employment, DPhil studies and membership of academic working groups. This is important to note since previous interactions with participants may have affected their response to interview questions. For example, it took less time to build rapport with participants that I had previously met compared to those who I was meeting for the first time. On one hand this might have led to some participants speaking more freely and having less reservations about anonymity, particularly where the participant and I shared knowledge or experiences of a particular clinical trial or research setting. On the other hand, some of the participants who I had previously interacted with may have had more reservations about sharing their personal views with me if they thought that I might disagree. All participants were told that I was conducting a DPhil in trial methodology research to investigate the progression of external randomised pilot trials to future definitive randomised controlled trials.

4.2.3 Study design and theoretical framework

In this section I provide a detailed description of the theoretical framework that guided my approach to this research.

A pragmatist ontology (what there is to know about the world and nature of reality) and epistemology (how we can know about the world and the nature of knowledge) underpins this study. Pragmatism is a research paradigm in which attention is focused on a research

question, and available approaches that will best address the question are used [170]. This philosophy also underpins the overarching mixed methods approach to this DPhil, where data are generated from both qualitative and quantitative research methods to best address the research question [171].

I considered various qualitative approaches for data analysis, including grounded theory and content analysis, before deciding that thematic analysis was most appropriate. Grounded theory involves taking a detailed focus on building theories to understand how the world or social systems work [172–174]. This approach takes longer than thematic analysis and was not suitable for my research because I am not seeking to re-structure or theorise how the world works, but instead better understand experiences of a particular phenomenon. Content analysis can follow either a quantitative or qualitative approach and involves establishing categories of data in a particular unit of analysis e.g. words or themes, and then counting the number of instances of those units to interpret the data [175]. In content analysis there is the risk that some prespecified categories, those that are less often observed in the text, are overlooked. In addition the context in which the text sits can be easily disregarded which can limit interpretation of the data [175]. Therefore, as I was seeking to gain an in-depth understanding of how external randomised pilot trial progression decisions are made, but not seeking to generate a new theory, I identified thematic analysis as an appropriate method to rigorously address my aims and objectives.

Thematic analysis is a well-established approach to qualitative data analysis that supports researchers to describe and interpret patterns identified by comparing and contrasting data across the data set (within and between participants or '*cases'*). This approach focuses on relationships between different parts of the data to form descriptive or interpretative

conclusions around themes [176,177]. Thematic analysis follows a clear pathway and is considered to be more straightforward, and often faster, than other qualitative research approaches making it well suited to applied research, and achievable within the time and resource constraints of this DPhil [177].

There are a range of approaches to thematic analysis. I considered the Framework Method, described by Gale et al. (2013), to be most appropriate for this research [178]. The Framework Method of thematic analysis was originally developed for large-scale policy research but has since been widely used in other areas including health research. The Framework Method can be distinguished by its matrix outputs (highly structured tables to chart 'codes' against 'cases' to summarise data). It is considered a good option for researchers with limited qualitative research experience because the clear and structured matrices facilitate a systematic approach to analysis by comparing and contrasting data across codes and cases, while contextualising data within cases [178]. The Framework Method is also not aligned to a particular epistemological position, it provides a flexible tool for data collection, and can be used where data collection and analysis is both inductive and deductive (i.e. data collection is initially based on a priori known issues, but iteratively revised in response to ongoing data collection and analysis).

More recently, Braun and Clarke outlined their approach to 'reflexive thematic analysis' [179], which is based on their widely used approach to thematic analysis initially published in 2006 [176]. Reflexive thematic analysis is underpinned by researcher meaningful reflection and engagement with the data and analytical process, to acknowledge that qualitative research is both creative and subjective [179]. Through reflexive practice (or 'reflexivity') researchers acknowledge, evaluate and challenge their own assumptions and positionings that have informed their research approach. As such,

I considered reflexivity to be an important consideration for this research and I aimed to incorporate reflexivity throughout my data collection and analysis. I perceived that by not being reflexive I would not be self-aware of, or able to challenge, my own assumptions and biases. This might have led me to over emphasise aspects of the research that I personally agreed with, or pay less attention to things that I was hearing for the first time or that contradicted the findings of research I had conducted in earlier parts of the DPhil.

I therefore used the Framework Method, drawing on additional principles of reflexive thematic analysis [179] to acknowledge my own active engagement in co-creating the research data and following my own 'analytical direction' i.e. developing and further exploring themes within the data and deciding which findings to highlight [180]. For example I kept a reflexivity journal throughout data collection and analysis, to document reflexive thoughts that guided my approach. This is further described at the end of this section in 4.2.8, and extracts from my reflexivity journal are presented in Appendix D8.

I considered different approaches to data collection including structured interviews, open interviews, free text surveys, and focus groups. I decided that semi-structured interviews were best placed to collect the type of rich data, containing detailed insights, that would allow me to best answer my research question. I felt that focus groups, i.e. recruiting a small group of people and encouraging an informal discussion focused on a particular topic, were not appropriate because I was interested in individual stakeholder perceptions and experiences which might have been lost within a group dynamic [175]. I also considered free text surveys, i.e. using pre-defined questionnaires to collect information from participants, to be inappropriate because surveys are inflexible tools that are better suited to collect data that can be reliably and relatively easily elicited [181]. I was also

unsure whether survey questions might be open to misinterpretation, a particular concern given that the topic of progression criteria has been relatively under researched. Instead, I decided to use interviews since I was interested in understanding peoples' individual experiences which I felt would be best gained using a series of open questions, and 'probing' participant responses to obtain in depth information. Interviews also allowed me to compare data between people to understand and identify common challenges, successes and differences in practice [175].

I opted to collect data using semi-structured interviews because this approach allowed probing for elaboration or clarifications as required to address the research aims, rather than complete adherence to a structured interview guide [175]. I aimed for interviews to follow a 'conversational' style which helped build rapport and allowed participants to present what they considered to be important, rather than the conversation being dictated by predefined question order and seeming more artificial [182]. I developed prespecified interview topic guides. However, these were considered flexible and evolving documents. I loosely adhered to the topic guide to ensure key areas were addressed, but I allowed the conversation to be guided by what I interpreted to be meaningful to the participant in relation to the topic, and iteratively updated the interview guide to add new topics and questions based on ongoing data collection and analysis [183].

4.2.4 Participant selection

4.2.4.1 Sampling strategy

Since there is no guidance for who should be involved in developing or assessing progression criteria for external randomised pilot trials, I did not have a clear understanding about which trial team members are involved in this aspect of pilot trials

and should be included in my sample. Therefore, I initially aimed for a sample with a broad range of characteristics seeking variation (purposive sampling). I then iteratively reviewed and updated my sampling approach (iterative purposive sampling) to further explore things I was learning from my ongoing data collection and analysis [184].

Purposive sampling is a type of non-probability sampling where the sample is not drawn with the intention to be statistically generalisable to a population. Instead, purposive sampling is a widely used technique to identify and select participants that are 'information rich' i.e. the sample is based on which participants are likely to provide in-depth data that is sufficient to address the research aims [184,185]. I initially wanted to include people who had different roles and experiences of contributing to external randomised pilot trials, so I designed my initial purposive sample to aim for maximum variation of institution, job role and years of research experience (i.e. 'criterion sampling' [185]). Through consultation with my supervisors and drawing on the research literature, I identified different roles in trial teams that were likely to be involved in decision making about trial design, including the CI, statistician, trial manager, PPI representatives, TMG members and TSC members, and I aimed to include a range of different participants from each of these roles. I also considered that including people from different institutions to be important because the roles and responsibilities of different trial team members might vary between research groups.

I wanted to sample participants who had 'typical' experiences of pilot trials that might reflect the experiences of other researchers (i.e. 'typical case sampling' [185]), so I aimed to include participants who had worked on pilot trials that were feasible and did progress, and those that were not feasible and did not progress. I also wanted to sample participants whose views might be relevant to other participants or the wider research field (i.e.

'critical case sampling' [185]). For example, the views of researchers who are affiliated to funding panels could be underpinned by experiences of multiple pilot trials and might provide an indication of broader research practice. I also wanted to include participants who could be considered experts in the field (i.e. 'expert sampling' [185]), for example people who conduct trial methodology research around pilot trials, or who contribute to an RDS and advise other researchers about their pilot trial design.

I then used a snowball sampling approach and asked individuals to share my study recruitment information with other people in their networks [186], for example PPI members on their trials or other researchers in their institutions. I did this because I was interested in the perspectives and roles of different trial team members, so if I had spoken to a trial statistician, it might then also be interesting to speak to the trial manager or CI. Snowball sampling was a particularly useful approach to identify PPI representatives who were less likely to engage with the research networks that were used to share the study recruitment information.

Once I had started data collection and analysis, I iterated my purposive sample, adding new sampling criteria in response to things I was learning [184]. This provided the freedom to adapt my sampling strategy to seek additional participants with certain characteristics to further explore things that I was noticing in the data, to ensure that categories and themes I was developing were explored in depth [184]. For example, I identified varied experiences of how researchers involved PPI representatives in decisions around what progression criteria to use and whether pilot trials are feasible and should progress. Most researchers described the importance of involving PPI representatives or having PPI input when deciding on progression criteria, however most of the PPI representatives I spoke to in the early stages of data collection were unfamiliar

with the concept of progression criteria and did not describe contributing to their development. I wanted to understand further whether PPI members contribute to progression criteria development, so I decided to sample more PPI representatives to see if they shared similar experiences. I also approached researchers who had published pilot trial publications that explicitly mentioned the role of PPI, to invite them to participate in this study so I could better understand their experiences of engaging PPI members in conversations around progression criteria.

4.2.4.2 Methods used to approach participants

I approached participants through known contacts and established research networks. My DPhil supervisors and members of a PAFS working group [187,188] shared information about the study with researchers within their networks who have experience of external randomised pilot trials. I asked established research networks including the UK Clinical Research Collaboration (UKCRC) [189], Trial Methodology Research Partnership (TMRP) [190] and UK Trial Managers' Network (UKTMN) [191], to disseminate study information through their newsletters or email distribution mailing lists. I emailed regional Research Design Services (RDS) groups [192] to ask whether they could share study information with RDS researchers who advise on pilot trial design. I also shared study information on social media (Twitter) and emailed corresponding authors of influential pilot trial methodology publications directly. Study advertisement wording and recruitment emails were pre-planned and ethically approved, presented in Appendix D2. Emails briefly described the study and eligibility criteria so participants could self-identify as eligible. Once a potential participant expressed interest in participating, I emailed them to arrange a convenient date and time for interview.

4.2.4.3 Sample size

There are different approaches to determine when you have included 'enough' participants in a qualitative research study. The two most common approaches are saturation [193] or information power [194].

There are different forms of saturation described in the literature, including theoretical, thematic and data saturation, each with different definitions and underlying principles [195]. Inconsistent use of these terms have led to discussion around what different terms mean and when they are appropriate [196,197]. In essence, the concept of saturation is achieved by making predictions about *what we have not yet observed* based on *what we have observed* [193]. In other words, it is based on accepting uncertainty about what we do not yet know, rather than a declaration of what we do know.

Information power is based on the principle that the more information the sample provides, the smaller the required sample size and vice versa [194]. This approach is underpinned by the realist assumption that data are gained directly from participants, rather than co-created (between researcher and participants) through an iterative and interpretive approach.

I chose to base my sample size on saturation rather than information power to account for my own contributions to the data, and only stop collecting data when I was confident that the themes I had developed reflected the data and were well explored and described. For the same reasons I also decided against using other methods to determine sample size a priori for qualitative research studies (e.g. using proposed rules of thumb or statistical calculations [198]).

The concept of saturation is widely debated. While some researchers have described it as vital for sampling and enhancing the quality of qualitative research [195], its relevance to applied qualitative research has been questioned [196] and some have warned that the term risks becoming meaningless where it is used without a clear explanation [199]. However, it is generally agreed that providing a clear definition for saturation in the context of a study is a mark of rigour in qualitative research [200]. To ensure that the sample was adequate to address the research question, I recruited participants up until thematic data saturation which I defined as the point at which no new themes were developed with additional data analysis, and existing themes were well explored and described with certainty and confidence [201]. Previous literature reporting interviews with trial methodologists had reported reaching saturation after 15-20 participants [166,167]. However, saturation is dependent on the research design and setting, and since my sample for this research was not restricted to one job role (e.g. only trial statisticians or CIs) I anticipated that more interviews would likely be required.

4.2.5 Data collection

4.2.5.1 Setting

Interviews were scheduled for one hour and were conducted remotely over Microsoft Teams (Office365/Nexus365) with meeting invitations sent from my University of Oxford email address. Participants were invited to suggest a date and time for the interview that was suitable for them. Participants virtually attended the interview from wherever was most convenient e.g. at home or work.

4.2.5.2 Informed consent

I sent potential participants a Participant Information Sheet (PIS) when arranging the interview so they had time to review the information in advance. I produced two PIS, one for participants who were researchers and another for participants who were PPI representatives (presented in Appendix D3). The PIS detailed the nature of the study, what it involved, the implications and constraints of the protocol, and any risks of taking part. It clearly stated that participants were free to withdraw from the study at any time, with no obligation to give a reason. Participants were advised that if they withdrew from the study during the interview, the interview audio recording would be deleted. However, if they withdrew after the interview, and their data had already been analysed, the data would still be included in the final analysis due to the complexities of withdrawing data that had been de-identified and analysed.

Prior to starting the interview, I offered participants the opportunity to ask any questions about the research and their involvement. All participants gave verbal consent (captured on the audio recording) to participate in the interview and for it to be audio recorded before the interview began.

4.2.5.3 Semi-structured interviews

Participants participated in one interview only. Semi-structured interview guides that detailed questions and prompts were developed a priori and were ethically approved (R72039/RE001). The first part of the interview explored the participants' role (such as their institution, job title, and any RDS, funding panel or journal affiliations) so that the sample could be adequately described. Subsequent open-ended questions explored participants' experiences and perceptions of pilot trial progression and any progression criteria used. For example, questions explored participants approaches to developing and

assessing progression criteria, any challenges faced, and whether participants would have done anything differently in relation to progression criteria if they were to conduct their research again. I produced a separate interview guide for PPI representatives since the extent to which PPI representatives are involved in decisions around pilot trial progression was less clear. Interview guides were reviewed by the DPhil supervisory team and by a researcher at the University of Oxford who had experience leading an external randomised pilot trial as a CI. The interview guides were piloted [182] in the form of mock interviews (with Dr Charlotte Albury and an external randomised pilot trial manager based at the University of Oxford) and were iterated following piloting to enhance clarity. The final interview guides that were used are detailed in Appendix D4.

All participants were invited to contribute to an optional post interview respondent validation or 'member checking' activity [199]. I gave participants the opportunity to read, comment and feedback on a brief description of the interview transcript, to ensure that any elements that they considered essential to their experience were included. One de-identified example is detailed in Appendix D5.

4.2.6 Data management

4.2.6.1 Data recording

I audio recorded all interviews on two Olympus Dictaphones (DS-650 and LS-P1) and uploaded the audio recordings immediately after the interview to a designated folder on the University of Oxford server. Since the audio recordings contained the source data and record of informed consent, they were destroyed by deletion only when the study findings were published so they could be accessed as required to facilitate data analysis until this time.

I used OxFile, the University of Oxfords restricted access server designed for large file transfer, to send audio recordings that I had encrypted in a password protected folder to a third-party transcription service. The transcription service I used was Prestige Network, which is the University of Oxfords preferred supplier for transcription, translation and interpreting services. I also produced OxFile folders to allow Prestige Network to return transcripts.

4.2.6.2 Data de-identification

In compliance with the General Data Protection Regulation (GDPR) [202] and Data Protection Act 2018 [203], I de-identified the data at the point of transcription or transcript checking. Participant name, trial names and acronyms, institutions, locations and names of other researchers that were offered by the participant were removed. I stored all study documents in designated password protected folders on the University of Oxford server using unique IDs in the file name that linked to individual participants. The password protected master list of unique IDs was destroyed by deletion when the research findings were published.

4.2.6.3 Participant reimbursement

Initially there were no expenses provided for participating in this study. However, due to poor recruitment of PPI representatives I submitted an ethics amendment to offer PPI representatives a £20 One4All e-voucher in appreciation for their time and insights. I considered this appropriate because PPI representatives often receive reimbursement for their time when contributing to pilot trials in their PPI role. PPI representatives provided electronic consent via email for their details (name and email address) to be shared with a third-party company (One4All) to process the e-voucher.

4.2.7 Data analysis

4.2.7.1 Overview of the Framework Method approach to data analysis

Data analysis followed the seven stages of the Framework Method as described by Gale et al (2013) [178], with reflexivity adopted throughout as advocated by Braun and Clarke's reflexive thematic analysis approach [179]. A summary of the framework method is presented in Figure D1 and key terms used throughout are described in the glossary.

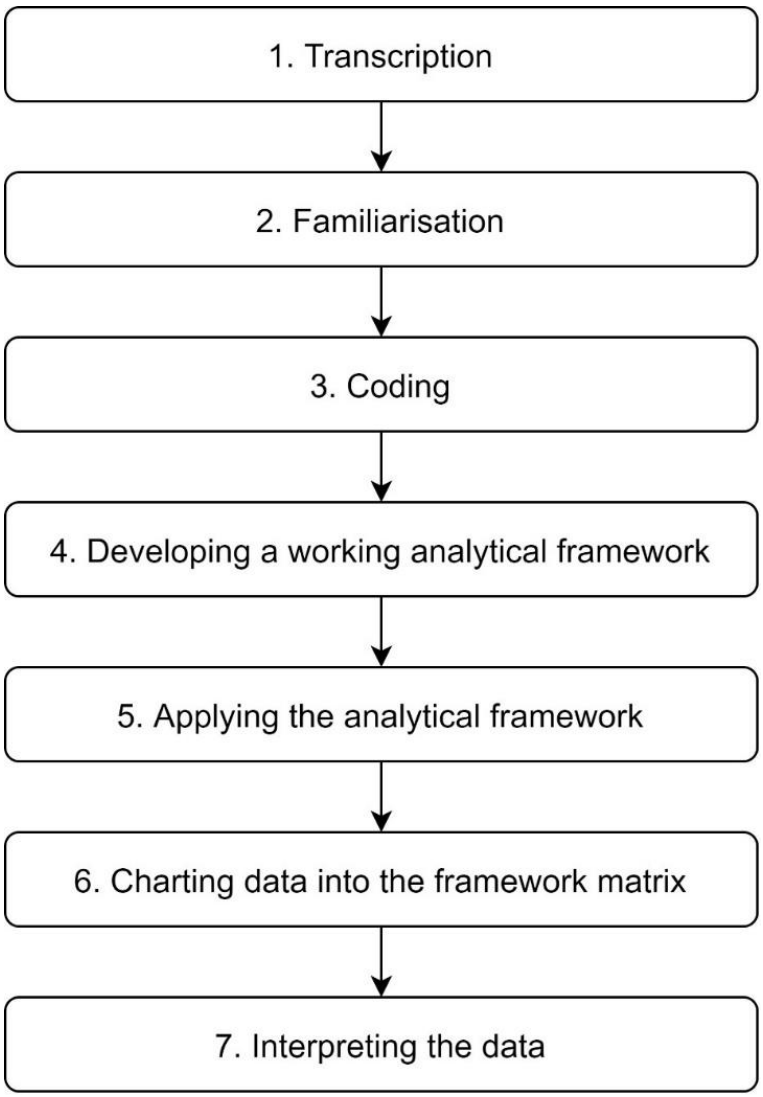


Figure D1 The seven stages of the Framework Method

Reported by Gale et al (2013) *BMC Med Res Methodol* **13**:117, published CC-BY 2.0

4.2.7.2 Step-by-step guide to the Framework Method approach

1) Transcription

Audio recordings were transcribed into Microsoft Word documents verbatim (I transcribed 10 and Prestige Network transcribed 25). Paralinguistic features were not transcribed since the research focused on *what* is said as opposed to *how* something is said. I read all transcripts in full whilst listening to the audio-recording to check for errors and remove identifiable data. I imported de-identified transcripts into NVivo (v12).

2) Familiarisation

I read all transcripts in full whilst listening to the audio recording prior to coding.

3) Coding

I coded transcripts using inductive open coding: codes were developed from the data, rather than prespecified. I coded the first 5 transcripts in full, line by line, assuming meaning in every sentence. I used participants' own words where it made sense to do so (in vivo coding) to highlight participants' own voices, without making interpretations or assumptions. I maintained a codebook (i.e. a list of the codes I had used along with brief descriptions) and added new codes periodically.

Dr Charlotte Albury also coded the first two transcripts in full and we peer discussed our choices and rationale for codes we had used. This allowed me to identify and draw on different perspectives and ideas to my own based on the initial data. Coding all transcripts in duplicate was not considered appropriate or necessary because the aim of this research was not to quantify the qualitative research findings, but instead to develop themes to describe patterns in the data, whilst acknowledging my own role in co-creating the research findings.

4) Developing a working analytical framework

Once I had coded the first five transcripts, I reviewed the codebook to group codes of similar content with linked properties and characteristics into categories and listed uncategorised codes in a 'other' section. This formed the first working analytical framework.

5) Applying the analytical framework

I coded subsequent transcripts against the analytical framework following an iterative process (alternating between steps 4 and 5) adding new codes (along with brief descriptions) as identified. A copy of the analytical framework was saved after coding of each transcript to document how it had evolved with continued data analysis. The analytical framework was only considered final once all transcripts were coded. The final analytical framework, presented in Appendix D6, contained eight categories: A priori uncertainties about feasibility, pilot trial stakeholders, pilot trial design and set-up, progression criteria, pilot trial conduct, pilot trial findings, the future definitive trial and time.

6) Charting data into the framework matrix

I charted data (by case and code) into framework matrices within Microsoft Excel (Office16). I produced one framework matrix for each category. To provide an example, the framework matrix for the pilot trial conduct category is presented in Appendix D7.

Participants' own words and phrases were abstracted into the matrix and summarised (verbatim data was underlined). Particularly interesting quotes were highlighted using a **Q**/**QQ**/**QQQ** designation so they could be easily retrieved. Any 'deviant' codes that did not conform to the developed categories were highlighted within the framework matrix to ensure careful attention to these. These were carefully reviewed to see if deviant views

could be explained from the existing data, or whether the interview topic guide or sampling strategy required an update to further understand the view.

7) Interpreting the data

The framework matrices helped me to look within and between cases and categories to explore concepts, relationships and to develop themes to offer possible explanations for the patterns observed within the data. I maintained a working document in Microsoft PowerPoint (Office16) to present themes and supplementary quotes to the supervisory team for peer discussion. This included a visual map to summarise each theme, the final version is presented in the results section of this chapter. To facilitate interpretation and focus on the key findings I produced a summary paragraph for each theme that distilled the essence of that theme.

4.2.8 Strategies to ensure data quality

I followed Lincoln and Guba's approach to maintain quality and rigour [204]. Although alternative checklists for trustworthiness have been proposed [205], I chose to use Lincoln and Guba's approach which was first published in 1985 as it is a widely accepted and highly recognisable approach to demonstrate trustworthiness.

Lincoln and Guba describe four criteria for trustworthiness of qualitative research studies: credibility, dependability, transferability and confirmability. I implemented several strategies for best practice in qualitative research to meet these criteria [204,206,207]. To demonstrate this, I have produced a checklist of trustworthiness which is presented in Table D1.

Table D1 Checklist of trustworthiness based on Lincoln and Guba's criteria

Criteria	Achieved	Techniques used
Credibility (internal validity) *Are the findings trusted? Do the findings provide a comprehensive and sensible interpretation of the data?*	✓	• **Triangulation**: I triangulated the findings with other methods for collecting data throughout the DPhil including the methodological review (Chapter 2) and the review of funding applications (Chapter 3). • **Peer discussion**: I discussed segments of coded transcripts and the analytical framework with an experienced qualitative researcher (Dr Charlotte Albury). Qualitative research data is *co-created* since different researchers will find and place importance on different things, and therefore the researchers themselves contribute to the findings. Engaging in peer discussion during data analysis allows researchers to challenge their presumptions. • **Respondent validation**: I invited all participants to take part in a respondent validation (or 'member checking') exercise. I sent a short summary of their interview transcript and gave them the opportunity to comment on how well they thought this summarised the interview and add any further comments. An example is presented in Appendix D5.
Dependability (reliability) *Is the research process transparent? Is the research auditable?*	✓	• **Transparent reporting**: I have reported the methods and findings of this study in line with the COREQ guidelines for reporting qualitative research [169]. • **Audio-recording**: I audio-recorded all interviews using two Olympus Dictaphones (DS-650 and LS-P1). • **Transcription**: I transcribed 10 interviews myself and arranged for the remaining 25 interviews to be transcribed by an experienced transcription service (Prestige Network). I checked all transcripts for errors by reading it while listening to the audio-recording. • **Computer software**: I used NVivo (v12) to store and organise data and facilitate coding. • **Audit trail**: I maintained an audit trail to document decisions made during the research study. Audit documentation included key questions and decisions documented in the reflexivity journal, project meeting minutes, and a record of memo's created within NVivo (v12) to draw attention to sections of the data that were particularly interesting during coding. I reviewed the audit trail during the later stages of data analysis to supplement interpretation of the findings.
Transferability (external validity) *Are the findings relevant or applicable to other contexts?*	✓	• **Thick description**: I have described in detail the sample and methods used in this DPhil chapter and in any associated outputs to allow other researchers to evaluate whether these findings might be relevant to other contexts or settings.

Criteria	Achieved	Techniques used
Confirmability (objectivity) *Do the findings reflect the perspectives of the participants and are linked to the data?*	✓	• **Reflexivity**: I documented reflections in a reflexivity diary throughout the study. Maintaining a reflexivity diary allowed me to recognise and challenge any implicit biases I had. The reflexivity diary was also important in guiding iterations to purposive sampling approaches and making updates to the interview guides. Example extracts are presented in Appendix D8. • **Inclusion of raw data**: I highlighted verbatim data in the framework matrices (underlined) and have reported direct quotes to illustrate and exemplify my findings.

4.3 Results

In this section I will first provide an overview of the sample, then I will present the themes that I developed.

4.3.1 Description of study sample

I interviewed 35 participants between December 2020 and July 2021. Interviews ranged in duration from 23m:50s to 1h:03m:04s (mean 44m:31s). Participants were affiliated to 12 research institutions, see Table D2.

Table D2 Institutional affiliations of participants

Institutional affiliations	**Number of participants**
Cardiff University	1
Keele University	1
Newcastle University	1
University of Bristol	1
University of Edinburgh	2
University of Glasgow	1
University of Leeds	4
University of Leicester	2
University of Nottingham	1
University of Oxford	8
University of Sheffield	6
University of York	1
N/A (PPI representative)*	6
Total	**35**

*Note institutional affiliations for participants who are PPI representatives are not included as many had or were participating in trials across multiple research groups and institutions

Participants included Chief Investigators (CIs), trial managers, trial statisticians, trial methodologists, PPI representatives and one health economist. Ten of the participants were considered senior researchers, i.e. they held trial oversight roles e.g. CTU directors. Participant roles and affiliations are presented in Table D3. Many participants held

multiple roles and Table D3 demonstrates this overlap. For example six trial managers were interviewed, two were senior researchers, and two had current or previous journal affiliations e.g. as a journal editor or peer reviewer.

Table D3 Roles and affiliations of participants

Roles and affiliations of participants	Chief Investigator	Trial Statistician	Trial Methodologist	Trial Manager	Health Economist	Senior Researcher/Trial Oversight	PPI representative	Affiliation to journal*	Affiliation to funding panel**	Affiliation to RDS***
Chief Investigator	**13**	1	1	0	0	2	0	13	9	2
Trial Statistician		**7**	4	0	0	3	0	6	5	4
Trial Methodologist			**8**	0	1	5	0	6	6	5
Trial Manager				**6**	0	2	0	2	0	0
Health Economist					**1**	1	0	1	1	1
Senior Researcher/Trial Oversight						**10**	0	8	7	3
PPI representative							**6**	1	2	2
Affiliation to journal*								**24**	16	7
Affiliation to funding panel**									**18**	8
Affiliation to RDS***										**9**

*Includes both current and previous affiliations in editorial or peer reviewer capacity.

**Includes both current and previous affiliations as formal panel member or peer reviewer of funding applications

***Includes both current and previous affiliations to an RDS

Three potential participants who initially expressed interest in participating in the study declined to participate after being sent the study information. Reasons for declining included illness, competing clinical commitments, and a significant length of time since the pilot trial was conducted.

4.3.2 Developed themes

In this section I will introduce the themes I developed based on my analysis and then describe each one in detail. Before doing so, I draw attention to the ongoing debate around when an external or internal pilot trial is appropriate. Although exploring when an internal versus external pilot trial is appropriate was not an objective of this study, it important to acknowledge this nuance because some (but not all) participants described different approaches to progression criteria depending on whether their pilot trial was internal or external.

Researchers described that the primary reason they did an external randomised pilot trial was to assess feasibility because they had significant uncertainties about their definitive trial design. Some researchers, those who had experience of different trial designs, outlined previous or hypothetical uncertainties that in their opinion would warrant an external pilot trial, and those that would warrant an internal pilot trial. In general this was based on the *'level of uncertainty'* that they had about their definitive trial design. Where researchers had significant uncertainties about trial design, and notably they considered that it was likely that changes to trial design would be required (for example to their choice of outcome measures or delivery of the intervention), they considered an external pilot trial to be suitable. Alternatively, where uncertainties were unlikely to lead to changes to the trial design, participants considered an internal pilot trial to be more appropriate.

In relation to the research question, I identified variation in how participants developed and assessed progression criteria for external randomised pilot trials. Participants described conflicting views on the importance of progression criteria, and many recalled other considerations, beyond the criteria, that can inform whether a pilot trial progresses.

I developed seven descriptive themes around these results:

1. Divided opinions on the value of progression criteria
2. Varied approaches to developing and applying progression criteria
3. (Avoiding) The potential for personal interest to influence progression criteria and progression decision-making
4. Stakeholder engagement in setting progression criteria and making progression decisions
5. Lessons learned from doing the pilot trial and their impact on progression criteria applicability
6. Factors, beyond the progression criteria, that inform the progression decision
7. Progression of external randomised pilot trials: Funding considerations and constraints

These themes were not interpretative, rather they are aggregations to describe what people said [208]. A visual map of these descriptive themes is presented in Figure D2. To unite and explain these themes I developed one overarching interpretive theme: *A one size approach to progression does not fit all*. Below I present anonymised quotes to illustrate and exemplify my findings.

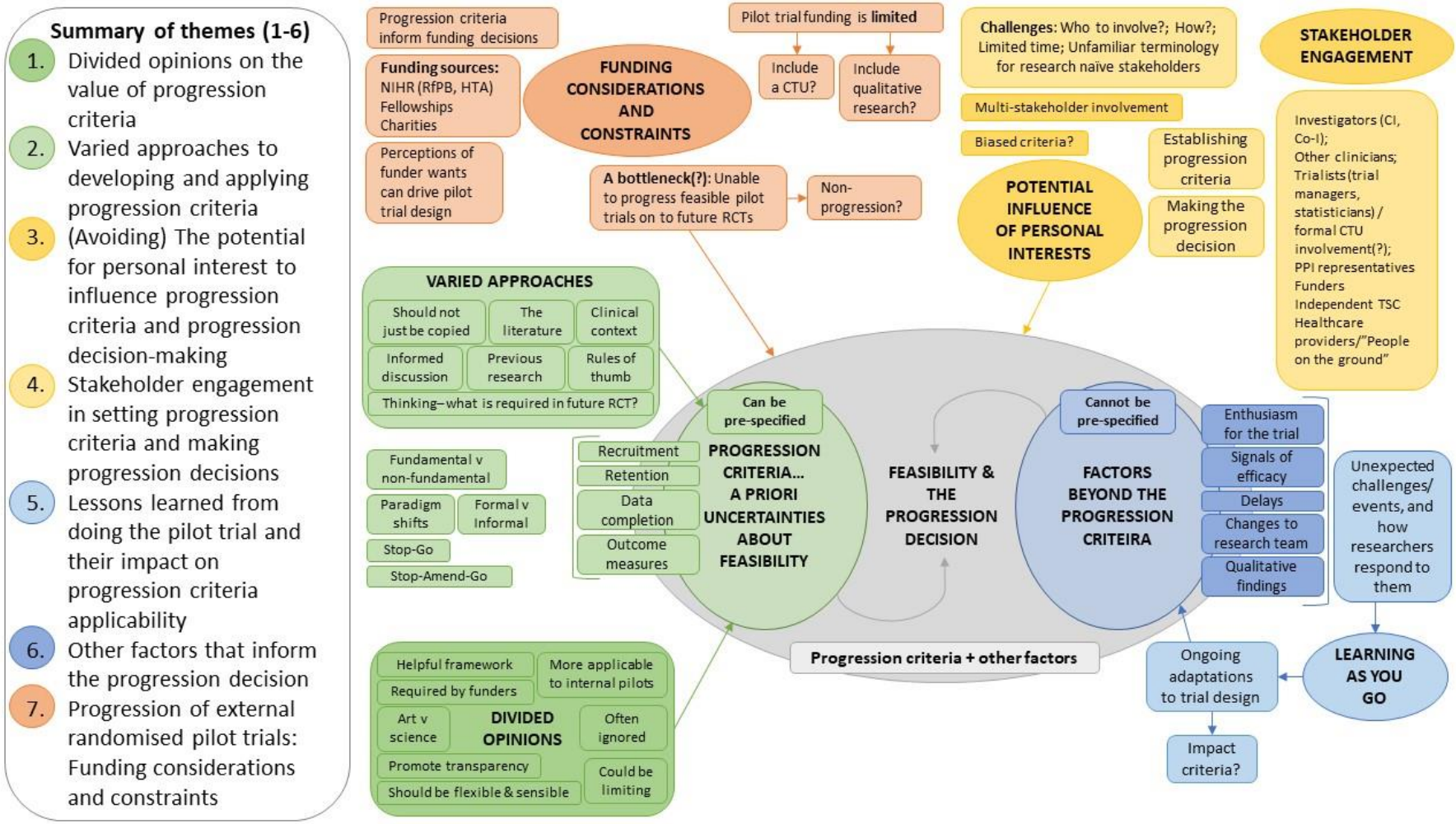


Figure D2 Visual map used to facilitate presentation and discussion of themes

4.3.2.1 **Theme 1: Divided opinions on the value of progression criteria**

Participants presented divided opinions about the importance of prespecifying progression criteria. Some expressed the view that progression criteria might be more appropriate to internal, rather than external, pilot trials.

4.3.2.1.1 Divided opinions about usefulness of progression criteria

Although most participants were in consensus that prespecifying how the pilot trial findings will be interpreted to draw a conclusion about feasibility is important, participants shared divided opinions about whether progression criteria are the best way to determine feasibility. In general, less experienced CIs described how progression criteria were a 'helpful framework'. One CI, who was conducting a pilot trial as part of their fellowship stated that the process of deciding on, and outlining, progression criteria provided the opportunity to spend time considering areas of uncertainty that they had about trial design and the potential problems that might be encountered. In their view, progression criteria were a *'no brainer'*, and should be a mandatory part of pilot trial design.

> *It just seems that it's a no brainer. I found it very helpful as a framework just to you know, to think about where the problems would be in the trial; I think it should be mandatory [P002; CI]*

Although more senior researchers generally also described that they considered progression criteria important to structure their thinking about the uncertainties they had, some expressed concerns that progression criteria could limit their interpretation of feasibility. Senior researchers generally considered that progression criteria should be open to interpretation rather than being completely definitive, suggesting that with

experience researchers place more emphasis on trusting their own inner judgement, with one stating that they consider progression criteria to be more of 'an art than a science'.

> *I think you do need them; I think it's necessary to kind of have something there so you're not- to sort of structure your thinking… But at the same time it is a bit more of an art than a science thinking about how do you interpret those and how do you move kind of… beyond them? [P027; Senior researcher with trial oversight]*

Experienced trial statisticians were generally less likely to place as much emphasis on progression criteria. One trial statistician described that in their opinion progression criteria are *'hypothesis tests in disguise'*; i.e. demonstrating feasibility is dependent on meeting progression criteria. They felt that progression criteria can be limiting and inflexible, leading to researchers not wanting to set them in the first place:

> *Progression criteria are hypothesis tests in disguise, and you need to appreciate that when you're trying to set them, and if you appreciate that you probably won't want to set them in the first place [P003; Trial statistician and trial methodologist]*

There were also divided opinions on how well progression criteria indicated feasibility. Experienced researchers described how feasibility is not straightforward, it is a complex concept which can mean different things for different trials. However, most researchers consistently emphasised the importance of demonstrating the ability to recruit participants to indicate trial feasibility. One trial manager described that they considered establishing the ability to recruit to be a priority. For them demonstrating recruitment would take precedence over other pilot trial findings as an indicator of feasibility:

> *If the rest of it goes really well but you still can't recruit you know, if you meet all the other criteria but you can't recruit it doesn't matter really [P006; Trial Manager]*

Not every participant agreed with this hierarchical approach to progression criteria. One trial statistician noted that progression criteria are often interlinked and are not completely independent entities; In their opinion progression criteria cannot be hierarchical as one often depends on another. To provide an example, they outlined how intervention acceptability can impact on site recruitment, as investigative sites will not sign up to deliver an intervention that they do not consider acceptable:

> *You won't recruit the site if it's not deemed to be a bit acceptable by the service provider. So they're not completely independent in any shape or form, they do interlink. [P007; Trial statistician and trial methodologist]*

4.3.2.1.2 Divided opinions about applicability of progression criteria to external pilot trials

For some experienced researchers, divided opinions on the value of progression criteria were underpinned by conflicting views about whether progression criteria are appropriate for external pilot trials. Some senior researchers, who had experience of different trials, described their perception that progression criteria might be more appropriate to internal pilot trials. The researchers described two key reasons for this distinction. Firstly, for internal pilot trials there often is more existing data that has been collected and can be used to inform specific progression criteria targets:

> *There were concerns raised [during the TSC] that using a traffic light system was aimed at internal pilot trials rather than external feasibility trials and are often based on previous available data [...] and we had no previous available data upon which to base criteria for success, and so that's why it was completely invalid. [P010; Trial Manager]*

The second reason is that external pilot trials are standalone studies, separate to the future definitive trial, and so they do not progress seamlessly into a main RCT. One trial manager described that they did not have formal progression criteria for their external pilot trial for this reason. They instead considered that their progression criteria was ultimately whether funding for further research can be obtained:

> *They were both external, so it wasn't progression criteria because we weren't progressing. The progression criteria is: Do we have any funding? [P006; Trial Manager]*

In contrast, some researchers described how they did not distinguish between their approaches to progression criteria based on whether their pilot trial was internal or external. One trial methodologist described the importance of taking a structured approach to progression criteria development from the earliest opportunity, irrespective of the (internal or external) pilot trial design:

> *I think any structured approach to defining and evaluating progression criteria should be done from the earliest opportunity and it should be done with flexibility and transparency in mind… definitely. I don't see that it really makes too much difference whether it's an internal or an external pilot trial other than that the level of uncertainty you have is probably greater when it comes to an external pilot trial. [P032; Trial Methodologist]*

In the absence of formal guidance for progression criteria for external pilot trials, some participants described drawing on recommendations for progression criteria for internal pilot trials. While some participants felt that these recommendations were applicable, others expressed the desire for more detailed guidance specific to external pilot trials. One CI described how progression criteria are the primary outcomes of the pilot trial, and

therefore are an important part of the funding application, so more guidance for how to come up with them would be helpful:

> *I think it would be helpful to have more resources to develop progression criteria because basically, it's the most important part of the application really because… well, it's not the most important part… but it's the primary outcomes. And so, I think more guidance would be helpful. [P024; CI]*

4.3.2.1.3 Theme 1 summary: Divided opinions on the value of progression criteria

In summary, there were divided opinions on the value of progression criteria in determining feasibility of a future definitive trial. While some researchers considered progression criteria to be a helpful framework, others were concerned about being limited by their a priori choice of progression criteria, and some questioned their applicability to external pilot trials altogether. In general, researchers expressed the need for more guidance for progression criteria in external pilot trials.

4.3.2.2 **Theme 2: Varied approaches to developing and applying progression criteria**

As well as divided opinions on the value of progression criteria, participants described inconsistent approaches to progression criteria development. Experienced researchers shared how they considered approaches to progression criteria to have evolved over time, with increasing focus on flexibility.

4.3.2.2.1 Variation in approaches to progression criteria over time

Participants who had more trial experience described two paradigm shifts in relation to their approaches to progression criteria: From initially not prespecifying progression criteria, to having quite strict thresholds *'stop, go'* (first paradigm shift), to a more flexible approach, such as a *'stop, amend, go'* or *'traffic light'* (second paradigm shift).

Although many participants presented their preference towards the more recent *'stop, amend, go'* or *'traffic light'* approach, one CI commented that this approach can often be used inconsistently between pilot trials emphasising the importance to outline what exactly is meant by *'red, amber or green'* where these terms are used. This CI described how tight word limits and no formal guidance to include this level of detail could deter researchers from reporting this information in research funding applications:

> *If I were to take this to where I think I would be more comfortable is you have your green, amber, red criteria, but then you explicitly have another column saying what you would do in those circumstances. I've tried to incorporate that in some on my funding applications, but word counts are obviously very strict and if people don't expect it then people aren't going to put it in. [P021; CI]*

Participants consistently emphasised the importance of flexibility–underpinning perceived preferences towards the stop, amend, go format–to avoid progression criteria being considered the *'be-all and end-all'*. Senior researchers described the importance of finding a balance between setting progression criteria that are stretching and ambitious, without being too strict and limiting. While most researchers credited the *'stop, amend, go'* approach with establishing flexibility in their progression criteria, some described building in flexibility in other ways. For example, one trial methodologist described having both *'formal*' progression criteria that are agreed with the funder, and *'informal'*

more flexible criteria for things that run in parallel that researchers 'keep an eye on'. Comparably, one trial statistician proposed that progression criteria should be structured into those that are *'fundamental'* for progression, and those that are *'non-fundamental'*, to outline those progression criteria that are more critical:

> *I think that there should be some flexible criteria and there should be some fundamental or inflexible criteria. [P007; Trial statistician and trial methodologist]*

4.3.2.2.2 Varied methods of progression criteria development

Just as participants had divided opinions in how helpful they perceived progression criteria to be, they also shared varied and inconsistent methods of criteria development. Participants described coming up with their progression criteria in various ways: Drawing on rules of thumb, observation work, previous research by their group or institution, published research of relevance, clinical experience, or contextual considerations such as what is considered achievable in the future definitive trial:

> *70% is always the number that I always have in the back of my mind […] I can't point you to a certain paper but it's kind of just, I think it's just what you generally look for [P001; Trial Statistician]*

> *The original targets were based on some of the observation work we had done before [P002; CI]*

> *I mean you're going to base it a little bit on what's been achieved so far by other people [P007; Trial Statistician and trial methodologist]*

> *You always have in mind what would be the future study is going to be so that's the way that how you plan the pilot study [P008 Trial Statistician and senior researcher/trial oversight]*

I think it's more like an intelligent discussion at that [P026; Trial methodologist and senior trial researcher]

Divided opinions on what constitutes best practice could mean that progression criteria were developed inappropriately. Some researchers described how progression criteria seemed to be just *'plucked out of the air'*, with minimal thought going into their development. One CI offered a potential explanation for this: they perceived that inconsistent approaches to progression criteria development are due to a lack of guidance or information for how to decide on progression criteria. One senior researcher who shared this view exemplified this point, describing progression criteria development as *'a bit of a dark art'*, foregrounding that there is sometimes a mystery around their origin.

There isn't really any information or there wasn't about how you would do that, how you would decide it just seemed to be kind of plucked out of the air [P028; CI]

To provide another example, some experienced researchers also recalled sharing examples of progression criteria from previously successful funding applications with junior researchers as a prompt so they could consider what criteria may be appropriate for their own pilot trial. Although senior researchers considered this practice, i.e. sharing of examples, to be appropriate, other participants shared concerns that this practice could lead to researchers directly copying criteria from previous applications, which they discouraged this on the basis that the same criteria were not likely to be applicable to different trial contexts. One CI described reviewing their pilot trial publication citations and noticing that the progression criteria they had developed had been copied and used for other trials, which they felt was inappropriate since their progression criteria had not been intended for that specific context:

There's been quite a few where they've just literally taken the progression criteria that I've developed for this particular study and applied it to their own study, but it's completely different […] in a completely different population [P028; CI]

4.3.2.2.3 Theme 2 summary: Varied approaches to developing and applying progression criteria

In summary, participants described how behaviours and attitudes towards progression criteria had evolved over time with increased focus on flexibility. However, approaches to progression criteria development were inconsistent, and some researchers described how this could result in inappropriate criteria for example where criteria are directly copied from other pilot trials.

4.3.2.3 **Theme 3: (Avoiding) The potential for personal interest to influence progression criteria and progression decision-making**

Some participants spoke about the potential for personal views or interests of key stakeholders, particularly CIs and PPI representatives, to influence the development of progression criteria which were more likely to indicate pilot trial '*success'*.

4.3.2.3.1 The potential for biased progression criteria

Some participants described how conducting a pilot trial that progresses could be viewed as good for a CI's career. They perceived that this could create a temptation to set low or 'loose' progression criteria to increase the likelihood of progression, which they advised against. They described how although low criteria are more likely to indicate that a pilot trial is feasible, and merit funding for a definitive trial, the assessment of feasibility would likely be inadequate. This practice may not truly reflect challenges that might be faced in a definitive RCT, and that key questions about trial design would remain unaddressed.

One CI highlighted the personal implications of setting loose criteria, stating that on one hand this may mean a CI is more likely to be awarded further funding, but on the other hand running a trial that has progressed inappropriately could result in years of '*struggling'*:

> *I think historically there's been a tendency to have too loose a criteria for progression. And this has resulted in trials being moved from pilot through to definitive phase 3 type designs inappropriately. And although that's good for your career to get this funding, it's a huge waste of time, money, and effort to do that. […] I think you have to have an honest conversation with yourself about do you want to spend your next five years struggling through a trial because you failed to answer that question around consent rates. Or withdrawal rates. Or proof of principle. Or acceptability. All of those kind of things. It's just not an easy way to make a career for yourself. [P021; CI]*

Although many warned against setting low criteria, that did not truly reflect feasibility, some senior researchers also had concerns about CIs setting *'overly ambitious'* criteria in an effort to '*impress research funders'*. Instead senior researchers described the importance of finding a balance, stating that progression criteria should be *'stretching but not so unrealistic that we're setting ourselves up to fail'*.

Just as some participants reported that it could be in the CIs interest to see their pilot trial progress, some had similar concerns about PPI involvement. One CI questioned the appropriateness of PPI in discussions around progression criteria. In their view, PPI representatives are *'advocates'* for research into a specific condition, so might have implicit biases when setting progression criteria that might stop further research in that area:

> *If you're a PPI member, the idea of equipoise, although it's discussed, it wouldn't sit naturally. You are an advocate for that*

condition. And therefore if you're deciding about what criteria you will use to stop that program of research into a condition that you yourself have been affected by, I think there's – I don't want to use the phrase conflict of interest there but it's kind of heading in that direction. [P021; CI]

Supporting this view, one PPI member similarly described how they consider themselves to have an *'added interest'*, having had the illness that is being researched, and wanting to see research around that illness progress:

Well, I suppose everybody comes with an agenda, whether you like it or not. I've had this illness and to see that progress through research to help me is something that I want to be involved with. So I've got an added interest [P033; PPI representative]

4.3.2.3.2 Strategies to mitigate against biased progression criteria

Many participants emphasised that this potential for bias could be mitigated by involving a range of stakeholders when developing their progression criteria. When asked who had contributed to progression criteria development, researchers generally described involving the TMG and an independent TSC. One trial statistician described how involving multiple stakeholders in this process can ensure that researchers acknowledge and present both the challenges and successes of the pilot trial, which can lead to a more informed progression decision. In their view, this would ensure better allocation of research funding and avoid wasting resources on definitive RCTs that fail.

If you're evaluating your own intervention, how do you get some, what they call, academic distance to do that? And it's a little bit like that with a pilot. It's almost in your interest that you want the pilot to work, and you will create a story… I'm not saying that it's erroneous, but people will tell a story around their pilot that may highlight the positives and less focus on the negatives. And we need to be careful about that because if that then leads to an inappropriate decision to fund a pilot that is then unsuccessful in full trial, that's not a good

outcome for anybody. The patients, healthcare systems or researchers. [P025; Trial statistician and senior researcher]

One trial methodologist described how engaging with an experienced Clinical Trials Unit (CTU) was instrumental when developing their progression criteria. They described how their CTU was able to draw on their experience of other, similar trials, to offer advice to guide progression criteria development so that the final agreed criteria were based on informed negotiations and were both sensible and realistic, rather than plucked out of the air based on nothing:

I think if you've got a good multidisciplinary team in place and you're working with a really experienced Trials Unit, you come up with sensible criteria. You come up with a sensible understanding of what the uncertainties might be and you discuss that freely and openly and you're realistic about it. And a trial team will do that for you. They will pull you up and they will say, 'come on, our experience is X, Y and Z. You're proposing this. That's far too different to what we've seen in similar trials.' So, I do think there's always a negotiation around what you would expect them to be, but I would like to think they're the most informed negotiations, rather than just plucking figures out of the air based on nothing. [P032; Trial methodologist]

Some researchers also described the importance of emphasising that pilot trials that are not feasible should not be considered as *'failed'* pilot trials. One senior researcher suggested that if nothing ever fails, researchers are *'probably not being particularly ambitious'*, to acknowledge that pilot trials shouldn't really be done where there are minimal uncertainties. One CI described the importance of recognising that pilot trials that do not progress have saved resources that might have otherwise been wasted on definitive trials that did not work. In recognising this, researchers might be less likely to equate *'failure to progress'* with *'personal failure'* and avoid progressing pilot trials without sufficient justification. This CI described the potential for wasted resources by

doing a pilot trial where researchers have the mentality that it will proceed regardless of its findings, adding that perhaps researchers and funders should consider at a broader level how many pilot trials should be proceeding to definitive trials:

> *I think if you go into a pilot trial with the mentality that we are going to do the definitive trial regardless, just don't do the pilot trial. Just go forward and do the definitive trial because otherwise you're wasting time and resources [P021; CI]*

4.3.2.3.3 Theme 3 summary: (Avoiding) The potential for personal interest to influence progression criteria and progression decision-making

In summary, some researchers identified the potential for personal interests of different stakeholders to influence progression criteria, and progression decisions, with stakeholders' keen for pilot trials to progress. Researchers highlighted that this could be mitigated by including a range of perspectives when developing their progression criteria and avoiding framing pilot trials that do not progress as *'failed'*.

4.3.2.4 **Theme 4: Barriers to stakeholder engagement in setting progression criteria and making progression decisions**

Whilst most participants considered involving multiple stakeholders when developing progression criteria to be important to provide different perspectives about feasibility and avoid the potential for bias, many described challenges to doing this in practice. I identified the following barriers to engaging stakeholders: lack of time, lack of information on who to engage and how, and lack of familiarity and understanding of the concept of progression criteria, and sometimes pilot trials more generally.

4.3.2.4.1 Lack of time

Participants described that often progression criteria are required in research funding applications, but that when writing the funding application there is often not enough time to convene a TSC, or involve a Trial Manager, until funding is awarded at which point the progression criteria had been set.

Although many CIs described wanting to involve an independent TSC, some suggested that in reality this presented a causality dilemma, as progression criteria were required in the funding application which was developed *before* they had convened a TSC. As a result often the criteria stipulated in funding applications had not been reviewed by a TSC but were instead reviewed post funding award. One trial statistician, and pilot trial TSC member, described how by the time the TSC has met it is often *'too late'*. They said that if progression criteria are already set, evidencing them can become a 'rescue mission' to save an application that is flawed by the inclusion of inappropriate progression criteria that are unlikely to indicate feasibility:

> *As a TSC statistician, by that stage, it's frankly, too late. You're assuming people have done their due diligence. And it becomes a rescue mission at this point and saying, look, I can't let you get away with this. Interestingly as a statistician, I find myself as the sometimes as the, 'are you sure about this?', you know, 'look at what your getting, look at your metrics, I know you're saying this, are evidencing this?' I'm not so sure [P029; Trial Statistician]*

Tight funding application deadlines and other time pressures on CI and stakeholder's capacity can mean that feedback on a protocol, including progression criteria, may be light touch, or not forthcoming in time. One CI described the process as 'balancing' between getting some feedback but also meeting deadlines – both could not be fully achieved within these existing constraints:

I know that our clinical stakeholders would have really important perspective to offer on this and I think they would be interested. It's just getting their time. Because you can send out a protocol and 'can you respond in a week?' and everybody's really busy so it's quite hard to get feedback on these things. Then you're balancing that with just trying to move forward with it [P019; CI]

As well as in setting progression criteria, participants also emphasised the importance of multi-stakeholder involvement in progression decision making. However, time was again a barrier. One CI described that this process is highly nuanced and took months to come to a decision that all stakeholders supported:

That takes a bit of time because you're then looking at the data to say 'ok well this didn't work, that didn't work' and combining the data with what the trial team say, and then combining the stats with what health economics want, and that takes 3-6 months. But that takes multiple iterations of conversations and then you get a design. [P020; CI]

4.3.2.4.2 Lack of information on who to engage and how

Theme one (*divided opinions on the value of progression criteria*) highlighted a lack of guidance for researchers to draw upon when developing their progression criteria. This lack of guidance presented difficulties with stakeholder engagement, as participants were unclear on who they should engage in this process, and how they should contribute. For example, one trial statistician described how in their opinion it was very important to involve the *'people on the ground'* who will be implementing the trial in discussions about progression criteria. They perceived that it is these people, the research nurses, therapists and interventionists, who are best placed to identify where potential challenges will be, and that it is the role of researchers to allow them to feel comfortable to speak honestly about these challenges.

Some participants drew on their own experiences of contributing to TSCs to describe how involving independent TSCs who act on behalf of research funders to approve progression criteria can mitigate against potential bias. Although most CIs wanted to have their progression criteria agreed by an independent TSC, not all opted to convene an independent TSC for their pilot trial. One CI described how they had not chosen to delegate progression decision making out to a TSC because it would be a beneficial training opportunity for them to be involved in making that decision:

> *I think that's probably partly because it's a fellowship, it's fellowship work and part of the work, the overall aim of it is a training vehicle for me, essentially. For instance if this was an external pilot of a HTA plan it probably would have a much more independent oversight committee. But we chose not to delegate that discussion out because it would be part of my training to be involved with it [P013; CI]*

Some participants described feeling uncertain about whether and how to involve the funder in discussions about progression criteria. For example, some CIs described how their perceptions of what they think funders want can drive decisions about pilot trial design, rather than these decisions (e.g. choice of progression criteria) being informed through discussion with funders directly. One trial statistician suggested that there is a lost opportunity for direct dialogue between researchers and funders, which they felt limits the choice of progression criteria, as researchers are keen to deliver funding applications that are likely to be successful by sticking to what they know or have done previously:

> *At a very early stage you don't have that room for you to approach funders or to have a discussion at all. So it limits the way you can think about those things. [P005; Trial statistician and trial methodologist]*

Participants who were affiliated to research funding panels described how panellists often reflect positively on the inclusion of clear progression criteria in funding applications, and that applications that included progression criteria might fare better than those that don't. One trial statistician described how in their experience applications that included clear progression criteria would likely lead to a higher scored application, as they viewed the inclusion of progression criteria as an indicator of application quality:

> *If it's got clear feasibility progression criteria, sure, I would score it higher. It gives it that extra quality in my view. [P007; Trial statistician and methodologist]*

4.3.2.4.3 Lack of familiarity and understanding of progression criteria

Researchers described how the concept of progression criteria often felt very abstract to stakeholders with less research experience, which meant that conversations around progression criteria could sometimes be challenging. When asked about whether researchers had involved PPI representatives in making decisions around future definitive trial feasibility and progression, CIs and trial managers generally reported that although they supported the involvement of PPI representatives, many had not discussed progression criteria with PPI representatives directly. One trial methodologist described how instead they had linked discussions about the pilot trial that *'indirectly informed the progression criteria'*:

> *I don't know that there were discussions specifically around progression criteria. What I think there were, were discussions that linked to progression criteria. So, they were broader discussions about recruitment and challenges with recruitment. Probably indirectly informed the progression criteria but I wouldn't say directly informed that. [P032; Trial methodologist]*

Consistent with this, most PPI representatives did not recall being directly involved in discussions around progression criteria, and those that were involved described how these discussions were often challenging. One PPI representative recalled attending a meeting to discuss whether the pilot trial would progress, where researchers talked *'round and round the topic',* leaving this PPI representative feeling unclear following the meeting about what decision had been made:

> *So we had a big meeting just on Monday gone, to decide the way forward and they talked round and round and round the topic and I'm not sure, even though I was there, I'm not sure what they've actually decided […] They're looking at it as traffic lights, and stop and go, and minor surgery, and major surgery, and these are all new terms for me completely. [P017; PPI representative]*

When asked whether they would like to contribute to discussions around progression criteria, most PPI members were generally in consensus that in their perspective these decisions should be made by people who are *'experts in the field who will know exactly what they're talking about'*. However, some did suggest that they would like to review and provide their opinion on any suggested progression criteria, with one saying:

> *I think the academic and clinician is in their rights to set the progression criteria, but patient and public involvement representatives might have an opinion on that to see how realistic it is… [P035; PPI representative]*

One CI who felt that it was important to capture the perspectives of PPI members when developing their progression criteria described how PPI representatives often had different levels of understanding and trial knowledge which was challenging to handle. To facilitate their discussions with PPI members they used analogies to help demonstrate what they meant by the term progression criteria. They found that using real world

hypothetical examples, that related to day-to-day decisions, promoted discussion among all PPI members, irrespective of their level of trial knowledge and experience.

> *There were some patient members who were maybe a little bit more experienced, and had an awareness of the need for like, statistical power. And they got maybe a little bit more confused. Because there were like we don't need to do this, because you just have like a sample size that's based on calculation. So why are you doing this? So that was one challenge, that really experienced group. And then on the other end of the spectrum, there were a group who really struggled because it was quite abstract. There wasn't anything concrete that they could look at, we were just kind of debating these questions, and then coming up with ideas and voting on them. I think they found that really difficult to do. [P028; CI]*

4.3.2.4.4 Theme 4 summary: Barriers to stakeholder engagement in setting progression criteria and making progression decisions

In summary, although researchers perceived that involving multiple stakeholders in discussions around progression criteria and progression to be beneficial, this was challenging in practice and only very few researchers stated that this was possible to do. Barriers included lack of time, lack of information on who to engage and how, and lack of familiarity and understanding of the concept of progression criteria, and sometimes pilot trials more generally.

4.3.2.5 **Theme 5: Lessons learned from doing the pilot trial and their impact on progression criteria applicability**

Many participants described how they viewed pilot trials as opportunities to learn. They learned from what did and did not work and changed aspects of their pilot trial in response to these lessons. This was illustrated by one CI who stated that in their view *'the great thing about a pilot trial is you can't do it wrong because it is all about learning'*. From

their perspective, there was no expectation to know everything, instead it was *'a time where you can be open and honest before going into the main trial'*.

Participants described learning from unexpected challenges they faced during their pilot trial. Broadly, the challenges that participants described that fell into two categories, those that are: (1) external to the pilot trial (for example a change to the trial setting), or (2) internal to the pilot trial design but unanticipated (for example an unforeseen problem with the intervention or methods).

Lots of participants described making changes or adaptations to pilot trials throughout their conduct, and one CI shared an example of how these changes had impacted the applicability of their progression criteria.

4.3.2.5.1 Adapting the pilot trial throughout its conduct

Researchers described that lessons that they had learned whilst running their pilot trial could result in making adaptations and amendments to improve their trial design. For example, one CI described drawing on findings from qualitative research to alter or refine the intervention and trial processes throughout the pilot trial. They said that as a result the pilot trial they ended up with looked different to their initial design – and it was their initial trial design that the progression criteria were based on.

> *The qualitative work was actually used to refine the intervention and the trial processes that were delivered as we went along […] What we ended up with was a trial design and an intervention that was slightly different to what we started with […] If we went to full trial, it would be more closely aligned to what we finished with than what we started with. [P004; CI]*

Some trial statisticians drew parallels between the flexibility of an external pilot trial and that of an adaptive trial. They described how small and frequent changes made throughout the pilot can lead to tricky statistical problems in the analysis:

> *It sounds like really tricky statistical problems because you've really got a dynamic process with changes that are happening all the time, it's really like another adaptive trial that you're actually doing just not from a statistical angle. [P003; Trial statistician and trial methodologist]*

4.3.2.5.2 Potential implications of these changes for progression criteria

One CI described how the changes they had made to their pilot trial impacted on their progression criteria. They described that changing how they delivered their intervention, due to unforeseen circumstances, meant that their fidelity progression criteria was no longer applicable. This participant recalled feeling unclear about how to address progression criteria that were no longer relevant to the pilot trial design. They opted to discuss this with their TSC and decided to keep the progression criteria but alter the way that it was defined so that fidelity was still assessed, but in a different way:

> *We had an interesting experience where because we changed the intervention from face-to-face delivery through to remote delivery what that meant was that, for reasons that I won't go into, the intervention has to be delivered by a single site rather than multiple sites […] And so the competency progression criteria and the fidelity criteria, they didn't really make any sense anymore because it's one therapist or maybe two therapists that you would be assessing. [P021; CI]*

When asked whether participants would consider making changes to their progression criteria, in general researchers were against this practice and considered it to be

inappropriate. One trial statistician suggested that instead, researchers should report transparent and honest reasons about why progression criteria are no longer applicable:

> *I'm not sure that changing the criteria is the best way to go about it, I think what you want to do is abandon your criteria at the end of the trial and to give like really transparent honest reasons about why you don't think its applicable anymore. [P003; Trial statistician and trial methodologist]*

One trial statistician described that in their opinion researchers should publish more *'lessons learned papers'* to share their pilot trial findings, and better account for changes that they made to their pilot trial design and how these changes informed the definitive trial. In their opinion this would avoid mistakes being repeated by other researchers. However, they considered that this might not be a popular approach as it requires researchers to be comfortable with the implication that they did not know as much as they initially thought:

> *What I'm leading up to say is we need more qualitative lessons learned papers but that implies that you didn't know as much as people think you might have known [P029; Trial statistician]*

4.3.2.5.3 Theme 5 summary: Lessons learned from doing the pilot trial and their impact on progression criteria applicability

In summary, many researchers stated that they consider pilot trials to be learning opportunities and described making iterative adaptations and amendments to their pilot trial throughout its conduct. Some researchers described how these changes can directly, or indirectly, affect the applicability of their progression criteria. Researchers were generally unclear about how to address progression criteria that are no longer applicable.

4.3.2.6 **Theme 6: Factors, beyond the progression criteria, that inform the progression decision**

Expanding on the previous theme, participants were generally conflicted on the extent to which they relied on progression criteria to inform their decision about feasibility. Many participants shared that progression decision making is *'not black and white'* and can be influenced by other factors.

4.3.2.6.1 Progression decision making is often not black and white

Some participants shared experiences of pilot trials that had met all their progression criteria, so they considered feasibility to be obvious. However, this was not true for all participants. One participant described the scenario of meeting all progression criteria, yet the pilot trial did not work in practice because there were additional considerations, beyond the progression criteria, that meant their trial was not feasible:

> *I think if anything, the trial showed that yeah you can have all the criteria but it still may not be something that's worth continuing with if you have other factors [P012; Trial Manager]*

Many participants described that their pilot trial had met some, but not all, of their progression criteria. These participants expressed that progression decisions were often more complex, as they had to *'balance'* those aspects of the pilot trial that worked well with the problems they had faced to make an informed decision about feasibility. One CI shared that his advice to other researchers would be to think in detail about how they would handle the *'very realistic eventuality'* that they only meet some of their progression criteria and prepare for it rather than regarding it as an *'unlikely or worst-case scenario'*. This complex decision-making process was exemplified by one trial methodologist who

described that while progression criteria might present a *'nice algorithm'* to help guide researchers to a progression decision, in practice this is not always as straightforward. In their experience, other factors including a good signal of efficacy and an enormous number of practical problems, also informed this decision:

> *But I felt… well, we all felt… it was really important to have some criteria because we generally thought how on earth are we going to make a decision at the end? How are we going to balance up the fairly good signal around clinical efficacy compared with the enormous amount of practical problems we'd had? So, we wanted a nice algorithm but, in fact, we didn't get one. [P026; Trial methodologist and senior trial researcher]*

Participants shared that a signal of efficacy, findings from qualitative research, contextual considerations and continuity and enthusiasm of the research team were also key drivers of pilot trial progression.

4.3.2.6.2 Signals of efficacy

No participant described conducting a pilot trial with the primary intention to assess efficacy. However, some perceived that observing a 'signal of efficacy' can influence the progression decision. These participants were conflicted about the potential impact of demonstrating a signal of efficacy on progression: while some perceived that demonstrating a signal of efficacy would facilitate progression, others perceived that this could be a potential barrier. On balance, more participants suggested that pilot trials are more likely to progress if they demonstrate a signal of efficacy, because the research team would have more enthusiasm to continue with a trial that showed promise:

> *We'd just tickled statistical significant difference. So it was small numbers. So one of the stats guys was like well I hope you're not deciding to progress to try and apply for money just because it looks*

like it might work. Which we weren't, but that was something that people had said oh that's interesting. [P011; CI]

Yet this did not reflect the experience of all participants. One trial statistician described that in their experience demonstrating a signal of efficacy deterred further funding investment, because the funders considered that the pilot trial has already demonstrated an effect therefore a definitive trial was not needed:

One [trial had] quite a large sample size for a pilot study and we showed actually a between-group difference. Even though statistically speaking we shouldn't be doing that or it's not what anybody wants to see, and we had veered away from showing the P-values or anything so it was kind of like confidence interval for between-group difference, the confidence interval was greater than 0, so you know that kind of stopped it a little bit and the funders were a bit uneasy because it's almost as if you've shown effect already. [P007; Trial statistician; trial methodologist]

Just as there were mixed opinions about how demonstrating a signal of efficacy might influence pilot trial progression, there were also mixed opinions about whether it is appropriate to look for signals of efficacy in pilot trials altogether. While no participants considered that this should be the primary aim of the pilot trial, one experienced trial statistician described feeling comfortable with this practice. They considered not looking for signals of efficacy to be a 'lost opportunity'; they described how using accumulating information about efficacy to guide trial design decisions is accepted practice for adaptive trial designs, and that in their view this principle should also apply to external pilot trials:

In an adaptive trial we use accumulating information about efficacy to make decisions about whether to progress or not. So to me it's a lost opportunity when we don't try to include the efficacy signals, whether from external pilot trial or not, to make decisions about whether we need to progress or not. [P005; Trial statistician and trial methodologist]

4.3.2.6.3 Findings from qualitative research

When asked whether qualitative research findings informed progression decisions, most participants emphasised the importance of considering qualitative data to help *'build a picture'* about the pilot trial, providing explanation and context for whether progression criteria were or were not met. Some trial statisticians described how qualitative indicators of feasibility can often be equally, if not more, important than quantitative indicators. This view was shared by many trial statisticians who described a preference towards qualitative interpretations of pilot trials, suggesting that they might be more appropriate than relying on progression criteria alone. One trial statistician said:

> *So I'm going to say something you wouldn't expect a statistician to say, I think it's very hard to quantify what you learn from a pilot study. And there's a lot of contextual factors that don't equate neatly into usual metrics. [P029; Trial Statistician]*

Another described that in their opinion the feasibility of a pilot trial should be first understood in a qualitative way, and then if appropriate quantitative predictions should be made about what could happen in the future definitive trial:

> *I think what you want to do is just do the pilot, get some information about what's happened, understand it like in a qualitative way, and then yes, maybe have some quantitative aspect after that where your taking information you've got and your making predictions about what's going to happen in the main trial. [P003; Trial statistician and trial methodologist]*

4.3.2.6.4 Contextual considerations

For some participants, the contextual considerations (e.g. those in relation to the challenges researchers described facing in the previous theme) had a bearing on pilot trial

progression. These challenges were unanticipated and so did not form part of the a priori specified progression criteria. To illustrate this one trial manager described how they had encountered a really high mortality rate in their pilot trial population. This had not been part of their progression criteria as it was an unanticipated problem, yet this was the thing that '*stole the headlines'* and indicated to the research team that the trial was not feasible.

> *The mortality rate was not included in the progression criteria but that was one of the big factors that obviously stole the headlines because if you're losing a third of the patients that's huge. So it was those unforeseen things [P012; Trial Manager]*

4.3.2.6.5 Stakeholder enthusiasm and continuity

Many participants described the importance of the research team in driving the progression of external randomised pilot trials. One trial manager described that in their perspective the CIs ability to drive enthusiasm and engagement with the pilot trial was a key component to its feasibility. In their experience a pilot trial with a disengaged CI was less likely to progress:

> *I think our issue was that we didn't have a CI that cared [P023; Trial Manager]*

Many CIs also described the importance of stakeholder continuity in driving pilot trial progression. They explained that a long delay between the external pilot and definitive trial can lead to changes to the research team. For example, they recalled trial managers leaving or moving to work on different studies, and some of the more junior CIs, e.g. those conducting their pilot trial as part of a fellowship, described the expectation that they return to clinical work once the fellowship was completed. These external pressures

and competing priorities that can result in changes to the research team following the external pilot trial can be a barrier to progression if the *'people knowledge'* is lost:

> *The people on the study are the clinical people, and if you have a gap your trial manager leaves and so on, and you're starting again a little bit. There's a bit of knowledge but it's mainly people knowledge I would say [P018; CI]*

> *I thought from my point of view is this going to be manageable to run while I do two more years of surgical training [P011; CI]*

4.3.2.6.6 Theme 6 summary: Factors, beyond the progression criteria, that inform the progression decision

In summary, researchers identified several factors that they considered in addition to progression criteria that inform progression decision making following an external pilot trial. These include whether there was a signal of efficacy, the findings from qualitative research that has been conducted, contextual considerations, continuation of the research team and their enthusiasm for the trial.

4.3.2.7 **Theme 7: Progression of external randomised pilot trials: Funding considerations and constraints**

In addition to the factors presented in the previous theme, researchers also described various challenges associated with the wider funding landscape that impact on pilot trial progression, as well as pilot trial design. Challenges identified include: (1) limited funding budgets available for individual pilot trials, (2) the potential inability to obtain further funding following pilot trial completion, and (3) the time associated with pilot trial progression.

4.3.2.7.1 Limited funding budgets

When asked about pilot trial funding, many researchers described that funding for individual pilot trials can be limited. Some researchers said that their pilot trials were delivered on a *'shoestring'* budget with their pilot trial design *'dictated by the cost-constraints'*. For some, this meant that intended elements of the pilot trial could not be delivered within the available budget. For example, some CIs were unable to include an embedded qualitative research study within their pilot trial because they did not have the funding to do so, even though as described in theme five (*lessons learned from doing the pilot trial and their impact on progression criteria applicability*), many researchers perceived qualitative findings to be important when considering trial feasibility. Similarly, one trial methodologist recalled using shorter-term outcomes in their pilot trial than they intended to use in the definitive full trial because it was *'probably too expensive to do a 12-month follow-up'*. As a result, for many researchers their pilot trial was not conducted as intended to truly pilot the definitive trial design.

> *We don't have that funding and we're always doing things on the cheap. We're always under pressure to reduce the costs. And to evaluate something there that isn't really all that close to what we do, and then jumping to the full trial [P029; Trial statistician]*

Some researchers described how funding availability also impacted which stakeholders they could engage in their pilot trial design. In theme four (*barriers to stakeholder engagement in setting progression criteria and making progression decisions*) I outlined how participants generally valued a multistakeholder approach to pilot trial design, however for some researchers this was not readily achievable. Most participants who had trial oversight roles described facing particular challenges of including the costs for pilot trial personnel and support, such as a CTU, qualitative researcher or health economist, in

their funding applications. To exemplify this, one trial manager described how their CTU is often unable to support pilot trials because doing so comes at a financial loss:

> *It's harder for CTUs to support RfPB now because the funding is so small, and the funding threshold hasn't gone up in light of salaries going up and every other inflation so we are increasingly having to turn investigators away and say we can't work on the RfPB because you basically can't afford a CTU or if we're doing it were doing it at a loss and then that becomes unsustainable [P010; Trial Manager]*

4.3.2.7.2 Time associated with pilot trial progression

As well as funding budgets, time was also a concern for many CIs, who described challenges associated with how long it took to proceed from their pilot trial to a future definitive trial. CI's described facing significant delays between their pilot and definitive trial while they disseminated their pilot trial findings and applied for definitive trial funding. One CI described how this process can take years and is not at all seamless:

> *The problem is that when you do an external pilot you have to wait for your external pilot to finish. You then have to analyse its results. You then have to publish them while simultaneously putting in another grant application. It then takes like 18 months to get through the other grant application. And what should be a seamless process is totally not [P020; CI]*

As outlined in theme six (*factors, beyond the progression criteria, that inform the progression decision*), researchers described how these delays could lead to changes to the research team and loss of *'people knowledge'*. Some CI's also described how these delays provided the opportunity for the wider research or healthcare landscape to change, and that this potentially limited the applicability of their pilot trial findings. For example, one CI described how a different research group started a trial that was recruiting from a similar population in a similar area after their pilot trial had completed. They shared their

concerns that this competing study would limit the recruiting potential of their definitive trial, and that their expected recruitment rate might now be quite different to that observed in their pilot study. Another CI described how the healthcare settings often change much faster than research is done. This posed the risk that the pilot trial might be assessing a definitive RCT that was addressing an outdated research question, or was studied in an outdated context, by the time it started.

> *Things are always changing within healthcare, at a rate that's much faster than you can keep up with when you're doing research. [P028; CI]*

Some researchers suggested that delays following external pilot trials can be further exacerbated where pilot trial funding is from non NIHR sources, for example charities, because there is less of a 'natural pathway' to definitive trial funding:

> *With [trial name] we may have regretted not going for research for patient benefit. And that's because there's a very natural pathway between the RfPB and then the future funding streams. If you get pilot funding there then you may well get funding elsewhere as well from NIHR. [P021; CI]*

4.3.2.7.3 Inability to obtain further funding

As described in theme one (*divided opinions on the value of progression criteria*), some participants considered further funding to be their ultimate criteria for pilot trial progression. Many researchers described facing challenges with obtaining further funding following their pilot trial, even if all progression criteria were met. One CI in this situation described how it is a 'big disappointment':

You can do a brilliant pilot study and everything goes absolutely to plan; you recruit, you show likely effectiveness and cost effectiveness and it still doesn't get funded for the full study. So, this is a big disappointment. [P031; CI]

Some senior researchers offered an explanation for this, suggesting that there might be more funding available for pilot trials than for definitive trials (not based on total spending, rather based on number of trials). One CI suggested that perhaps researchers and funders should consider more broadly whether as many pilot trials should proceed to definitive trials. They described how resources are wasted where external randomised pilot trials are conducted, their findings indicate that they are feasible, yet they do not progress further because funding for further research is not awarded. One trial statistician described that this might be causing a 'bottleneck' of pilot trials flooding the research landscape:

I'm not saying it's causal, but I think the way that funding mechanisms are set up does incentivise certain types of research behaviour. Researchers are a little bit chase-the-money. And RfPB and CSO in Scotland and their funding envelopes have set up a situation where it's quite acceptable and lucrative to apply for external pilots on a regular basis. […] There is a supply and demand issue that there's probably more demand for funding successful external pilots than there might be funding to do definitive trials. So, there's a bottleneck [P025; Trial statistician and senior researcher]

In parallel to this suggestion, many participants also described how they had conducted external pilot trials upon funder request, because they had not obtained funding for a definitive RCT, or because the CI was less experienced.

I did have an NIHR application that went in, and they told me that doing such a big study for someone of my experience was unachievable [P011; CI]

In response to these challenges, some researchers described their hope for a more streamlined route of progression from a feasible external pilot trial to the future definitive trial. Some suggested that there could be an 'understanding' with funders that if the pilot trial goes well there is a good chance that a definitive trial would be funded. Others suggested that the funding process should be sped up or fast tracked, so there is a shorter time frame between an external pilot finishing and definitive RCT starting. Some described that if there were minimal changes made during the pilot trial, there's a benefit to funders (as well as researchers and trial participants) in allowing an external pilot trial to transition seamlessly into a definitive RCT. As a result what might initially start as an external, standalone pilot trial might resemble the design of an internal pilot trial upon completion with the data collected contributing to that of the future definitive trial. Some researchers described how in exceptional cases certain funders had facilitated this streamlined progression, but that this was far from the norm, with one saying:

> *You want to be able to write it as an external that you can go straight in and carry on. And that you have a checkpoint and then you get the rest of the funding. Definitely. [P026; Trial methodologist and senior trial researcher]*

4.3.2.7.4 Theme 7 summary: Progression of external randomised pilot trials: Funding considerations and constraints

In summary, researchers described inefficiencies with pilot trial funding and the pilot to definitive trial research pathway. Some researchers were unable to obtain further funding following a pilot trial that proved to be feasible, and others faced slow progression and significant delays between their pilot and definitive trial. Many researchers expressed their desire for a faster and more streamlined route of progression from pilot trial to further research funding.

4.3.2.8 Overarching theme: A one size approach to progression does not fit all

A common thread across all themes was the highly context dependent nature of external pilot trials. I therefore developed the overarching theme, *'a one size approach to progression does not fit all'*, to illustrate this broader understanding. I found that there is not one approach that fits all trials, and trial teams, for the development of progression criteria and progression decision making. To illustrate this view, one participant said:

> *It's not a one size fits all, so there's always a bit of room for a… or there needs to be some room for context [P031; CI]*

Prespecification of progression criteria at the start of the pilot trial is considered a way to avoid bias in progression decision making at the end of the pilot trial. However, progression criteria might not always be as transparent as they appear due to inconsistent methods of development and the potential for criteria to be biased by personal vested interests of stakeholders to see pilot trials progress. A lack of resources and guidance for developing progression criteria, combined with limited time and funding, can contribute to inappropriate criteria being set. Researchers considered it important to get the perspectives of different stakeholders when developing progression criteria to avoid potential '*spin'* of pilot trial findings – where conclusions are biased to favour feasibility to meet vested interests of progressing the research forward. However, members of pilot trial research teams can have different views on the importance of progression criteria when interpreting pilot trial findings. This can mean that reaching a conclusion about feasibility that all researchers agree on can be challenging, as '*feasibility'* of the same pilot trial may be interpreted differently by stakeholders who value progression criteria to different extents.

Looking beyond the progression criteria, many researchers described how the progression decision is influenced by additional factors, such as unanticipated events faced during the pilot trial (i.e. are internal to the pilot trial but were not pre-empted) including challenges with delivering the intervention, qualitative research findings, and signals of efficacy, and factors outside (i.e. external to) the pilot trial such as changes to the setting, trials competing for the same population, continuity of the research team, and availability of definitive trial funding. Participants articulated a preference towards the more flexible *'stop-amend-go'* format to progression criteria, to accommodate the contextual nature of external pilot trials, and acknowledge that progression decision making is *'not black and white'*.

Despite the concerns of some researchers that progression criteria can be easily flawed, they are still considered to be an important aspect of research funding applications and are viewed in high regard by funding panellists to support pilot trial funding decisions. This aligns with the perceptions of some researchers who stated that in their opinion pilot trial progression ultimately depends on *'whether you can make a credible case to your funder that they should invest in this next stage'*, and that progression criteria can help make that case. However, researchers shared varied experiences to indicate that there is no guarantee that meeting all progression criteria will result in a successful funding award, implying that external factors within the wider research and funding landscape can also have a bearing on pilot trial progression.

4.4 Discussion

4.4.1 Summary of findings

This study presents key stakeholders' experiences and perspectives of progressing from an external randomised pilot trial to a definitive RCT, and how progression criteria inform these decisions. Researchers had mixed perceptions of the value of progression criteria and described inconsistent approaches to their development and use. This could result in setting inappropriate progression criteria that are biased by personal interests of key stakeholders or re-using criteria from other pilot trials without careful consideration of their applicability. Researchers suggested that a multi-stakeholder approach to setting progression criteria and making progression decisions can help avoid biases, as well as avoiding describing pilot trials that do not progress as *'failed'*. However, they also shared that in reality effective involvement of multiple stakeholders presented major challenges and many suggested that more guidance and resources would be beneficial to facilitate stakeholder involvement in this process.

My findings also highlight preference amongst some researchers towards qualitative interpretations of feasibility, drawing on lessons learned and experience from doing the pilot trial itself. Researchers described several other factors, in addition to qualitative interpretations of feasibility, that informed their progression decisions. These include looking for signals of efficacy, contextual considerations, continuation of the research team and enthusiasm for the research. For many researchers, the ultimate barrier to pilot trial progression was whether further funding could be obtained, even if all criteria were met. These findings led to the development of an overarching interpretive theme to

capture the highly context-dependent nature of external pilot trials: a one size approach to progression does not fit all.

4.4.2 Findings in context

Researchers endeavoured to apply many of the tips that have been previously proposed for progression criteria in internal pilot trials [22] to their external pilot trials, including the stop-amend-go approach and striking a balance between flexibility and firmness. However, some were not as easily achieved, for example agreeing and assessing criteria with an independent oversight committee. In addition, I identified inconsistencies between researcher and PPI representative experiences. Researchers were conflicted on whether, and how, to involve PPI in key decisions about progression criteria, with many suggesting that they are primarily involved through their roles on TMGs and TSCs. However, PPI representatives rarely provided their perspectives on how they had contributed to these discussions.

In Chapters 2 and 3 I identified that although many pilot trials include a qualitative research component, progression criteria are almost always described in numerical terms e.g. as specific targets to meet. The value of including qualitative research in pilot trials has previously been highlighted [75], and many researchers interviewed also emphasised their perceived benefit of doing qualitative research in pilot trials. Whilst many researchers considered qualitative findings when determining feasibility, they generally did not describe including qualitative findings in their progression criteria. Researchers also described how progression criteria are based on a priori assumptions and so do not account for unforeseen events that can occur during the pilot trial, their experiences of conducting the trial and any lessons learned from doing the pilot trial. This could indicate that the shift towards framing pilot trial findings around formal prespecified progression

criteria restricts how researchers consider, interpret and determine feasibility, with increased focus on addressing anticipated problems rather than focusing on identifying and appraising potential solutions to problems that were faced during the pilot trial [82].

Some researchers questioned the appropriateness of setting progression criteria where they had no existing data to inform them. Others considered criteria to be altogether more applicable to internal pilot trials where meeting them would almost certainly result in progression to the main RCT phase, for which funding had already been awarded. For external pilot trials meeting progression criteria did not necessarily guarantee progression, instead, some researchers described how obtaining funding was the ultimate barrier and perhaps an overriding progression criterion. This supports previous research which identified the potential for wasted resource and opportunities where feasibility studies that were considered to be feasible do not proceed to future research [30].

My findings also suggest that pilot trials are not always conducted as intended to truly pilot the future definitive trial design due to limited funding awards. Researchers described conducting pilot trials with shorter outcomes, without adequate support and expertise, or without embedded qualitative research. Some researchers described how the funding landscape itself can also present barriers to pilot trial progression. Significant delays between the external pilot and definitive trial can present an opportunity for the setting in which the trial is conducted to change (i.e. the healthcare context moves faster than the research), thus limiting the applicability of pilot trial findings and potentially disregarding the need for the definitive trial altogether.

4.4.3 Strengths and limitations

A strength of this study is the inclusion of a diverse sample of participants with a range of skills and experiences. A further strength is the comprehensive range of strategies that I used to ensure trustworthiness and rigour of this study including reflexivity, peer review and respondent validation. I also followed best practice and pursued an iterative approach to the research, simultaneously collecting and analysing data as I went along so that I could iteratively update my sampling strategy and interview topic guide, allowing myself to be guided by my early analytical findings.

A key limitation is the lack of PPI representatives identified who consented to participate in this study. PPI representatives often contribute to TMGs and independent TSCs. Recommendations have been made to involve the TSC in assessing progression criteria for internal pilot trials [22] so I made the assumption that this might also be the case for many external randomised pilot trials. PPI representatives were particularly difficult to sample, and I was only able to interview six. Although I asked researchers about their experiences of involving PPI representatives in discussions around pilot trial progression and progression criteria, exploration of the views and experiences of PPI representatives themselves is an area for further research (further described in Chapter 7) that would require more time and focused attention.

A further limitation is the potential for social desirability bias [209], where study participants might have responded to interview questions to present a reality that aligns with that they perceive to be most acceptable. However, I employed strategies to mitigate against this. I provided clear information about the study in advance of the interview which detailed how the interview data would be managed and used, and I outlined my approaches to maintain confidentiality and anonymity. I also made efforts to establish

rapport with study participants both before and during the interviews by presenting a positive, friendly attitude and showing genuine interest in the experiences that participants were sharing with me.

Finally, my findings are also limited to a sample of study participants based within the UK so it is unclear whether these findings are generalisable outside of the UK. I found describing the sample itself to be quite challenging due to the overlapping roles that study participants held. Upon reflection, if I was to conduct qualitative research with a similar sample in the future, I would consider sending study participants a short questionnaire prior to interview to confirm information such as affiliations to funding panels and journals to aid interpretation of the data. Perhaps a more efficient sampling strategy would have been to first sample and interview CIs, and then broaden my sample to speak to other members of trial teams based on the data I was collecting from CIs. This might have avoided interviewing as many PPI representatives who were not involved in discussing progression criteria.

4.4.4 Chapter summary

This chapter presented the methods and findings of a qualitative interview study to examine how progression decisions are made following external randomised pilot trials. An overarching interpretative theme was developed to capture the highly context-dependent nature of progression decision making in external pilot trials: a one size approach to progression does not fit all. Although many (but not all) researchers considered progression criteria to be important, they also highlighted that a lack of knowledge, time and resources for developing progression criteria can be challenging, and many suggested that more guidance would be beneficial. Progression criteria are rarely the only consideration informing the decision to progress to future research. Other

considerations I identified included: signals of efficacy, qualitative interpretations of feasibility, contextual considerations, continuation of the research team and enthusiasm for the research. Many described that the ability to obtain further funding was the ultimate barrier to progression (i.e. an overriding progression criteria).

Chapter 5 An international web-based survey study to explore the feasibility and progression of a cohort of external randomised pilot trials

Associated research outputs:

The protocol for this chapter is registered on the *Open Science Framework* [1] and the results have been accepted for publication in *Trials* [2].

[1] Mellor K, Dutton S J, Hopewell S. Feasibility and progression of a cohort of external randomised pilot trials: A web-based survey study. *OSF* 2021. doi:10.17605/OSF.IO/D28HR

[2] Mellor K, Dutton S J, Hopewell S. Feasibility and progression of a cohort of external randomised pilot trials: A web-based survey. *Trials* 2022. In press.

5.1 Chapter introduction

5.1.1 Rationale for web-based survey study

The qualitative research study, presented in Chapter 4, highlighted that sometimes researchers are unable to obtain funding for further research despite demonstrating feasibility of their pilot trial. This supports the findings of a previous review of pilot trials that were funded by NIHR RfPB which described that although a pilot or feasibility study might suggest that a definitive trial will be feasible, this does not guarantee that funding applications for the main trial will be successful, or that the research team will pursue funding for the definitive study [30]. This lack of progression where a future study is deemed to be feasible has been identified as a source of research inefficiency and waste [30]. This phenomenon has also been observed in the context of specific medical specialties. For example, a previous analysis of pilot trials published five or more years ago in six anaesthesia journals suggested that around half (54%) progressed onto definitive studies, despite all reporting the intention to progress to a future trial [38].

Previous assessment of pilot trial progression could be biased by the inclusion of pilot trials that were published prior to wide endorsement of the CONSORT extension for PAFS [24] and so might not be a good reflection of current practice. The publications included in the methodological review, presented in Chapter 2 were all published after publication of the CONSORT extension for PAFS, hence present a more recent sample of external pilot trials. In this chapter I present the methods and findings of an international web-based survey to explore the outcomes in terms of feasibility and progression of the recent cohort of external randomised pilot trials that were studied in Chapter 2.

5.1.2 Aim and objectives

I aimed to explore the outcomes, in terms of trial feasibility and progression, of the recent cohort of external randomised pilot trials that I identified and included in my earlier methodological review, presented in Chapter 2 [210].

The primary objective was to examine how trial investigators of a recent sample of external randomised pilot trials published between January 2018 and December 2019 assess future definitive trial feasibility both where trialists had and had not prespecified formal progression criteria in their pilot trial publications.

The secondary objectives were to:

- determine how many trialists indicated that their pilot trial was feasible, and whether their pilot trial progressed to a future definitive trial
- determine how well progression criteria informed the assessment of trial feasibility from the trial investigators' perspective
- examine how investigators that did not report progression criteria in their pilot trial publications decided whether their pilot trial was feasible
- identify potential barriers to pilot trial progression that trial investigators face

5.2 Methods

5.2.1 Protocol and registration

I published a protocol for this study on the Open Science Framework, reference osf.io/d28hr [211]. The NDORMS Information Governance Manager helped me to produce a Data Protection Agreement (DPA) for this research. The DPA was approved by the Departmental Administrator and Senior Information Risk Owner and was reviewed at 6-monthly intervals throughout the study. I received ethical approval for this study from The University of Oxford MS IDREC, reference R78375/RE001. My reporting of this chapter has been guided by established reporting guidelines and follows the 2021 Consensus-Based Checklist for Reporting of Survey Studies (CROSS), presented in Appendix E1 [212].

5.2.2 Study design

This study is a cross-sectional web-based survey that is underpinned by a pragmatist ontology and epistemology (these terms were described in detail in Chapter 4 and are included in the glossary). Cross-sectional surveys have previously been conducted to address other important research questions related to clinical trial methodology [213–215] and are a useful tool to provide a snapshot of research practice at one point in time. I used a survey design that contained both closed and open-ended questions to obtain a comprehensive understanding of the process of trial feasibility assessment from the pilot trial investigators' perspective [88]. Closed questions allowed me to collect data that was easily quantifiable and could be coded (such as the number of investigators who considered their pilot trial to be feasible), and open-ended questions allowed respondents to provide information that was not limited to pre-defined options (e.g. to describe

barriers to pilot trial progression based on their knowledge and experiences) or provide further detail on previous answers given.

I considered a web-based survey to be the most appropriate method of data collection compared to alternatives (such as a conventional paper survey or face-to-face methods) for multiple reasons: I included an international sample of participants, and a web-based approach allowed me to reach them quickly and cheaply; I was able to electronically link information about the study to the data capture platform to provide all necessary information that study participants needed to make an informed decision about participation without overwhelming them; I was able to apply logic and branching rules to ensure surveys were as user friendly as possible [216], and include a pre-populated question function to capture respondents' email addresses so I could target follow-up emails only to corresponding authors who had not completed the survey (i.e. non-responders).

I used conventional content analysis to analyse qualitative data collected through open-ended survey questions. Content analysis is less interpretive than other qualitative research methods such as thematic analysis that was used in Chapter 4. It operates closer to the surface of data and is considered more of a descriptive or aggregative method as opposed to interpretative [208]; therefore it is well suited to analyse data that is brief and contains less information such as short survey responses [217]. I conducted a *manifest analysis*, describing what respondents said (using their words where possible) and staying very close to the data, as oppose to a *latent analysis* where an interpretative approach is used to identify deeper underlying meaning [218]. There are different approaches to content analysis described in the literature, including conventional, directed or summative [219]. I used a conventional approach and developed codes directly from the

data [219]. I considered this to be the most appropriate method because the existing research literature on external pilot trial progression decision making is limited, so I wanted to avoid using preconceived codes, that might have omitted things of importance, and instead inductively developed descriptive codes based on the data collected.

5.2.3 Sample characteristics

The sample of trial investigators I included in this study were the corresponding authors of the pilot trial publications that I identified in the methodological review, reported in detail in Chapter 2.

To summarise the methods presented in Chapter 2, I searched four journals through PubMed for pilot trial protocol and results publications between January 2018 and December 2019 inclusive: *British Medical Journal (BMJ) Open*, *Pilot and Feasibility Studies (PAFS)*, *Trials* and *Public Library of Science (PLoS) One*. The search terms I used included '*pilot'* or '*feasibility'* in the title, and '*trial'*, '*study'* or '*protocol'* in the title or abstract [210]. I included 278 eligible randomised pilot trial publications published between January 2018 and December 2019 in the review, of which 160 (37 completed trials and 123 protocols) reported detailed progression criteria and an additional 118 (34 completed trials and 84 protocols) did not report formal progression criteria but did report a recruitment or sample size target for their pilot trial, see Figure B1.

5.2.4 Data collection

My approach to data collection followed two stages: In December 2021 I searched the literature for corresponding pilot trial result publications for all pilot trial protocols in the original sample, and I retrieved corresponding author's email addresses. Then, in January 2022 I conducted an international web-based survey of corresponding authors.

5.2.4.1 Searching for pilot trial results publications and corresponding author contact details

For the 207 pilot trial protocols identified in Chapter 2, I searched PubMed in December 2021 by author name, trial name or acronym, and I searched trial registries by trial registration number, to identify whether a pilot trial result publication had been published since the methodological review was conducted. I maintained a table in Microsoft Excel (Office16) to track whether I had identified a corresponding pilot trial results publication. Where a results publication was identified I checked to see whether progression criteria were reported. I then retrieved the publicly available corresponding authors contact email for each included pilot trial results publication, or the protocol publication where a corresponding results publication was not identified.

5.2.4.2 Web-based survey of corresponding authors

I produced four web-based surveys using Jisc online surveys (formerly Bristol Online Surveys), an easy to use and GDPR compliant online survey tool for developing, deploying and analysing online surveys [220]. I sent corresponding authors one of four survey versions based on whether their publication reported a pilot trial protocol or the results, and whether or not progression criteria were prespecified. Table E4 details the four surveys, and Figure E1 presents a survey decision flow diagram:

Table E4 Survey outlines

Survey number	**Publication type**	**Progression criteria***
Survey 1	Protocol	Yes
Survey 2	Results	Yes
Survey 3	Protocol	No
Survey 4	Results	No

*No: Did not report detailed progression criteria but did report prespecified targets relating to recruitment or sample size

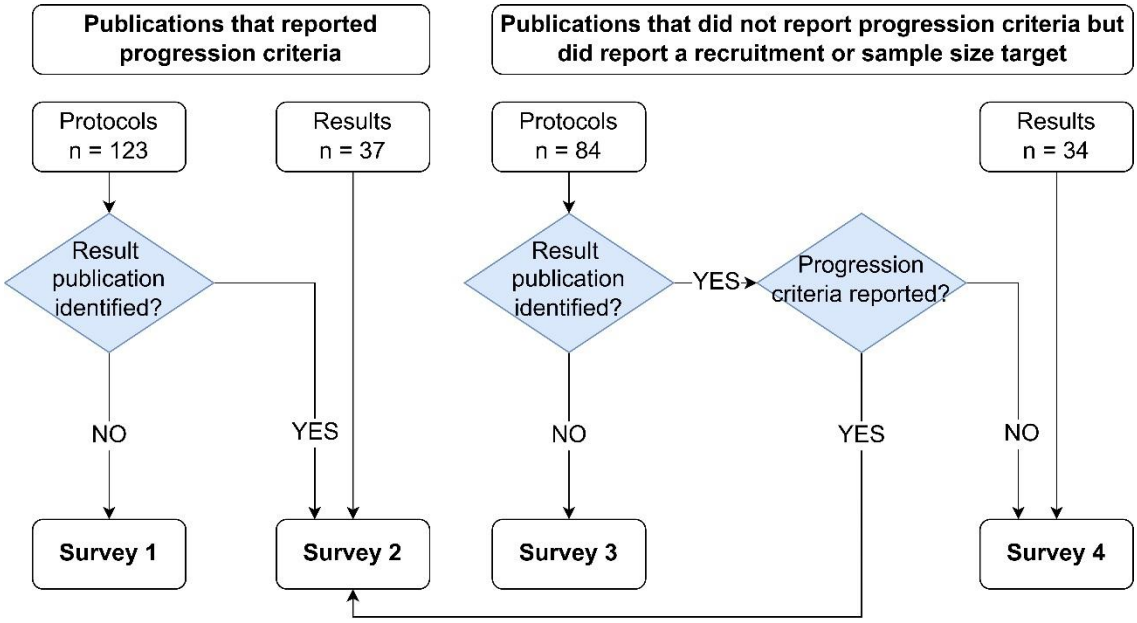


Figure E1 Survey decision flow diagram

I opened the surveys on Monday the 17th of January 2022. They were open for four weeks, closing on Monday the 14th of February 2022. I designed each survey to take between 5-10 minutes to complete. Surveys asked whether the pilot trial found a future RCT to be feasible, and whether the pilot trial has progressed to further research. Where publications reported progression criteria surveys asked whether they were met and whether any other factors informed the assessment of future definitive trial feasibility. Where publications did not report progression criteria surveys asked authors how they had determined feasibility and what this was based on.

The surveys for authors of pilot trial protocols (surveys 1 and 3) were the same as the corresponding survey for authors of pilot trial result publications (i.e. surveys 1 and 2, and surveys 3 and 4 respectively), except they included additional questions at the start to determine whether the pilot trial had completed, and whether the findings had been

published. Surveys did not collect any personal identifiable information about the respondent.

All surveys concluded with two open-ended questions that asked whether there was anything else that respondents would like to share regarding the findings of their pilot trial, and whether their pilot trial did or did not progress to a future definitive trial. These questions formed a 'safety net' to identify issues which might complement the previous questions, and allowed respondents the opportunity to elaborate or expand their previous responses further [221].

The pdf outline of one survey is presented in Appendix E2, and pdfs of all surveys are available from the Open Science Framework (reference osf.io/7jnvx) [222].

5.2.5 Survey development and administration

5.2.5.1 Survey piloting

Two trial statisticians based at the Centre for Statistics in Medicine (CSM) piloted two surveys (survey one and survey three, see Table E4). I also provided survey demonstrations to my supervisory team to obtain further feedback on functionality and design.

5.2.5.2 Survey administration

I used Mail Merge in Microsoft Word (Office16) to email each corresponding author to invite them to complete the survey. I personalised each email to include the corresponding author's name, the title of their publication, and provide a unique URL link to the appropriate survey that I had constructed within Jisc's survey access control. Personalised URLs allowed me to track survey completion, which would not be possible

if I had only provided a generic survey URL. Personalised URLs also inhibited multiple participation i.e. the same respondent completing the survey multiple times.

I emailed corresponding authors (email wording detailed in Appendix E3) on Monday the 17th of January 2022 at approximately 11am. I chose this date because it was sufficiently after the Christmas period that I anticipated that very few researchers would be on annual leave. Where I received automated email responses that provided a forwarding or alternative email address, I forwarded the email on.

To encourage a high response rate, I sent non-respondents a personalised reminder email two weeks after the initial contact email. I also invited all respondents to opt into a prize draw to win a £50 One4All voucher upon survey completion. I listed the email addresses of all respondents who entered the prize draw in Microsoft Excel (Office16) and used the rand() function to generate a random number value for each email address. I then selected the winner based on the lowest random number.

5.2.5.3 Informed consent

I provided all potential participants with an electronic information leaflet about the study that was based on the University of Oxford's Best Practice Guidance for internet-mediated research [223]. I provided this information (detailed in Appendix E4) as a pdf link from the Jisc website on the first page of each survey prior to the survey questions. The information included my contact details to allow participants to ask questions before completing the survey. Study participants provided electronic consent through the Jisc platform before they were able to proceed to the survey questions.

I informed study participants that the prize draw winner's email address would be shared with One4All to process the e-voucher, and One4All would hold their email address for

13 months for the purpose of issuing and managing the digital gift card, in line with the General Data Protection Regulation. By entering the prize draw, participants provided implied consent for me to share their email address with One4All if they were to win.

5.2.6 Data analysis

I produced descriptive statistics within Jisc to present the responses to the survey questions. I determined the number of pilot trials that indicated that a future definitive trial is feasible, feasible with changes to trial design, not feasible or unclear. I determined the extent to which progression criteria were met (where reported) and whether investigators considered progression criteria to be very helpful, somewhat helpful, not helpful or not a consideration when interpreting feasibility. I also determined the proportion of trial investigators who intend to conduct a future definitive trial, and whether they had obtained funding to do so.

I used conventional content analysis (described in section 5.2.2) [219] to analyse open-ended survey questions and have synthesised my findings using tables and narratively. I exported raw survey data from Jisc into Excel files, which I then imported into NVivo (v12) to facilitate this process. Content analysis involved coding the data, then counting the number of instances of coding units across different respondents to analyse the data [175]. I grouped codes with similar or linked properties into categories following a descriptive rather than interpretive approach [208] (i.e. describing the kinds, or types, of barriers to progression faced, as opposed to why those barriers exist or what has led to them). For example, I used content analysis to explore the changes that respondents intended to make to their definitive trial design (e.g. altering their recruitment strategy or adding more investigative sites). I also explored other factors, in addition to, or instead of, formal progression criteria, that trial investigators described considering when making

their progression decision, and reasons for pilot trial non-progression from the trial investigators' perspective. I then compared these reasons for non-progression to the indicators of feasibility that most often contributed to prespecified progression criteria, presented in Chapter 2, to assess whether barriers to progression are typically pre-empted at the start of the pilot trial.

Finally, I also used content analysis to analyse responses to the final two open-ended questions that aimed to capture any further information or comments from study participants. This allowed me to assess whether all relevant issues had been covered in the survey, document any new issues raised that had not been covered, and expand on earlier responses to supplement interpretation and analysis [221].

5.3 Results

5.3.1 Survey responder characteristics

The original sample of pilot trial publications, presented in detail in Chapter 2, included 278 randomised pilot trials (207 protocols and 71 results publications). I identified corresponding results publications for 111 of the 207 included protocols. The original sample included both a protocol and results publication for two trials, in these instances I obtained the corresponding author details from the results publication only.

I received 44 automated responses to my initial survey email: 29 were out of office responses, and 15 were automated mail server responses to notify that the email address was not recognised or no longer existed. Twelve of the 29 out of office responses provided an alternative forwarding email address that I forwarded the original email on to. For the 15 automated mail server responses I googled the email address to cross check against publicly available contact information to confirm accuracy. I found one instance where the corresponding author email address provided in the publication did not match the email address listed on the researcher's university webpage. In this instance I forwarded the original email to the email address listed on the webpage and notified the respondent of this inconsistency.

Five protocols that originally did not report progression criteria did in their results publication. I retrieved the email address of the corresponding author for all publications included in the final sample (96 protocols and 180 result publications), summarised in Table E5.

Table E5 Details of included publications compared to the original sample

Survey number	Publication type	Progression criteria*	Original	Final
Survey 1	Protocol	Yes	123	55
Survey 2	Results	Yes	37	108
Survey 3	Protocol	No	84	41
Survey 4	Results	No	34	72
Total**	-	-	278	276

*No: Did not report detailed progression criteria but did report prespecified targets relating to recruitment or sample size

**There were two instances where the protocol and results publications for the same pilot trial were included in the original sample

5.3.2 Response rates

The response rate varied across the four surveys from 19% to 41%, summarised in Table E6. In total, 98 of 276 trialists responded, giving an average response rate of 36% across all surveys.

Table E6 Survey response rates

Survey number	Publication type	Progression criteria*	Response rate	
Survey 1	Protocol	Yes	19/55	(34%)
Survey 2	Results	Yes	41/108	(37%)
Survey 3	Protocol	No	8/41	(19%)
Survey 4	Results	No	30/72	(41%)
Average	-	-	98/276	(36%)

*No: Did not report detailed progression criteria but did report prespecified targets relating to recruitment or sample size

In general response rates were lower from corresponding authors of pilot trial protocol publications compared to results publications. No study participants shared any reasons over email for not completing the survey, however two authors emailed to ask whether they should complete the survey since their pilot trial had not yet completed (I invited both to complete the survey).

Each of the four surveys asked respondents whether there was anything else that they would like to share regarding the findings of their pilot trial (37/98 responses provided), and about whether their pilot trial did or did not progress to a future definitive trial (40/98 responses provided). Although many responses were not applicable e.g. the respondent stated 'no' or simply provided a link to a publication, some responses did highlight further challenges with assessing future definitive trial feasibility, and barriers to pilot trial progression that trialists face. Examples are included throughout the results to supplement the findings.

5.3.3 Responses from trialists who reported a protocol publication

In total 27 (27/96, 28%) responses (Survey 1 19/55; Survey 3 8/41) were received from corresponding authors of protocol publications. These respondents answered additional questions at the start of their respective surveys about the current stage of their pilot trial and whether it had completed, presented in Table E7.

Note that these responses, from authors of protocol publications, are presented separately in this section because whether the pilot trial had completed indicated how much of the survey respondents could complete. For example, corresponding authors of pilot trial protocol publications who indicated that their pilot trial had completed or was in the reporting or dissemination stage were able to complete the full survey to answer questions about pilot trial findings in relation to feasibility assessment and progression decision making. Whereas, corresponding authors of pilot trial protocol publications who indicated that their pilot trial was in the planning and design, set up, or conduct stage were unable to provide responses to questions about pilot trial findings since their pilot trials had not yet completed.

Table E7 Survey responses from corresponding authors of protocol publications

	Total (n = 27)		Survey 1 (n = 19)		Survey 3 (n = 8)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Which of the following best describes the current pilot trial stage?						
Trial planning & design	2	(7%)	0	(0%)	2	(25%)
Set up	0	(0%)	0	(0%)	0	(0%)
Conduct	4	(15%)	3	(16%)	1	(13%)
Analysis	3	(11%)	2	(11%)	1	(13%)
Reporting or dissemination*	18	(67%)	14	(74%)	4	(50%)
Are the pilot trial findings published?*						
*Yes***	*5*	*(28%)*	*3*	*(21%)*	*2*	*(50%)*
No	*13*	*(48%)*	*11*	*(79%)*	*2*	*(50%)*
Do you plan to publish the pilot trial findings in the future? **						
Yes	*13*	*(100%)*	*11*	*(100%)*	*2*	*(100%)*
No	*0*	*(0%)*	*0*	*(0%)*	*0*	*(0%)*
Has the pilot trial recruitment period been extended beyond the original proposed timeframe?						
Yes	15	(56%)	10	(53%)	5	(63%)
No	12	(44%)	9	(47%)	3	(38%)

Responses presented were reported by 27 corresponding authors of protocol publications who completed surveys 1 and 3

*, ** Asterisks indicate where conditional formatting was used within the survey, i.e. only people who indicated that their pilot trial was in the reporting or dissemination stage were asked whether the findings were published

Most indicated that their pilot trial was in the reporting or dissemination stage (18/27, 67%). Of these, five respondents indicated that they had published their pilot trial findings, yet I did not identify these five publications when searching the literature. The other 13 respondents indicated that they had not yet published their pilot trial findings but intend to in the future.

More than half of the respondents outlined that they had extended their pilot trial recruitment period beyond their original proposed timeframe (15/27, 56%). Nine respondents described that their pilot trial was still in set up (2/27, 7%), conduct (4/27, 15%), or analysis (3/27, 11%) stage at the time of survey completion.

5.3.4 Responses from trialists whose pilot trial had completed

In total, 91% of all respondents (89/98, 91%) across all four surveys had authored publications for pilot trials that had completed by the time of survey completion. These respondents were therefore able to complete all their respective survey, and their responses have contributed to the data presented in the rest of this chapter.

5.3.5 Responses from trialists who reported progression criteria

Of the 163 corresponding authors of pilot trial publications that reported progression criteria, 55 (55/163, 34%) completed all of survey 1 and 2[1], see Table E8.

[1] Although 19/55 respondents completed survey 1, 5/19 did not complete the full survey as their pilot trials had not yet completed analysis, therefore 14 respondents completed all of survey 1

Table E8 Survey responses from trialists who reported progression criteria in their publication

	Total (n = 55)		Survey 1 (n = 14*)		Survey 2 (n = 41)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
What were the pilot trial findings in relation to the feasibility of a future definitive trial?						
Future definitive trial is feasible	25	(45%)	4	(29%)	21	(51%)
Future definitive trial is feasible with changes to design**	23	(42%)	8	(57%)	15	(37%)
Future definitive trial is not feasible	4	(7%)	1	(7%)	3	(7%)
Feasibility of the future definitive trial is unclear**	3	(5%)	1	(7%)	2	(5%)
***Do you intend to do any further feasibility assessment?*						
Yes	*6*	*(23%)*	*1*	*(11%)*	*5*	*(29%)*
No	*20*	*(77%)*	*8*	*(89%)*	*12*	*(71%)*
To what extent were the prespecified progression criteria met?						
Met all criteria	26	(47%)	5	(36%)	21	(51%)
Met some criteria	26	(47%)	8	(57%)	18	(44%)
Met none of the criteria	1	(2%)	1	(7%)	0	(0%)
Other	2	(4%)	0	(0%)	2	(5%)
How helpful were progression criteria in informing the assessment of trial feasibility?						
Very helpful	36	(65%)	10	(71%)	26	(63%)
Somewhat helpful	15	(27%)	3	(21%)	12	(29%)
Not helpful	1	(2%)	0	(0%)	1	(2%)
Not a consideration	3	(5%)	1	(7%)	2	(5%)
Did other factors (in addition to progression criteria) inform the assessment of trial feasibility?						
Yes	34	(62%)	8	(57%)	26	(63%)
No	21	(38%)	6	(43%)	15	(37%)
Do you intend to conduct a future definitive trial?						

	Total (n = 55)		Survey 1 (n = 14*)		Survey 2 (n = 41)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Yes	37	(67%)	9	(64%)	28	(68%)
Has funding for the definitive trial been applied for?						
Yes	*19*	*(51%)*	*3*	*(33%)*	*16*	*(57%)*
Funding awarded	*12*	*(63%)*	*2*	*(67%)*	*10*	*(63%)*
Funding not awarded	*4*	*(21%)*	*1*	*(33%)*	*3*	*(19%)*
Application outcome unknown	*3*	*(16%)*	*0*	*(0%)*	*3*	*(19%)*
No	*18*	*(49%)*	*6*	*(67%)*	*12*	*(43%)*
What best describes the current stage of the definitive trial?						
Trial planning & design	*25*	*(68%)*	*7*	*(78%)*	*18*	*(64%)*
Set up	*5*	*(14%)*	*1*	*(11%)*	*4*	*(14%)*
Conduct	*5*	*(14%)*	*1*	*(11%)*	*4*	*(14%)*
Analysis	*0*	*(0%)*	*0*	*(0%)*	*0*	*(0%)*
Reporting/dissemination	*1*	*(3%)*	*0*	*(0%)*	*1*	*(4%)*
Did not answer	*1*	*(3%)*	*0*	*(0%)*	*1*	*(4%)*
No	15	(27%)	5	(36%)	10	(24%)
Did not answer	3	(5%)	0	(0%)	3	(7%)

Responses presented were reported by 55 trialists who reported progression criteria in their publication, and whose pilot trials had completed

*Although 19 respondents completed survey 1, only 14 described that their pilot trial was in the reporting or dissemination stage and so responded to the questions presented in this table

**Respondents were asked whether they would conduct further feasibility assessment only where they considered their pilot trial to be feasible with changes or where feasibility was unclear

In total, 87% of respondents stated that their pilot trial was feasible (25/55, 45%) or was feasible with changes to trial design (23/55, 42%). Only four respondents stated that their pilot trial was not feasible (4/55, 7%) and three stated that feasibility was unclear based on their pilot trial findings (3/55, 5%). All three provided reasons for why they considered feasibility to be unclear, including challenges with recruitment, Covid 19, low adherence to the intervention, and challenges with implementing the intervention in the current context given availability of funding. Of the 26 respondents who stated that their pilot trial was feasible with changes to its design, or that feasibility was unclear, six described the intention to conduct further feasibility assessment (6/26, 23%).

Equal proportions of respondents described meeting all their progression criteria (26/55, 47%) as those who described meeting some of their progression criteria (26/55, 47%). Only one respondent described meeting none of their progression criteria (1/55, 2%). Two respondents instead stated that they had not provided prespecified progression criteria. I reviewed these two respondents' publications, and both detailed how they planned to assess feasibility to decide whether to progress to a definitive RCT, which I interpreted to be their progression criteria, although one did not state any specific quantifiable targets against which feasibility would be assessed (i.e. non-numerical).

When asked how helpful respondents found progression criteria to be in informing assessment of feasibility, the majority stated that progression criteria were very helpful (36/55, 65%). Fifteen respondents considered progression criteria to be somewhat helpful (15/55, 27%), one stated that progression criteria were not helpful (1/55, 2%) and three stated that progression criteria were not a consideration (3/55, 3%), two of these three respondents had stated that they did not have prespecified progression criteria.

Over two thirds of respondents reported the intention to conduct a future definitive trial (37/55, 67%) with the majority of these stating that their intended definitive trial was in the trial planning and design stage (25/37, 68%). Fifteen respondents reported that they did not intend to do a future definitive trial (15/55, 27%) and three did not provide a response to this question (3/55, 5%). Just over half of those that stated the intention to do a future definitive trial had applied for further funding to do so (19/37, 51%). Of these, 12 had been awarded funding (12/19, 63%), four were unsuccessful (4/19, 21%) and three had not yet received their application outcome (3/19, 16%).

Nineteen respondents specified the funding sources they had applied to for their definitive trial. These included the NIHR (12/19, 63%; eight awarded, three unsuccessful, one outcome unknown), the Australian National Health and Medical Research Council (3/19, 16%; all three awarded), the Health Research Council of New Zealand (1/19, 5%; unsuccessful), the Canadian Institute of Health Research (1/19, 5%; outcome unknown), one charitable foundation (1/19, 5%; awarded), and one respondent specified that they had applied for a government funding source (1/19, 5%; outcome unknown).

5.3.6 Responses from trialists who did not report progression criteria

In total 34 respondents (34/113, 30%) completed all of survey 3 and 4[1], see Table E9.

[1] Although 8/41 respondents completed survey 3, 4/8 did not complete the full survey as their pilot trials had not yet completed analysis, therefore 4 respondents completed all of survey 3

Table E9 Survey responses from trialists who did not report progression criteria in their publication

	Total (n = 34)		Survey 3 (n = 4*)		Survey 4 (n = 30)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
What were the pilot trial findings in relation to the feasibility of a future definitive trial?						
Future definitive trial is feasible	17	(50%)	2	(50%)	15	(50%)
Future definitive trial is feasible with changes to design**	15	(44%)	2	(50%)	13	(43%)
Future definitive trial is not feasible	1	(3%)	0	(0%)	1	(3%)
Feasibility of the future definitive trial is unclear**	1	(3%)	0	(0%)	1	(3%)
***Do you intend to do any further feasibility assessment?*						
Yes	*4*	*(25%)*	*0*	*(0%)*	*4*	*(29%)*
No	*12*	*(75%)*	*2*	*(100%)*	*10*	*(71%)*
Did you consider prespecifying progression criteria?						
Yes	10	(29%)	1	(25%)	9	(30%)
No	23	(68%)	3	(75%)	20	(67%)
Did not answer	1	(3%)	0	(0%)	1	(3%)
Do you intend to conduct a future definitive trial?						
Yes	22	(65%)	2	(50%)	20	(67%)
***Has funding for the definitive trial been applied for?*						
Yes	*15*	*(68%)*	*0*	*(0%)*	*15*	*(75%)*
Funding awarded	*9*	*(60%)*	*0*	*(0%)*	*9*	*(60%)*
Funding not awarded	*4*	*(27%)*	*0*	*(0%)*	*4*	*(27%)*
Application outcome unknown	*2*	*(13%)*	*0*	*(0%)*	*2*	*(13%)*
No	*7*	*(32%)*	*2*	*(100%)*	*5*	*(25%)*

	Total (n = 34)		Survey 3 (n = 4*)		Survey 4 (n = 30)	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
What best describes the current stage of the definitive trial?						
Trial planning & design	*12*	*(55%)*	*2*	*(100%)*	*10*	*(50%)*
Set up	*3*	*(14%)*	*0*	*(0%)*	*3*	*(15%)*
Conduct	*3*	*(14%)*	*0*	*(0%)*	*3*	*(15%)*
Analysis	*2*	*(10%)*	*0*	*(0%)*	*2*	*(10%)*
Reporting/dissemination	*1*	*(5%)*	*0*	*(0%)*	*1*	*(5%)*
Did not answer	*1*	*(5%)*	*0*	*(0%)*	*1*	*(5%)*
No	12	(35%)	2	(50%)	10	(33%)

Responses presented were reported by 34 trialists who did not report progression criteria in their publication, and whose pilot trials had completed

*Although 8 respondents completed survey 3, only 4 described that their pilot trial was in the reporting or dissemination stage and so responded to the questions presented

**Respondents were asked whether they would conduct further feasibility assessment where they considered their pilot trial to be feasible with changes or where feasibility was unclear

Ninety-four percent of respondents said that their pilot trial was feasible (17/34, 50%) or was feasible with changes to trial design (15/34, 44%). Only one responder said that their pilot trial was not feasible (1/34, 3%) and one said that feasibility was unclear based on their pilot trial findings (1/34, 3%), stating that although the trial and intervention could be delivered, there were local practical implementation issues around staffing and resource availability. Again, around one quarter of respondents who said that their pilot trial was feasible with changes to its design, or that feasibility was unclear, described the intention to do further feasibility assessment (4/16, 25%).

Over two thirds of respondents did not consider prespecifying progression criteria for their external pilot trial (23/34, 68%), and ten respondents described having considered prespecifying progression criteria (10/34, 29%). One participant did not respond to this question (1/34, 3%). Of the ten respondents who indicated that they had considered prespecifying progression criteria, five stated that they had prespecified criteria. I reviewed these five respondents' publications and was unable to identify within the publication any sections that specifically outlined the criteria against which feasibility would be assessed.

Around two thirds of respondents reported the intention to conduct a future definitive trial (22/34, 65%) with the majority also stating that their intended definitive trial was in the trial planning and design stage (12/22, 55%). Over two thirds of these respondents described having applied for further funding (15/22, 65%): nine were awarded funding (9/15, 60%), four were unsuccessful (4/15, 27%) and two had not yet received their application outcome (2/15, 13%). Thirteen respondents specified the funding sources they had applied to, including: NIHR (8/13, 62%; five awarded, two unsuccessful, one outcome unknown), German Federal Government (1/13, 8%; awarded), Australian

National Health and Medical Research Council (1/13, 8%; awarded), Australian Heart Foundation (1/13, 8%; outcome unknown), and the Swedish Research Council (1/13, 8%; awarded). One respondent described applying to various funding sources without success including the Australian National Health and Medical Research Council, Australian Medical Research Future Fund, and state-based Translational Research Grants (1/13, 8%; unsuccessful). Twelve respondents reported that they did not intend to conduct a future definitive trial (12/34, 35%).

5.3.7 Proposed changes to the future definitive trial

I used branching logic within the survey so that the 38 participants who indicated that a future definitive trial would be feasible with changes to design (38/98, 39% of respondents across all four surveys) were invited to briefly specify what changes they would make. Information about intended changes to definitive trial design was offered by 37 of the 38 respondents, see Table E10.

Table E10 Intended changes to future definitive trial design

Described changes to trial design	**(n=37)**			
	n	**(%)**		
Changes to the intervention	17	(46%)		
Intervention development or refinement			*9*	*(24%)*
Intervention delivery			*8*	*(22%)*
Intervention training			*2*	*(5%)*
Changes to recruitment	12	(32%)		
Recruit more sites			*3*	*(8%)*
Approach to site recruitment			*1*	*(3%)*
Approach to staff recruitment			*1*	*(3%)*
Recruitment timeframe			*1*	*(3%)*
Changes to outcome measures	5	(14%)		
Data collection or follow up methods	5	(14%)		
Patient population or eligibility	4	(11%)		
Trial design e.g. no of arms, randomisation	4	(11%)		
Less arms			*1*	*(3%)*
Changes to control arm	3	(8%)		
More support or personnel	3	(8%)		
Integration into healthcare setting	1	(3%)		
Method of consent	1	(3%)		
Optimise adherence	1	(3%)		
Randomisation procedures	1	(3%)		
Other changes (non-specified)	2	(5%)		

Responses presented were reported by 37 of 38 trialists who indicated that a future definitive trial would be feasible with changes to design

Most participants described more than one change

Respondents described varied changes, and many stated the intention to make multiple changes to their definitive trial design. The most frequent changes described related to the intervention (17/37, 46%) with nine respondents describing how their intervention needed further development or refinement, and eight suggesting that they would change their mode of intervention delivery. Two respondents described how they would provide more training to those delivering the intervention in the definitive trial. Twelve respondents suggested that they would make changes to their recruitment strategy (12/37, 32%): three suggested that they would recruit more sites in their definitive trial, one suggested they would alter their recruitment timeframe, one stated that they would make changes to 'recruiting staff', and one stated that instead of recruiting sites consecutively they would opt to recruit sites simultaneously.

Further changes described include: Changing the trial outcome measures (5/37, 14%), changing the methods of data collection or follow up (5/37, 14%), changing the patient population or eligibility criteria (4/37, 11%), changing the overall trial design (4/37, 11%; e.g. adding or dropping arms, and moving to a cluster randomised design). Three respondents stated that they would change what they considered to be the control treatment between their pilot and definitive trial (3/37, 8%) and three described how their definitive trial would require additional personnel or support staff (3/37, 8%).

Responses to the final open-ended questions highlighted positive perceptions amongst eight respondents about the benefits of doing a pilot trial to guide and fine-tune the definitive trial design. One respondent described how doing the pilot trial '*saved us lots of future headaches*,' and another described how doing the pilot trial was important to '*build research capacity and research skills*.' However, the potential to make multiple changes to trial design during a pilot trial was noted in the final open-ended question by

one respondent who raised concerns about whether too many changes could lead to the need to conduct further feasibility assessment, stating that they:

> *have a slight issue with feasibility studies that make so many changes or recommendations in order to demonstrate feasibility to progress, that they have become effectively an entirely different study design that probably needs testing all over again.*

5.3.8 Other considerations for pilot trial progression

Each of the four surveys also asked respondents about the factors that they consider when assessing future definitive trial feasibility. For those who had prespecified progression criteria, the surveys (survey 1 and 2) asked whether there were other, additional factors that informed feasibility assessment. For those who did not specify clear progression criteria, the surveys (survey 3 and 4) asked which findings they based their feasibility assessment on.

5.3.8.1 Specified other factors, in addition to progression criteria, that informed feasibility assessment

Over 60% of respondents described considering other factors, in addition to their progression criteria, which informed their assessment of trial feasibility (34/55, 62%). All but one (33/34, 97%) provided details about other factors that they considered, presented in Table E11.

Table E11 Specified factors that informed assessment of trial feasibility in addition to progression criteria

Other factors considered	**(n=33)**			
	n	**(%)**		
Qualitative data	12	(36%)		
Process evaluation			*5*	*(15%)*
*Participant feedback**			*3*	*(9%)*
Qualitative interview data			*3*	*(9%)*
Qualitative data about implementation			*1*	*(3%)*
Trial design	6	(18%)		
Outcome measures			*3*	*(9%)*
Data collection			*1*	*(3%)*
Performance of trial pathways			*1*	*(3%)*
Protocol adherence			*1*	*(3%)*
Selection bias			*1*	*(3%)*
Recruitment	5	(15%)		
Recruitment processes and ability to recruit			*4*	*(12%)*
Difficulty with screening			*1*	*(3%)*
Contextual challenges	4	(12%)		
Covid 19			*2*	*(6%)*
Healthcare context			*2*	*(6%)*
Changing policy			*1*	*(3%)*
Implementation of the trial	3	(9%)		
Resources required			*2*	*(6%)*
Enthusiasm of researchers			*1*	*(3%)*
Number of recruiting sites needed			*1*	*(3%)*
Funding considerations	3	(9%)		
Indication of efficacy or effectiveness	3	(9%)		
Interest, acceptability or uptake of intervention	3	(9%)		
Expectations of collaborators	1	(3%)		
Retention or attrition	1	(3%)		

Responses presented were reported by 33 of 34 trialists who considered other factors, in addition to their progression criteria, to assess trial feasibility

*Unclear whether participant feedback was collected through formal qualitative research methods

Most participants mentioned more than one factor

The most frequent consideration were qualitative research findings (12/33. 36%), including process evaluations and qualitative data about implementation. Three respondents stated that they considered qualitative interview data, although it was unclear from their responses exactly what the interviews aimed to assess, and three stated that participant feedback informed their interpretation of feasibility, however they did not specify whether feedback was collected using formal qualitative research methods, or informally e.g. through conversations.

Considerations about trial design, such as choice of outcome measures, methods of data collection, ability to reduce selection bias, performance of trial pathways and protocol adherence informed assessment of trial feasibility for six respondents (6/33, 18%).

Five respondents stated that recruitment and screening processes and challenges (5/33, 15%), and four stated that contextual challenges (4/33, 12%), such as the impact of Covid-19, changes to the healthcare context and policies, informed assessment of trial feasibility.

Implementation of the trial, including the resources and number of sites required, and researcher enthusiasm, informed feasibility assessment for three respondents (3/33, 9%). Three respondents stated that funding considerations such as whether funding for a future trial is available informed their assessment of feasibility (3/33, 9%). Three respondents considered whether there was any indication of efficacy or effectiveness when deciding whether a definitive trial was feasible (3/33, 9%), and three considered whether there was sufficient interest, acceptability or uptake of intervention (3/33, 9%). One respondent described how unrealistic expectations of collaborators was the reason that a larger trial was abandoned (1/33, 3%) and another stated that their ability to retain participants informed feasibility assessment in addition to progression criteria (1/33, 3%).

5.3.8.2 Findings that informed feasibility assessment where progression criteria were not stipulated

Of the 34 respondents who had authored pilot trial publications that did not include progression criteria, 32 (32/34, 94%) provided details about the findings they considered when determining feasibility, presented in Table E12.

Table E12 Factors that informed feasibility assessment where publications did not report progression criteria

Factors considered	**(n=32)**			
	n	**(%)**		
Qualitative data	17	(53%)		
*Acceptability to participants**			*11*	*(34%)*
*Participant feedback**			*3*	*(9%)*
Qualitative data about implementation			*3*	*(9%)*
Qualitative interview data			*2*	*(6%)*
*Acceptability to healthcare providers**			*2*	*(6%)*
Process evaluation			*1*	*(3%)*
Recruitment	14	(44%)		
Recruitment rate			*11*	*(34%)*
Recruitment processes			*2*	*(6%)*
Consent rate			*1*	*(3%)*
Recruitment time			*1*	*(3%)*
Indication of efficacy or effectiveness	10	(31%)		
Trial design	10	(31%)		
Sample size required for the definitive RCT			*5*	*(16%)*
Data collection			*3*	*(9%)*
Ability to do internal pilot as part of future def RCT			*1*	*(3%)*
Need to further development the intervention (not possible in an RCT)			*1*	*(3%)*
Retention or attrition	9	(28%)		
Interest, acceptability or uptake of intervention	9	(28%)		
Intervention adherence or engagement			*5*	*(16%)*
Completion or withdrawal rates			*3*	*(9%)*
Willingness to be randomised			*1*	*(3%)*
Implementation of the intervention	7	(22%)		
Intervention delivery			*3*	*(9%)*
Intervention fidelity			*2*	*(6%)*
Intervention feasibility			*1*	*(3%)*
Complexity of the intervention			*1*	*(3%)*
Implementation of the trial	4	(13%)		
Acceptability or willingness of healthcare professionals			*2*	*(6%)*
Patient acceptability of study procedures			*1*	*(3%)*
Resources required			*1*	*(3%)*
Safety or adverse events	3	(9%)		
Contextual challenges	1	(3%)		
Healthcare context			*1*	*(3%)*
Funding considerations	1	(3%)		

Responses presented were reported by 32 of 34 trialists who authored pilot trial publications that did not include progression criteria

*Unclear whether participant feedback and acceptability data were collected through formal qualitative research methods

Most participants mentioned more than one factor

Again, the most frequent consideration was qualitative research findings (17/32, 53%). Eleven respondents indicated that participant acceptability informed their assessment of feasibility, with two indicating that they also considered acceptability to healthcare providers. However, it was not always explicit whether acceptability was being investigated through qualitative methods and if so, which methods were used. Three respondents described considering participant feedback, three described considering qualitative data about implementation, and one described considering findings from a process evaluation. Two respondents specified that data collected using qualitative interviews had informed their assessment of feasibility.

Fourteen respondents described that recruitment had informed their assessment of trial feasibility (14/32, 44%), such as considering the recruitment rate, recruitment processes, consent rate, and timeframe associated with recruitment. Ten respondents considered whether there was any indication of efficacy or effectiveness when deciding whether a definitive trial was feasible (10/32, 31%).

Ten respondents described considering findings in relation to the trial design (10/32, 31%). For example, five described considering whether the sample size required for the definitive trial was achievable, three described considering their methods of data collection, one described how their definitive trial feasibility had instead been informed by their internal pilot trial as part of their definitive trial and one described that an RCT was not feasible as it would inhibit further development of the intervention.

Nine respondents described considering retention or attrition when determining feasibility (9/32, 28%), and nine described considering whether there was sufficient interest, acceptability or uptake of intervention (9/32, 28%) including intervention adherence or engagement, completion or withdrawal rates, and willingness to be

randomised. Seven respondents described considering whether the intervention could be implemented (7/32, 22%), for example whether it could be delivered, was feasible or too complex, or through assessment of intervention fidelity. Implementation of the trial, such as the resources and sites required, willingness of healthcare providers to implement the study and acceptability of study procedures to respondents informed feasibility assessment for four respondents (4/32, 13%).

Three respondents stated that they considered safety or adverse events when determining feasibility (3/32, 9%), one described considering the changing clinical context (1/32, 3%), and one described how the low cost of delivering the intervention factored into their assessment of feasibility (1/32, 3%).

5.3.9 Identified barriers to pilot trial progression

Of the 80 respondents across all four surveys (80/89, 90%) who stated that their future trial would be feasible or feasible with changes to trial design, 18 (18/80, 23%) indicated that they did not intend to conduct a future definitive trial. Using branching logic these respondents were invited to provide reasons for why they did not intend to conduct a future definitive trial: Seventeen respondents provided reasons (17/18, 94%), these are summarised in Table E13, with many participants providing more than one reason.

Table E13 Reported barriers to progression of feasible pilot trials

Identified barrier	**(n=17)**			
	n	**(%)**		
Funding considerations	6	(35%)		
CI priorities	5	(29%)		
Healthcare context	3	(18%)		
Changing healthcare landscape			*1*	*(6%)*
Covid 19			*1*	*(6%)*
Intervention is no longer required			*1*	*(6%)*
Indication of efficacy or effectiveness*	3	(18%)		
No indication of efficacy or effectiveness			*2*	*(12%)*
A different trial has provided evidence of efficacy			*1*	*(6%)*
Resources required*	2	(12%)		
Definitive trial sample size required is too large*	1	(6%)		
Further feasibility or piloting is required	1	(6%)		
Lack of participant interest in the intervention*	1	(6%)		
Recruitment was difficult*	1	(6%)		
Reliability of data*	1	(6%)		
Success of collaborations	1	(6%)		

Responses presented were reported by 17 respondents who considered their pilot trial to be feasible or feasible with changes, but did not intend to conduct a future definitive trial

*Items that have previously been identified to contribute to progression criteria

Most participants provided more than one reason

Funding considerations, such as whether funding for the definitive trial would be available and sufficient, was the most frequently reported reason for not doing a definitive trial where the pilot trial proved to be feasible, reported by six respondents (6/17, 35%).

Responses to the final two open-ended questions further highlighted difficulties with obtaining funding even where respondents had been successful in doing so. For these respondents funding was not necessarily a barrier to progression, but they felt that obtaining it was challenging. To exemplify this, one respondent stated that '*the complexity of funding streams has made the application for further funding quite a task*'. However, this was not true for all respondents. One described how pilot trial funders had instead facilitated their ability to obtain further funding, stating that they '*received very positive feedback*' about their end of feasibility trial report, which they believed was '*influential in securing funding for a main trial*'.

A further barrier to pilot trial progression identified was changing CI priorities (5/17, 29%). Five respondents reported that they had decided to pursue other research interests instead of a definitive trial; two of these stated that their pilot trial had formed part of their PhD, and that they themselves were not resourced to take it forward and the final decision regarding a future definitive trial was not in their '*competence*'.

Three respondents (3/17, 18%) described how changes to the healthcare context e.g. changing service delivery, the implementation of other interventions, or the impact of Covid 19 meant that they could not justify a definitive RCT. Two respondents described that they would not pursue a definitive trial because there was no indication of efficacy (2/17, 12%), and one described how efficacy had since been proven in a different fully powered RCT (1/17, 6%). Other barriers identified included the resources required (2/17, 12%), that the definitive trial sample size was too large (1/17, 6%), that further feasibility

or piloting was required (1/17, 6%), a lack of interest in the intervention (1/17, 6%), challenges with recruitment (1/17, 6%), reliability of data collection (1/17, 6%) and that stakeholder collaborations had not been successful (1/17, 6%).

Five respondents who did intend to progress to a definitive trial described facing delays in doing so. Three attributed these delays to the ongoing impacts of Covid-19, and one described how staff changes had delayed progression. One respondent described facing delays caused by the NHS ethics committee reviewing the definitive trial ethics application; the ethics committee opposed the definitive trial primary outcome, which had been tested in the pilot trial. This participant described how they used a different primary outcome which led to a completely different definitive trial sample size.

I identified very few of these barriers in Chapter 2 as uncertainties that are often included in progression criteria, including the three most frequently reported barriers to pilot trial progression (funding considerations, CI priorities, and a changing healthcare context).

5.4 Discussion

5.4.1 Summary of findings

This cross-sectional study presents the responses of 98 corresponding authors of pilot trial publications to a web-based survey (response rate 36%; 98/276) which explored the outcomes in terms of feasibility and progression of their pilot trial.

The key finding of this study is that 90% of the 89 respondents across all four surveys whose pilot trial had completed stated that their pilot trial was either feasible (42/89, 47%) or feasible with changes to trial design (38/89, 43%), yet only two-thirds reported the intention to conduct a future definitive trial (59/89, 66%). Only nine of these 89 respondents stated that a future definitive trial is not feasible, or that feasibility of the future trial is unclear (9/89, 10%). This suggests that just under one quarter (21/89, 24%) of respondents considered their pilot trial to be feasible, or feasible with changes, yet did not indicate their intention to conduct a definitive trial.

Respondents reported varied barriers to pilot trial progression in these instances, with the most frequently reported barriers being availability of funding for a future definitive trial and changing priorities of the CI. Other barriers included changing healthcare context, having no indication of efficacy or effectiveness, and the resources required to deliver the definitive trial.

5.4.2 Findings in context

It has been suggested that authors of pilot trials that do not report progression criteria, or report unclear progression criteria, may be optimistic in reporting that a definitive RCT is feasible [31]. My findings identified that only slightly more respondents who did not

report clear progression criteria in their pilot trial publication considered their pilot trial to be either feasible or feasible with changes compared to those who did include progression criteria (94%, 32/34 versus 87%, 48/55 respectively). This could indicate that even where progression criteria are reported researchers might be over optimistic in reporting that their pilot trial is feasible.

Notably, the feasibility rates observed in this study were also higher than those that have been previously reported in pilot trials, ending between 1995 and 2019, that were registered on the International Standard Randomised Controlled Trials Number (ISRCTN) registry (83%) [31], and in NIHR RfPB funded pilot trials that had completed by May 2016 (64%) [30]. Since the sample of pilot trials included in this review was more recent, my findings might suggest that the proportion of pilot trials that indicate feasibility has increased. It has also been suggested that non-feasible pilot trials might be subject to publication bias [31], but since many of the respondents surveyed were identified from pilot trial protocol, rather than result, publications it is unclear whether this is the case. However, it is highly possible that authors of pilot trials that were feasible were more likely to respond to the survey and so bias the results.

It has also been previously suggested that some pilot trials might be redundant, i.e. they are conducted without sufficient uncertainty about feasibility that they are likely to show that an RCT will be feasible, and so waste time and resources [31]. My findings support this hypothesis and suggest that some pilot trials might be contributing to research waste if they are conducted with no intention to progress to further research.

Finally my findings also highlight the need for clearer guidance for progression criteria reporting. I identified instances of conflict between authors and myself about whether progression criteria were stipulated. Potential explanations for this are that authors had

prespecified progression criteria, but that this was not clearly reported in the publication, or that the author and my own interpretation of progression criteria differ, which is likely given that there is no clear agreed definition for what progression criteria are.

5.4.3 Strengths and limitations

A strength of this study is my comprehensive use of open and closed questions to appropriately address the study aim and objectives. The inclusion of open questions allowed respondents to expand on answers that they provided. However, surveys are generally considered to be inflexible tools, and although the inclusion of open-ended questions mitigated against this inflexibility, they still did not allow respondents to go into further depth in all aspects of the survey which might have limited my interpretation of the data.

Although I identified 111 corresponding results publications where the original publication included in Chapter 2 was for a pilot trial protocol, five respondents indicated that they had published their pilot trial results, yet I did not identify the publication. This highlights the difficulty in linking corresponding pilot trial protocols and results publications, even when a systematic approach is used. Possible explanations for this are that the corresponding first author changed, that the pilot trial title or acronym changed, or that the results publication was published in the time between the literature search and sending of the survey.

Although the response rate (average 36%) could be considered low, it was on par with response rates observed in other studies where trialists have been surveyed [214,215]. However, I did find that authors of pilot trial protocols had a slightly lower response rate compared to authors of pilot trial results publications. One potential explanation for this

is that the survey title '*Progression of external pilot trials*' may have implied that researchers should not complete the survey unless their pilot trial had completed, which was a question posed by two potential participants who were unsure whether they should complete the survey or not. In addition, all questions were optional rather than required, and some respondents chose not to respond to all questions.

Although one potential disadvantage of web-based surveys is that they are limited to those who are computer literate [216], this was not a big concern as I was contacting corresponding authors via their publicly available email address, so I could assume that they would be able to complete the survey electronically. However, I did receive some automated response emails for authors whose email addresses are no longer active e.g. they were on leave or had moved to a new role. This was a limitation of my approach and meant that some corresponding authors did not get the opportunity to participate.

5.4.4 Chapter summary

This chapter presented the methods and findings of an international web-based survey to explore the outcomes in terms of feasibility and progression of the recent cohort of external randomised pilot trials that were studied in Chapter 2. The key findings were that although 90% of respondents across all surveys whose trial had completed considered their pilot trial to be either feasible or feasible with changes, only two-thirds reported the intention to conduct a future definitive trial, indicating potential inefficiency and research waste. I identified the following barriers to pilot trial progression: availability of funding, CI priorities, changing healthcare context, lack of indication of efficacy and requirement of too many resources.

Chapter 6 Recommendations for using progression criteria in external randomised pilot trials to determine future definitive trial feasibility

Associated research outputs:

I presented initial recommendations at the Oxford-MRC DTP Symposium (2022, Oxford), and I presented the final recommendations, reported in this chapter, at the *6th International Clinical Trials Methodology Conference* (2022, Harrogate) where I was a runner up for the student oral presentation award. These recommendations have been submitted as a commentary for publication to *Pilot and Feasibility Studies* [1].

[1] Mellor K, Albury C, Dutton S J, et al. Recommendations for progression criteria during external randomised pilot trial design, conduct, analysis and reporting. Under review.

6.1 Chapter introduction

In this chapter I will delineate the key areas of concern identified throughout the previous thesis chapters and draw on my findings and any external evidence to recommend some practical recommendations for progression criteria for researchers to follow when designing, conducting, analysing and reporting external randomised pilot trials.

6.2 Identification of key concerns

Methodological or method triangulation was first described in the 1970s as a social science research method [181], and is now widely used throughout healthcare research [224,225]. Method triangulation is a type of triangulation that involves the use of multiple methods to study a phenomenon (or situation) to gain a better understanding than would be obtained using a single method. It is based on the rationale that the strengths of one method may compensate for the deficiencies of another [87,181].

I triangulated the findings of the research I presented in Chapters 2 to 5 with my experiences of designing, conducting and analysing this research, and my knowledge and understanding of external randomised pilot trials from the literature (introduced in Chapter 1) to identify key concerns and areas where improvement is required. The identification of areas for improvement was an iterative process, with any questions about what constitutes best practice further developed throughout the DPhil based on the emerging findings of each study that was conducted. A summary of the key concerns identified is presented in Table F1 and are described in detail in section 6.3.

6.3 Summary of key concerns identified

A summary of key concerns in relation to progression criteria are presented in Table F1, and are elaborated on in this section.

Table F1 Key concerns identified with regards external randomised pilot trial progression criteria

Domain	Key concerns identified
Design	**How should researchers develop progression criteria for an external randomised pilot trial?** 1. When should progression criteria be considered? 2. What should progression criteria include? 3. How should progression criteria targets be chosen (rationale)? 4. How strict should progression criteria be? 5. Who should be involved?
Conduct	**Should researchers consider progression criteria during external randomised pilot trial conduct?** 1. Should researchers review progression criteria? If so, how often? 2. What considerations should be given to progression criteria if the pilot trial design changes?
Analysis	**How should external randomised pilot trial progression criteria be assessed to determine future definitive trial feasibility?** 1. What if only some of the progression criteria were met? 2. Who should be involved in assessing progression criteria? 3. Should researchers consider other factors beyond progression criteria to determine feasibility? 4. What if progression criteria are met (i.e. pilot trial is feasible) but it does not progress for other reasons?
Reporting	**How can researchers transparently report their external randomised pilot trial progression criteria?** 1. How should progression criteria be reported in pilot trial protocols? 2. How should progression criteria be reported in pilot trial result publications?

My findings highlight several inconsistencies between what the research community consider to be best practice for developing progression criteria, and what happens in reality. For example, although it is generally agreed that progression criteria should be specified a priori [69] my findings indicate that progression criteria are not always stipulated in funding applications or reported in pilot trial protocol publications. Although

many researchers perceive that progression criteria should vary between pilot trials to account for context, the same two indicators of feasibility (recruitment and retention) dominated most of the pilot trials studied. Although most researchers do not view progression criteria as strict targets, the majority of pilot trials studied did not opt to present criteria in the more flexible stop-amend-go (traffic light) format suggested in the CONSORT extension for PAFS [24] and recommended for internal pilot trials [22]. Researchers also generally supported the inclusion of qualitative findings to inform feasibility assessment [75]. However, qualitative findings much less often informed progression criteria which were largely based on quantitative, numerical targets, highlighting a missed opportunity for prespecifying how the findings of qualitative research can inform feasibility assessment.

My qualitative study highlighted varied and inconsistent methods of progression criteria development including drawing on rules of thumb, observation work, previous research conducted by investigators, published research, clinical experience, or contextual considerations. Some researchers described how progression criteria are often seemingly '*plucked out of the air*', raising concerns that this might lead to inappropriate feasibility assessment and trial progression. Researchers also described the perceived benefit of involving various stakeholders, for example clinical colleagues and PPI members, when developing progression criteria but highlighted various challenges to doing so including limited time and resources, and a lack of knowledge for who to involve and how.

The extent to which researchers should consider progression criteria during their pilot trial conduct is unclear. However, some researchers described how changes made to their pilot trial design during its conduct can impact applicability of prespecified progression

criteria, for example altering intervention delivery might impact on data collection if certain measures are more difficult to collect.

It is also unclear who should be involved in progression criteria assessment, and how progression criteria are best interpreted where some, but not all, have been met. Researchers described not wanting to be bound or limited by their progression criteria, for example where one target is '*red'* or '*stop'*, yet there is a clear reason why this is the case which might be remedied in the definitive trial. My findings also suggest that often feasibility assessment goes beyond the progression criteria, raising questions about how researchers should account for other factors that they might consider when interpreting feasibility, that were not prespecified in the progression criteria, and what to do where interpretation of feasibility and final progression criteria metrics do not necessarily align.

Finally, although the CONSORT extension for PAFS lists progression criteria as a suggested reporting item (item 6c) [24], my findings indicate that many pilot trial publications still do not report progression criteria altogether, and those that do often lack detail. For example, how progression criteria were developed, what rationale they were based on and who was involved in their development was often not reported. The findings of my qualitative study suggest that tight word limits and unclear reporting expectations are barriers to clear progression criteria reporting. There is also no guidance for reporting progression criteria in pilot trial protocols, which may be further contributing to inadequate reporting [69]. Inconsistent and insufficient progression criteria reporting reduces the transparency of feasibility assessment following external pilot trials.

Not only do these uncertainties about best practice underpin the need to develop more guidance for progression criteria, but a desire for more guidance was directly highlighted by researchers who participated in the qualitative research study presented in Chapter 4.

6.4 Development of recommendations

Once the four studies presented in Chapters 2 to 5 had been conducted and the findings were known, I developed recommendations to address the key concerns I had identified. These recommendations were developed iteratively over several months towards the end of the DPhil. Initial drafts were based on examination of the data I had collected and continued review of the literature throughout the DPhil which was facilitated by weekly publication alerts for relevant journals such as *Pilot and Feasibility Studies* and *BMC Medical Research Methodology*. Early recommendation drafts were presented to my supervisory team at monthly supervision meetings for discussion, and were shared with PAFS working group members [187] who were invited to provide feedback.

I developed 13 practical recommendations (one provides a summary of eight reporting items) to address the key concerns I had identified. I also produced an infographic to visually, and simply, present a recommendation summary. The initial recommendations I developed are detailed in Appendix F1, along with a short elaboration and explanation for each. Once I had drafted this complete first set of initial recommendations, I sought external input and critical feedback from key stakeholders outside of my supervisory team and working group to ensure that they were useful, complete and not misleading. Details of the stakeholder involvement activities conducted, and how these informed the final set of recommendations, is provided in the next section.

6.4.1 Stakeholder involvement activities

To inform the development of these recommendations I convened two stakeholder workshops (12th and 14th of July 2022).

Potential stakeholders were identified from their previous contributions and involvement in aspects of this thesis (for example as participants), or through my supervisory team and PAFS working group [187]. I invited potential stakeholders to participate in a stakeholder workshop via email (wording presented in Appendix F2) to review and provide critical feedback on the initial recommendations I had developed.

Fourteen stakeholders attended the workshops over two days. Stakeholders included three CIs, four trial statisticians, five trial methodologists/health services researchers, one research manager at NIHR RfPB and one professor of primary care pharmacy.

The initial recommendations that I had developed prior to stakeholder workshops (presented in Appendix F1) were circulated to attendees via email along with an agenda one week prior to the workshop. The first workshop was held face to face in person in The Botnar Research Centre, University of Oxford with five stakeholder attendees and myself as the facilitator. The second workshop was held virtually over MS Teams, in order for more external people to attend, with nine stakeholder attendees, myself as facilitator, and two supervisors as co-facilitators. Since this was an engagement activity (not research) ethical approval was not required (see Appendix F3 for MS IDREC confirmation that ethical review was not required for this activity).

Both workshops were 1 hour 30 minutes in duration. At the start of the workshop I invited all attendees to introduce themselves, and then I briefly presented a summary of the research presented in this thesis to provide context for why I had developed the recommendations. The main duration of the workshop (one hour) was allocated to discussion of the initial recommendations. I produced detailed meeting notes to inform subsequent refinements that I made to the recommendations based on stakeholder feedback.

6.4.2 Examples of how stakeholder involvement activities informed final recommendations

I made several refinements and clarifications to the recommendations, and infographic, based on stakeholder feedback. For example, stakeholders suggested that '*frame* around feasibility objectives and outcomes' should be changed to '*map* feasibility criteria to pilot trial objectives', since this was clearer and less prone to misinterpretation. Stakeholders also felt that the traffic light image was not appropriate for '*develop guidelines rather than rules*' since traffic lights are innately associated with rules (e.g. red = stop). Instead they suggested that this image would be more suitable for the '*revisit regularly*' recommendation. This discussion point also led to the inclusion of text in the elaboration to acknowledge that often pilot trials might have some 'red' criteria but do not necessarily stop which might be misleading.

Another key topic discussed during the workshops that shaped the final recommendations was around the importance of accounting for qualitative research findings in pilot trials, but with the understanding that sometimes researchers are unable to embed qualitative research in their pilot trial due to funding limitations. Stakeholders felt that it was important to expand on this point in the elaboration and suggest alternative ways that researchers might consider qualitative interpretations of trial feasibility, such as keeping a 'lessons learned' document to highlight things that had and had not worked.

Notably, no feedback was given to suggest that any of the proposed recommendations should be removed, or that there were any key recommendations missing. The final recommendations developed are presented below in section 6.5.

6.5 Proposed recommendations

The final proposed practical recommendations, along with a short explanation and elaboration are presented in this section. These recommendations are structured to indicate considerations for progression criteria when (1) designing, (2) conducting, (3) analysing and (4) reporting external randomised pilot trials.

I have also produced an infographic to summarise and present these recommendations, presented in Figure F1. This concise image presents a snapshot of the recommendations developed and should provide a helpful tool for researchers to refer to at key stages of external randomised pilot trials.

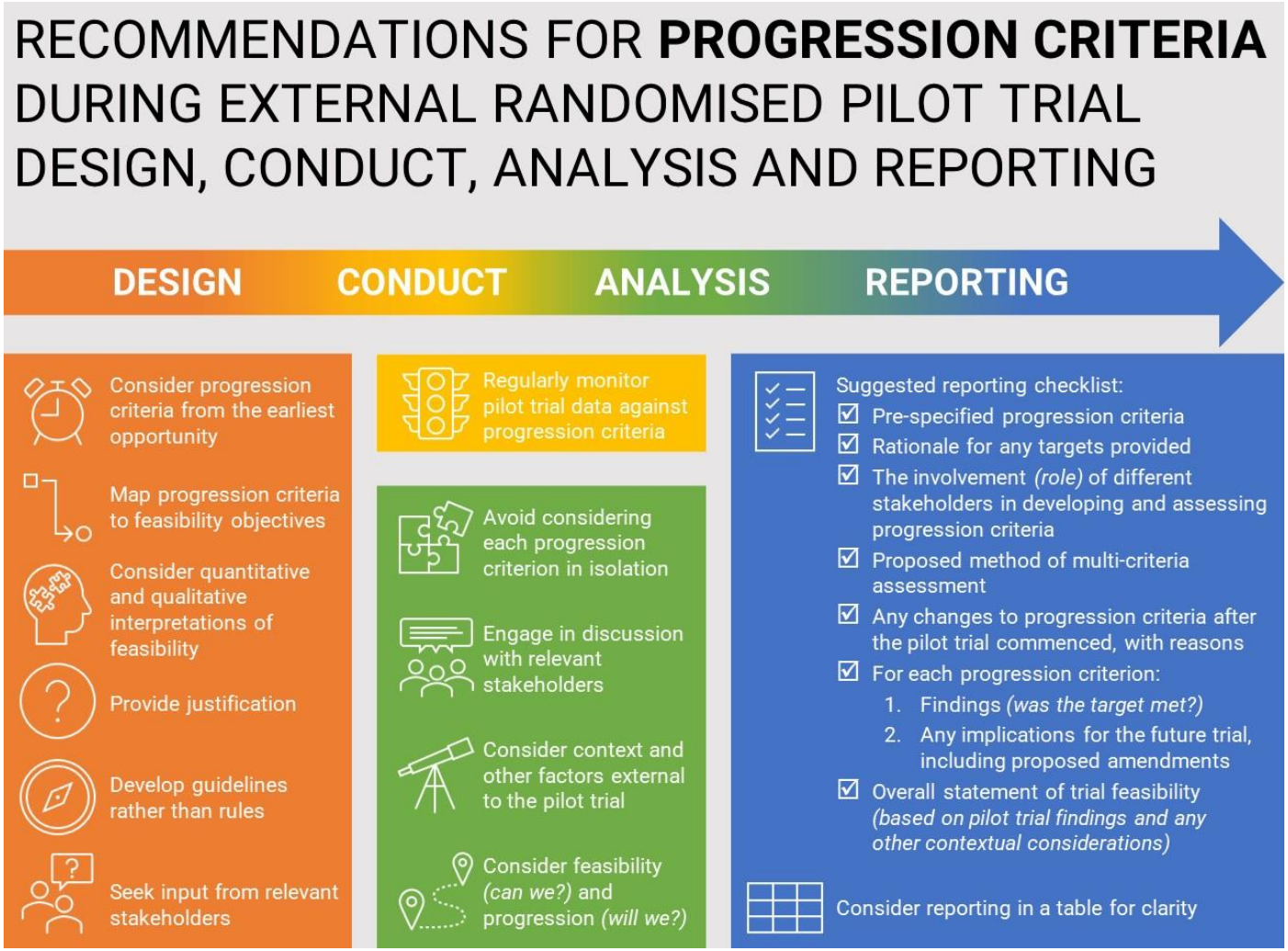


Figure F1 Infographic summary of recommendations

6.5.1 Recommendations for progression criteria during pilot trial design

6.5.1.1 Consider progression criteria from the earliest opportunity

Researchers should consider progression criteria from the onset when designing their pilot trial, and some research funders now require that progression criteria are included in pilot trial funding applications. Early consideration of progression criteria provides a valuable opportunity for researchers to think about where their uncertainties lie and what problems that they might face, potentially saving time and effort in the long run.

6.5.1.2 Map progression criteria to feasibility objectives

Researchers should consider whether progression criteria are needed for each of their feasibility objectives. Too often progression criteria only focus on recruitment and retention and do not account for other feasibility issues that might also be pertinent to the success of the definitive RCT. For example, if researchers are conducting qualitative research as part of their pilot trial, they should consider whether, and how, these findings will inform progression criteria. Not all data collected during the external pilot trial needs to inform progression criteria, some might be collected to pilot and refine trial processes without being regarded as an uncertainty that impacts on trial feasibility. However, mapping progression criteria to feasibility objectives as appropriate can ensure that they are developed with the definitive trial in mind. To contextualise progression criteria researchers might also find it useful to associate criteria with specific timeframes or settings e.g. monthly or site-specific targets.

6.5.1.3 Consider quantitative and qualitative interpretations of feasibility

Although it has become standard practice to use numerical targets for progression criteria, researchers should be mindful that this might not always be appropriate. Although quantifiable targets might seemingly ensure transparent progression criteria assessment, they should be avoided where they are not meaningful.

Mixed method approaches to PAFS data collection have been recommended [226–228], and feasibility questions that might be best addressed using qualitative research methods have been outlined [75]. Researchers might therefore opt to have a combination of numerical and non-numerical progression criteria, see Figure F2 for an example of this approach [229].

	Go—proceed with RCT	Amend—proceed with changes	Stop—do not proceed unless changes are possible
1. Feasibility of practice recruitment Can 16 practices be recruited to take part in 3 months (8 practices in NI and 8 in ROI)?	If ≥ 14 practices are recruited to take part in 3 months	If ≥ 14 practices are recruited, but it takes longer than predicted (e.g. 3–6 months)	Unable to recruit practices
2. Feasibility of patient recruitment Can 20 patients per practice (total *N* = 320) be recruited?	If 20 patients are recruited in one month per practice; a total of 320 (100%)	If 10–19 patients are recruited in one month per practice; a total of 160–319 (50 to < 100%)	If < 10 patients are recruited in one month per practice; a total of ≤ 159 (50%)
3. Feasibility of practice retention Can ≥ 14 practices be retained in the study until completion?	≥ 14 (88%) retained	≥ 12 (75%) retained	< 12 retained
4. Feasibility of patient retention Can at least 80% of recruited patients be retained in the study until completion?	≥ 256 (80%) retained	224–255 (70–80%) retained	< 224 retained
5. Intervention implementation	Delivery of intervention judged strongly feasible by qualitative data	Delivery of intervention judged feasible by qualitative data	Delivery of intervention judged possibly feasible by qualitative data

Figure F2 Example progression criteria including quantitative and qualitative data

Reproduced from Table 2 Hynes et al (2022) *Pilot Feasibility Stud* **8**:1–16, published CC-BY 4.0

Not every pilot trial will have a formally embedded qualitative research study e.g. a process evaluation. However, this does not negate the importance of considering other '*soft intelligence*' gained from conducting the pilot trial which might be interpretated qualitatively, for example through '*informal conversations*' with healthcare professionals who are implementing the trial at investigative sites [230]. These informal conversations can occur anywhere at any time and are likely already widely being used by research teams to generate new ideas about intervention or trial deliverability that are investigated by changing aspects of the pilot trial design. However, new strategies are needed to ensure that any data generated through informal conversations that informs and underpins changes to trial design does not go undocumented. One example is to maintain a '*lessons learned*' document to capture problems faced during the pilot trial and any attempts to resolve these issues, irrespective of whether they worked or not.

6.5.1.4 Provide justification

Researchers should provide some justification for any progression criteria including any stated numerical progression criteria targets to indicate how they were derived. Rationale need not be statistical as pilot trials are usually underpowered for hypothesis testing, but some rationale for criteria should be given. Examples include: based on feasibility objectives; clinical or contextual assumptions; pragmatically derived; based on previous feasibility or observational work; developed using consensus methods. Investigators should be aware that small pilot trial sample sizes might mean that any estimates of rates are subject to considerable uncertainty [231].

6.5.1.5 Develop guidelines rather than rules

Progression criteria are best viewed as guidelines rather than strict rules. Researchers should therefore develop progression criteria that will help identify and explore potential challenges with their trial design to inform the development of actionable solutions.

For example, it is becoming increasingly common for investigators to use a traffic light or Red Amber Green (RAG) approach for progression criteria. This approach is also recommended and widely used in RCTs with internal pilot trial phases [22,152]. There are no agreed hard and fast rules for the meanings attributed to each colour, but typically measures below a lower (red) threshold have indicated that the pilot trial is not feasible [stop], above a higher (green) threshold that it is feasible [go], and between the two (amber) that it might be feasible if appropriate changes can be made [amend] [24]. However, for many external pilot trials a red criterion might not necessarily mean that the definitive trial is not feasible. Instead, it might be more appropriate to think of the RAG system as a way to highlight, and draw attention to, problems that have been faced in the pilot trial, with red indicating major problems that require urgent attention (and perhaps cannot be remedied), amber indicating minor problems that require attention, and green indicating areas of no concern.

6.5.1.6 Seek input from relevant stakeholders

Researchers should try to involve a broad range of stakeholders to develop, or agree, progression criteria so that targets are more meaningful and less prone to bias. A multidisciplinary approach to progression criteria development might involve consulting a Research Design Service (RDS) or Clinical Trials Unit (CTU). Seeking input from clinical colleagues, including those who are implementing the pilot trial but are not necessarily part of the research team, can help ensure that progression criteria make sense

for different clinical contexts, recognising that pilot trial sites are not always reflective of the sites used in the main trial. Researchers might also want to involve PPI representatives to agree their progression criteria, and if applicable, agree progression criteria with their Trial Steering Committee (TSC) in advance, as is recommended for internal pilot trials [22]. Finally, researchers should also consider appropriate funding sources for their future definitive trial if they are able to demonstrate feasibility and ensure that progression criteria encompass any recommendations for feasibility assessment made by the intended definitive trial funder.

6.5.2 Recommendations for progression criteria during pilot trial conduct

6.5.2.1 Regularly monitor pilot trial data against progression criteria

Researchers might find it useful to revisit their progression criteria targets regularly throughout their pilot trial at important trial milestones, or as a standing agenda item at multidisciplinary team meetings e.g. the TMG and/or TSC. This might be particularly important when any changes to the pilot trial design are made, so that researchers can determine whether these changes have improved the trial design (i.e. whether indicators of feasibility are improving or trending towards green progression criteria). Criteria that fall within the 'red' domain will signify where urgent attention is needed to identify, outline and pilot actionable solutions in response to problems that are being faced.

There might be instances where changes to the pilot trial design might directly or indirectly affect the applicability of the a priori specified progression criteria. In these instances, researchers might re-define their progression criteria, following consultation with relevant stakeholders such as those who initially input into their development and

any newly identified stakeholders of relevance, to ensure that they are still usable indicators of trial feasibility. Where any changes to progression criteria are made, reasons for these changes should be fully reported in pilot trial publications.

6.5.3 Recommendations for progression criteria assessment during pilot trial analysis

6.5.3.1 Avoid considering each progression criterion in isolation

Most pilot trials will have multiple progression criteria, so researchers should consider their method of multi-criteria assessment. Researchers might opt to take a holistic approach to feasibility assessment and consider criteria in relation to each other, the implications for the future definitive trial, and whether any solutions to poorly performing criteria have been identified to come to an overall conclusion of feasibility. This may or may not involve weighting specific criteria that are regarded as more fundamental than others. Outlining clear, actionable solutions where progression criteria are not met (e.g. are within red or amber ranges) is an important component of feasibility assessment that should not be overlooked. This is in line with recommendations for evaluating the feasibility of internal pilot trials which suggests that definitive trial funders acknowledge the importance of considering supplementary data e.g. a '*rescue plan'* that outlines any problems encountered and how they were addressed [22]. An alternative approach suggested for multi-criteria assessment is to determine overall progression based on the worst-performing criterion, i.e. if one criterion is not met then the trial is not feasible [71].

6.5.3.2 Engage in discussion with relevant stakeholders

Just as it is important to engage a broad range of stakeholders in developing progression criteria, it is important to engage different stakeholders at the end of the pilot trial when determining feasibility. At this stage it might be particularly useful to speak to people outside of the immediate trial team, e.g. clinical and healthcare professionals who were implementing the intervention or trial processes, to gain a comprehensive understanding about what might have worked well and what might require improvement in the definitive trial. For example, a behavioural science approach might be used to identify specific challenges and potential solutions [232].

6.5.3.3 Consider context and other factors external to the pilot trial

Since progression criteria are developed during the early pilot trial design stage, they do not account for unforeseen events and challenges researchers might face whilst conducting the pilot trial. Researchers should account for these factors, drawing on evidence and experience generated from doing the pilot trial, and any relevant external evidence generated outside of their pilot trial, when drawing conclusions about feasibility and progression.

6.5.3.4 Consider feasibility (can we?) and progression (will we?)

Researchers should recognise that feasibility assessment (can we do it?) and progression decision making (will we do it?) are complementary but distinct considerations. There might be instances where pilot trials are considered feasible based on progression criteria and assessment of deliverability, but do not progress for other reasons that are external to the pilot trial design for example funding might not be available, the healthcare context might have changed, the intervention might now be superseded, or the CI might not

intend to pursue the definitive trial at this time. It is important to be transparent about both whether the pilot trial is considered feasible, and whether researchers intend to progress to further research. Doing so might further evidence wider challenges with pilot trial progression for the research community to address, or even present the opportunity for other research groups to advance completed pilot trials that were feasible but might not otherwise progress.

6.5.4 Recommendations for progression criteria reporting

6.5.4.1 Suggestions for what information to report

Clear and transparent reporting of progression criteria ensures that trial feasibility is assessed with integrity and rigour. Clear reporting also enhances the wider usability of pilot trial findings. For example researchers can adequately determine whether progression criteria for one pilot trial might be applicable to another if information about how criteria were developed is provided. This should encourage better research practice and avoid researchers providing generic progression criteria that are not meaningful.

To improve transparency of progression criteria reporting, I propose that the following information detailed in Table F2 is included in external randomised pilot trial publications. The suggested items for protocol publications might also be applicable to researchers who are developing funding applications for external randomised pilot trials.

Table F2 Suggested progression criteria reporting items and rationale

Suggested item	Rationale	Protocol	Result
METHODS			
Pre-specified progression criteria	To ensure the pilot trial meets its (feasibility) objectives, specific measures or assessments should be defined to address each separate objective or research question [a]. A range of methods can be used to address the objectives in a pilot trial. These methods are often based on descriptive statistics such as means and percentages but might also be narrative descriptions [b]. It is these feasibility objectives and measures that progression criteria should be based on. Providing information about what the progression criteria are, and how they will be assessed, ensures that findings can be verified, and feasibility assessment is transparent. Not every objective might have associated progression criteria, for example some data might be collected to refine the trial processes rather than as an indication of feasibility. Although it has become standard practice to provide numerical targets for progression criteria, researchers should be mindful that this might not always be appropriate, and qualitative interpretations of feasibility should also be considered to inform progression criteria. Furthermore, investigators should also be aware that estimates of rates in pilot trials may be subject to considerable uncertainty, so it is best to be cautious about setting definitive thresholds that could be missed simply due to chance variation. Instead it is becoming increasingly common for investigators to use a traffic light system for criteria used to judge feasibility, whereby measures (e.g. recruitment rates) below a lower (red) threshold indicate major problems that require urgent attention (and perhaps cannot be remedied), amber indicating minor problems that require attention, and green indicating areas of no concern [c].	✓	✓
Rationale for progression criteria, including any data or clinical assumptions supporting any targets provided	It should be stated how progression criteria were derived to ensure transparent feasibility assessment. Rationale need not be statistical as pilot trials are usually underpowered for hypothesis testing, but some rationale for criteria should be given (e.g. based on feasibility objectives; clinical or contextual assumptions; pragmatically derived; based on previous feasibility or observational work; developed using consensus methods). Reporting this information might also enhance the wider usability of pilot trial findings (e.g. progression criteria developed for one pilot trial might inform progression criteria used in another).	✓	*

Suggested item	Rationale	Protocol	Result
Brief description of the involvement (role) of different stakeholders in developing, or agreeing, progression criteria	There is potential for bias when progression criteria are developed in isolation as different stakeholders might have competing interests to demonstrate feasibility to justify progression to further research funding. For this reason a multidisciplinary team of stakeholders may be involved in developing, or agreeing, progression criteria. Example stakeholders who might contribute to progression criteria development include: Clinical Trials Unit; Research Design Service; clinical professionals who will be implementing the pilot trial; PPI representatives; research funders; an independent Trial Steering Committee.	✓	*
Proposed method of multi-criteria assessment	Many pilot trials will have multiple progression criteria, so researchers should indicate a proposed method of multi-criteria assessment. Researchers might opt to take a holistic approach to feasibility assessment and view progression criteria as guidelines rather than strict rules. In this approach, they might instead consider whether targets were met, the implications for the future definitive trial, and whether any solutions to poorly performing criteria have been identified to come to an overall conclusion of feasibility. This may or may not involve weighting of specific criteria that are regarded as more fundamental than others. Alternatively, researchers might opt to take a more structured approach to multi-criteria assessment and determine overall progression based on the worst-performing criterion (if one criterion is not met then the trial is not feasible) [71].	✓	*
RESULTS			
Any changes to progression criteria after the pilot trial commenced, with reasons	An assessment or measure might change during a pilot trial because the change enables investigators to glean more information about the operation of the intervention or for reasons of acceptability or practicability [d]. These changes might directly or indirectly impact on the applicability of the pre-specified progression criteria. For example, progression criteria might be linked to a specific measurement instrument that might change during the conduct of the pilot trial, and so the progression criteria itself might require alteration to reflect this change. Because of the usefulness of such information to the overall assessment of trial feasibility, all changes to progression criteria, with reasons, should be reported.		✓
For each progression criterion, findings in terms of whether criteria indicate feasibility and if applicable, whether numerical targets were met	Findings for each progression criteria should be provided to demonstrate which aspects of the pilot trial were considered feasible. Where a RAG system was used researchers should indicate whether progression criteria were above the upper threshold (green), below the lower threshold (red), or between the two (amber). For any progression criteria that are not based on numerical targets, a clear statement to reflect whether the findings indicate feasibility is sufficient.		✓

Suggested item	Rationale	Protocol	Result
For each progression criterion, implications for the future definitive trial, including any proposed amendments	It is important to understand how the pilot trial findings have informed the definitive RCT [e]. For each progression criterion researchers should state any implications that their findings have for the definitive trial design. For example, if progression criteria were not met but proposed changes for definitive trial design have been identified these should be stated. However, any suggested changes should be based on evidence, or experience, generated from doing the pilot trial. This aligns with the revised Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare (CReDECI 2) which recommends that researchers provide a description of how intervention piloting has impacted a definitive intervention, including any changes made [233].		✓
Overall statement of trial feasibility (based on pilot trial findings and any other contextual considerations)	Researchers should provide an overall statement of feasibility based on their pilot trial findings and any other contextual considerations or external evidence generated whilst conducting their pilot trial. This is important because sometimes progression criteria do not adequately reflect trial feasibility. For example, a pilot trial might be feasible based on assessment of progression criteria but might not progress for other reasons such as unanticipated challenges faced, or factors external to the pilot trial. This aligns with the ADePT framework approach to identify and appraise potential solutions to problems that were faced during the pilot trial [82].		✓

*Items might be omitted from pilot trial results publications if the pilot trial protocol is published and can be referenced

a CONSORT 2010 statement: extension to randomised pilot and feasibility trials, Item 6a

b CONSORT 2010 statement: extension to randomised pilot and feasibility trials, Item 12a

c CONSORT 2010 statement: extension to randomised pilot and feasibility trials, Item 6c

d CONSORT 2010 statement: extension to randomised pilot and feasibility trials, Item 6b

e CONSORT 2010 statement: extension to randomised pilot and feasibility trials, Item 22a

6.5.4.2 Consider reporting in a table for clarity

To promote clarity researchers should consider reporting progression criteria and their associated findings in a table format. This is particularly useful for completed trials to report the progression criteria set, the corresponding finding and the implications for the future RCT design. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) is a transparent approach to grading the quality of evidence to inform healthcare recommendations. GRADE recommends using Summary of Findings (SoF) tables to provide a concise summary of key information that underpins recommendations. This format of evidence synthesis and reporting strikes a balance between simplicity of information presentation and completeness (or transparency) [234], and some pilot trial publications have effectively reported pilot trial findings in a similar format [139–142]. One example is presented below in Figure F3 [142].

Objectives	Criteria for success	Considerations
To evaluate the feasibility of procedures (e.g. randomisation, recruitment, collecting data, management and follow-up)	The trial would be considered feasible if it was run smoothly without serious problems or obstructions that were able to stop the study.	All research procedures were feasible but the following issues should be considered:
○ Randomisation		➢ No issue regarding the randomisation (i.e. no report regarding participants' disagreement with treatment allocation).
○ Recruitment		➢ Ideally, double blinding should be kept in order to maintain the quality of the trial but more assessors need to be provided for every clinic in order to reduce the risk factor of journey issues (patients did not want to travel to other physiotherapy clinics) if a future trial is to be sufficiently funded.
		➢ Increase the number of recruited physiotherapy clinics/ insurance companies in order to increase the recruitment rate.
		➢ An increase in the number of assessors may be considered. Setting assessment centres did not work in this trial due to participants' journey issues. It would be ideal to have an assessor in each clinic to enable the baseline assessment to take place local to each clinic prior to the first treatment session. That would then stop the patient needing to make the separate journey for the assessment or travelling to different physiotherapy clinics.
○ Collecting data		➢ Information for cost-effectiveness analysis should be considered in another way (set up an electronic system by collaborating with an insurance company or a physiotherapy company in order to record relevant information rather than giving a diary pocket book to participants).
		➢ Collecting level of education (less than post-secondary), headache at inception and low back pain, which are the significant predictors of persistent WAD.
○ Management		➢ No difficulty with the management for the trial.
○ Follow-up		➢ Face-to-face follow-up may be an issue because participants get back to their normal life and they may not want to come to a clinic owing to their work commitments. Telephone follow-up may be an interesting option for a future trial.
To evaluate recruitment rates, refusal rates and retention in the private sector in the UK	The trial would be considered feasible if • ≥ 50% of eligible patients were recruited • At least 3 participants a week per intervention arm were recruited • ≥ 80% of all recruited participants completed the follow-up at 3 months	Overall, the trial was feasible as: • 70% of eligible patients were recruited • An average of one (1.27) person was recruited per week (excluding temporary stopping of the trial). This point was an issue to modify in the future trial. An increase in the number of recruited physiotherapy clinics may be an option. • ~93% of recruited participants completed 3-month follow-up
To evaluate dropout rates of participants in the private sector in the UK	The trial would be considered feasible if ≤ 20% of all recruited participants dropped out	2/8 (25%) participants were lost to follow-up at 3 months. Therefore, the overall dropout in this trial was ~7%.
To estimate the required sample for a definitive trial	The trial would be considered feasible if it was feasible to achieve the sample size for a cluster RCT based upon recruitment data	The required sample size for a cluster RCT is 238 patients using 24 physiotherapy clinics based on power = 90%, significance level = 0.05, difference of NDI = 4 and cluster size = 10.

To evaluate the feasibility of data collection for cost-effectiveness analysis	The trial would be considered feasible if the following components of the cost-effective analysis were collected with minimal missing data:
	• General information (e.g. current work status and salary)
	• Direct medical costs
	  • Medical costs (e.g. physiotherapy, general practice and complementary medicine)
	  • Resource uses (e.g. diagnosis tests)
	• Indirect medical costs
	  • Participant journey costs
	  • Training costs for physiotherapists in the experimental arm
		Only 2 participants returned their diary pocket book. Another strategy for collecting information for cost-effectiveness analysis should be considered in another way for a future trial. Setting up an electronic recording system by collaborating with an insurance company or a physiotherapy company may be a good option in order to collect relevant information.

WAD, whiplash-associated disorder; RCT, randomised controlled trial; NDI, neck disability index.

https://doi.org/10.1371/journal.pone.0215803.t008

Figure F3 Example table reporting progression criteria findings and implications for definitive RCT

6.5.5 Chapter summary

This chapter presents a set of practical recommendations, including a simple infographic, for progression criteria for researchers to follow when (1) designing, (2) conducting, (3) analysing and (4) reporting external randomised pilot trials. These recommendations have been developed to address key concerns that were identified in earlier chapters of this thesis. The final recommendations presented in this chapter were informed by discussions that took place at two consultation workshops where key pilot trial stakeholders were invited to review, critique and provide feedback on early recommendation drafts.

Chapter 7 Discussion

7.1 Summary of findings

The overarching research question for this thesis, introduced in **Chapter 1**, was how should researchers use progression criteria in external randomised pilot trials to determine future definitive trial feasibility? This question was examined through four distinct research studies presented in Chapters 2 to 5.

Chapter 2 presented a methodological review of progression criteria reporting in 278 external randomised pilot trial publications published between January 2018 and December 2019. Many external randomised pilot trial publications screened were ineligible because they did not report prespecified progression criteria. Where progression criteria were reported researchers rarely stated who had decided on the progression criteria or how targets were chosen. Logistic regression indicated progression criteria reporting to be associated with some publication characteristics including journal and region. Journal prepublication peer review likely improved progression criteria reporting, with some peer reviewers requesting the inclusion of progression criteria in submitted manuscripts.

Chapter 3 presented a cross-sectional study of progression criteria, where stipulated, in 95 pilot trial funding applications submitted to the NIHR RfPB funding stream, with a funding decision made between July 2017 and July 2019. Half of the applications assessed at Stage 1 and nearly three quarters of those assessed at Stage 2, included progression criteria. Many applicants did not provide justification or rationale for any progression criteria targets stipulated in their applications. Prompts from funding committees, and publication of guidance by RfPB, likely increased progression criteria inclusion in subsequent funding applications.

Chapter 4 presented a qualitative study of 35 pilot trial stakeholder interviews, conducted between December 2020 and July 2021, that examined how stakeholders make progression decisions following external randomised pilot trials. I identified that a one size approach to progression does not fit all pilot trials. Researchers highlighted that a lack of knowledge about progression criteria, as well as limited time and resources led to challenges when developing progression criteria, and many suggested that more guidance would be beneficial. Researchers outlined other factors, in addition to progression criteria, that they have considered when assessing feasibility. Some described that feasibility assessment and progression to further research do not always align e.g. where a pilot trial is feasible but further funding cannot be obtained.

Chapter 5 presented an international web-based survey of 98 trialists, conducted over a four-week period between January 2022 and February 2022, that explored the feasibility and progression of the cohort of external randomised pilot trials studied in Chapter 2. An overwhelming majority of the surveyed trialists considered their pilot trial to be feasible or feasible with changes, however this did not always mean that they had or intended to progress to further research. Two key barriers to pilot trial progression identified included availability of funding for the future trial, and alternative CI priorities.

The findings from Chapters 2 to 5 supported the need for clearer guidance for using progression criteria in external randomised pilot trials to determine future definitive trial feasibility. This was addressed in **Chapter 6**, which presented a set of practical recommendations for progression criteria to guide researchers when (1) designing, (2) conducting, (3) analysing and (4) reporting external randomised pilot trials.

In this final chapter I will present my findings in context of the wider research, the strengths and limitations of this thesis, and outline the implications of these findings for different stakeholder groups.

7.2 Findings in context

Recommendations are often developed through a formal consensus method i.e. a structured facilitated technique to synthesise the opinions of a group of stakeholders to achieve agreement [235]. Examples include the Delphi process, which may also involve a formal consensus meeting, and the Nominal Group Technique (NGT) [80]. Many of these consensus methods require a lot of time, expert facilitation, and importantly are based on the existence of an evidence base upon which consensus is required [80], which did not exist prior to this thesis. While the recommendations I have presented in this thesis have not been formally developed and agreed using consensus methodology, they are based on multiple data sources including pilot trial funding applications, protocol and result publications, and the experiences and perspectives of different pilot trial stakeholders. They have also been revised based on feedback from external stakeholder experts outside of my supervisory team. Using quantitative and/or qualitative research methods to identify concerns or problems and propose practical solutions has previously been used to develop various recommendations for clinical trials [236,237]. The recommendations for progression criteria in internal pilot trials, described in Chapter 1, were also developed through a literature review and stakeholder workshop [22]. Although external validation of the recommendations presented in Chapter 6 of this thesis is required, they should be considered a good starting point to improve the feasibility assessment of clinical trials using external randomised pilot trials.

Some of the challenges associated with progression criteria described in this thesis are not specific to external randomised pilot trials. For example, publications of RCTs with internal pilot trials also do not often report, or lack detail on, how progression criteria are developed or used [22]. However, others are unique to the context of external pilot trials. For example, it would be considered very unusual for a feasible internal pilot trial to *not* progress to the definitive study, yet my findings indicate that this is not entirely uncommon for a feasible external randomised pilot trial, therefore the interlink between feasibility and progression is less straightforward.

Feasibility assessment through external pilot trials might also be considered more nuanced since there is often more uncertainty to begin with. Having the flexibility to make changes and adaptations to the pilot trial design throughout its conduct is one of the key benefits of external pilot trials and allows rigorous assessment of feasibility. To encourage this, pilot trials should be viewed as opportunities to learn, adapt and refine processes in preparation for a definitive trial, embracing the opportunity to explore alternative approaches until the trial design is optimal and all uncertainties have been sufficiently addressed. This supports earlier recommendations for determining trial feasibility following external randomised pilot trials [82,86], with increased focus on exploring challenges experienced and identifying potential solutions. However, there are also reasons why researchers might be reluctant to make too many changes to their pilot trial. Too many adaptations might mean that pilot trial processes and observed findings do not reflect those to be expected in the definitive trial e.g. observed effect rates [54,61], and more substantial changes might require further feasibility assessment before proceeding to a definitive trial.

Feasibility is not a static concept, what is considered feasible to one person might be infeasible to another. For example, a CI might consider that their pilot trial is feasible, but the healthcare providers implementing the trial might not. It has also been suggested that researchers might consider and frame feasibility from the perspective of funders [32], in an effort to obtain investments in further research. My findings indicate that recruitment and retention dominate uncertainties that are assessed in external pilot trials to determine feasibility. This corroborates previous findings [22,32] and might be expected given that poor recruitment has been identified as the most common reason that RCTs are discontinued across and within various specialties [6,10,238,239], which is often preventable. Furthermore recruitment and retention can directly impact, or be proxies for, other feasibility indicators. For example patient-initiated withdrawal (or retention) is the most common cause of missing data in trials registered to UK Clinical Trial Units (CTUs) [240], and (lack of) intervention acceptability has been associated with poor recruitment [241]. Not only are there multiple facets of feasibility, but interpretations of feasibility can change with time and context. The impact of Covid-19 demonstrates this. During the pandemic many pilot trials did not meet their progression criteria, and almost every non-Covid trial was considered infeasible because research priorities unexpectedly shifted.

My findings also provide further evidence to support the value of doing qualitative research within, or alongside, pilot trials [43,57,75,82,84,85], and suggest that where conducted, qualitative research findings often inform feasibility assessment, but are less often included in the progression criteria. This might be surprising given that a meta-epidemiological study published in 2020 reported that many researchers do not often embed qualitative research within their pilot trial design [242]. A potential explanation identified for this is that many CIs simply do not have sufficient funding to conduct

qualitative research within their pilot trials, despite considering it to be a valuable component of feasibility assessment.

The topic of funding was a recurring theme throughout this thesis. Researchers described having insufficient funding to conduct pilot trials as intended, and some considered availability of definitive trial funding to be the ultimate barrier to pilot trial progression. Researchers described how obtaining smaller pilot trial funding awards was comparatively easier than obtaining funding for a definitive RCT. This relative availability of pilot trial funding might result in some pilot trials being conducted unnecessarily without sufficient uncertainty, for example where a previous trial funding application was unsuccessful. This hypothesis would be supported by the vast number of pilot trials identified throughout this thesis that concluded that a future definitive trial would be feasible; greater than the exceedingly high rates of feasibility that have been previously reported in the literature [30,31]. An alternative hypothesis for this finding is that the competitive nature of academia can put pressure on investigators to demonstrate trial feasibility following external randomised pilot trials, as doing so forms a strong basis for further funding applications. This would suggest that more education is needed around when an external randomised pilot trial is appropriate, and further endorsement of the notion that every pilot trial is a success (and should be published), since those that are not feasible have avoided resources being wasted on large, expensive definitive trials that were likely to fail [15].

For a more junior investigator, pilot trials present an introduction to research irrespective of whether they demonstrate feasibility. They provide a comprehensive experience of applying for, and managing, research funding, developing research applications, navigating regulatory approvals, and managing a research study to completion. They take

less time, require less funding and can be integrated into a doctorate or fellowship. For research institutions, pilot trials allow CTUs and universities to work with new, perhaps less experienced investigators on smaller projects that are less financially risky. If the collaboration is successful, the CTU might then consider supporting the definitive RCT.

For the NIHR, pilot trials do not only advance research through better designed RCTs, but they also advance the careers of junior CIs by allowing them to develop necessary basic and applied research skills that have been associated with RCT success [243]. Therefore secondary to determining RCT feasibility, pilot trials might also promote better research through training and development of many early career researchers. However, this comes at a cost: my findings indicate that changing CI priorities can also present a barrier to pilot trial progression, with junior CIs returning to clinical work or not being considered competent enough to lead the subsequent definitive trial, contributing to research waste.

These considerations further underpin the main finding of this thesis: the need for guidance for how to use and report progression criteria in external pilot trials. This is timely since progression criteria are increasingly expected to be stipulated in both pilot trial funding applications and research publications yet are still widely under reported.

I hope that these recommendations, presented in Chapter 6, will support researchers to design good quality pilot trials that include clear and sensible progression criteria, often with limited time, funding and resources, and sometimes with limited research experience and skills. I also hope that these recommendations will encourage CIs to engage in wider discussion around progression criteria, for example with clinical colleagues and PPI members, and avoid developing them in isolation. In addition, I hope that these recommendations can support journal editors and peer reviewers when assessing

reporting quality of pilot trial manuscripts, and support research funder assessment of pilot trial funding applications.

7.3 Strengths of this research

The key strength of this research is the use of a mixed methods triangulation approach. By using both qualitative and quantitative research methods, I was able to draw on the strengths of different methodologies to gain a comprehensive understanding of this topic. For example, the methodological review indicated that many researchers do not report how they develop their progression criteria in pilot trial publications, and the study of RfPB applications indicated that progression criteria are also not often stipulated in pilot trial funding applications. The qualitative interview study provided potential explanations for these findings, identifying that many researchers are unsure how best to develop progression criteria so inconsistent methods can be used, and it can be challenging to stipulate progression criteria in funding applications and trial publications given tight word limits available.

The use of qualitative research methods in the interview study and open-ended questions in the survey might be criticised for potentially introducing bias, with researchers providing idealised responses i.e. articulating what they thought I wanted to hear, as opposed to what they do in reality. However, this limitation is perhaps not unique to qualitative data collection. I cannot be certain whether other researchers always do exactly what they have proposed in their funding application, nor can I assume that researchers report everything that they did in their pilot trial in their results publication. This further exemplifies the strength of using a triangulation approach to explore current

practice in relation to progression criteria from different perspectives along the life cycle of a pilot trial (i.e. application, conduct, reporting and progression).

7.4 Limitations of this research

The main limitation of this thesis is that it is unclear how generalisable the findings are. The RfPB study focussed only on pilot trial funding applications submitted to NIHR RfPB, and although the qualitative study involved researchers who worked on pilot trials funded through different sources, all participants were based in the UK. The pilot trials included in the methodological review and survey study were not restricted by funding source or country, however they too included predominately non-industry sponsored, UK based, pilot trials published only in four key journals in the field. Regional differences in pilot trial reporting (and therefore likely design) have been identified, with pilot trials from Canada associated with higher odds of reporting progression criteria in Chapter 2. This supports previous research which also identified that pilot trials from North America were associated with higher odds of progression criteria reporting compared to elsewhere [69]. Furthermore, a commentary published in September 2022 has suggested that National Institutes of Health (NIH) funding allocation disproportionally favours larger trials in the USA, and the authors outline how reinvestment of funding from larger trials could increase funding available for PAFS alongside other preliminary studies [244]. This highlights differences in funding mechanisms between countries. It is therefore unclear whether these findings and recommendations can be generalised to other settings.

It is also unclear whether these findings and recommendations are applicable to industry. The methodological review identified very few pilot trials that were industry sponsored, suggesting that industry rarely sponsor these types of studies. This might be because

industry sponsored trials are subjected to more time pressures and therefore cannot accommodate the additional time required to conduct an external pilot trial. Another potential explanation is that industry sponsored trials are predominately CTIMPs (Clinical Trial of an Investigational Medicinal Product, i.e. a drug trial) as opposed to trials of complex interventions, where there is potentially less uncertainty to begin with. The fact that pilot trials of drug interventions were less frequently identified in the methodological review (Chapter 2) and study of funding applications (Chapter 3) supports this hypothesis. Instead, most of the pilot trials identified were for complex interventions including counselling, lifestyle or physiotherapy interventions, followed by surgical interventions. However, industry sponsored RCTs can still fail, and it has been suggested that reasons for clinical trial failure might be different between industry and investigator sponsored trials [245]. In addition, the benefits of feasibility testing of industry sponsored trial designs has been described in a pharmaceutical industry media article [246]. Therefore it is unclear whether, and how, these findings can be used to support researchers conducting industry sponsored pilot trials.

Finally, there is no consensus based agreed definition for the concept of progression criteria, and the term progression criteria is not currently included in the NIHR glossary, despite its frequent use [247]. My methodological assessment of progression criteria was based on my own interpretation of this concept, and it is not unreasonable to assume that my interpretation might vary from other researchers' interpretations. This might have introduced bias to the sample of pilot trials studied throughout this thesis. This was highlighted in the survey study where there were discrepancies about whether progression criteria had been reported. In hindsight and if time and resources had been available, duplicate publication screening in Chapter 2 and further double data extraction in Chapters 2 and 3 might have mitigated against this limitation.

7.5 Implications of this research

The research presented in this thesis have implications for researchers, journal editors and research funders.

7.5.1 Implications for researchers

I hope that the recommendations presented in Chapter 6 will be of practical support to researchers when considering progression criteria for external randomised pilot trials across different pilot trial stages to promote rigorous and transparent trial feasibility assessment. I also hope that they might provide a useful tool to structure discussions around progression criteria with members of trial teams who might be less familiar with this concept e.g. PPI members (see future research for further discussion on this point).

By outlining *why* there was a need to develop these recommendations, I hope that researchers will recognise the importance of prespecifying clear, useful and informative progression criteria for external randomised pilot trials. To ensure usability I obtained critical feedback on initial recommendations and developed a simple infographic tool that can be quickly referred to during different pilot trial stages. To disseminate and encourage uptake, I presented these recommendations (oral presentation) at the 6th International Clinical Trials Methodology Conference (2022, Harrogate), and I have submitted a commentary manuscript reporting these recommendations to the *Pilot and Feasibility Studies* journal (under review).

7.5.2 Implications for journal editors and peer reviewers

The recommendations I have developed can further support journal editors to improve progression criteria reporting in submitted manuscripts, enhancing the overall quality of the pilot trials reported in their journals.

Peer review aims to ensure that publications conform to high standards of research and reporting, and informs fair editorial decision-making [248], however evidence for the effectiveness of peer-review is limited [249] and training, specialisation and appraisal of peer reviewers has been encouraged [250]. My findings identified the potential for peer reviewers to guide, prompt and ultimately improve quality of progression criteria reporting in pilot trial publications. Therefore, dissemination of these recommendations to peer reviewers might facilitate training and understanding of pilot trial progression criteria, to enhance the peer review process and subsequent publication quality [33].

7.5.3 Implications for research funders

My findings suggest that clear guidance from research funders is both appreciated and followed by funding applicants. Funders might consider embedding these recommendations into their guidance documents to improve overall quality of pilot trial applications and definitive trial feasibility assessment. Improved pilot trials would yield better returns on research funder investment in two directions: (1) avoid inappropriate progression of pilot trials to definitive RCTs that are not feasible and (2) avoid pilot trials being conducted unnecessarily (e.g. without sufficient uncertainty or clear progression criteria). Promoting transparent feasibility assessment might also benefit definitive trial funders, who can be more confident that feasibility has been adequately assessed before awarding larger research grants.

7.6 Recommendations for future research

My findings point to a number of areas for future trial methodology research for external randomised pilot trials, including the need to: embed findings into future development, and update, of established reporting guidelines; develop further resources for best practice to avoid randomised pilot trials being conducted unnecessarily; investigate generalisability of randomised pilot trials; consider the development of a PAFS repository; reduce inefficiencies associated with randomised pilot trials; explore the role of Research Ethics Committees and unique ethical considerations for randomised pilot trials; and identify opportunities and provide resources for better embedding PPI throughout randomised pilot trials. Each recommendation is elaborated on in this section.

7.6.1 Embed within established reporting guidelines

The primary aim of a reporting guideline is to improve reporting standard of research studies. Therefore, it is important that evidence based reporting guidelines are developed to meet researcher needs, and that existing reporting guidelines are periodically updated to include and reflect new evidence [251]. Reporting guidelines also have wider impact: by outlining what researchers should consider reporting, they can be used as a tool to support researchers when designing research studies. The EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network maintains an up-to-date electronic library of reporting guidelines and policy documents related to health research reporting [252]. At the time of writing (15th June 2022), the library contained 527 reporting guidelines which can be searched by study type and clinical area [252].

Journal editors can help improve pilot trial reporting by endorsing reporting guidelines [33,253], and encouraging publication of PAFS that are not considered feasible [46]. For

these recommendations to be most effective, they need to be embedded within reporting guidelines that have been produced using established research methods [251], are widely disseminated, and endorsed by journals and other research organisations [254]. Specifically, these recommendations should be considered for inclusion when updating the CONSORT extension for PAFS [24], and they should inform the proposed development of a SPIRIT extension to protocols of pilot and feasibility studies [41] to guide the design, and reporting, of external randomised pilot trial protocols.

7.6.2 Develop further resources for external randomised pilot trials

My findings highlighted that most published pilot trials are considered feasible or feasible with changes. It has been suggested that progression criteria might help avoid over enthusiastic interpretation of feasibility [31], however I found little difference in feasibility outcomes between pilot trials that did and did not report progression criteria. This might suggest that many external randomised pilot trials might be conducted unnecessarily, i.e. without sufficient uncertainty, that are highly likely to demonstrate feasibility. This highlights the need to promote existing resources to educate researchers about what PAFS are and when they should be conducted, to maximise research benefit and reduce research waste [63].

In 2011, Shanyinde et al. distinguished uncertainties that might be best investigated through randomised pilot trials from those that could be addressed through simpler non-randomised pilot and non-pilot feasibility studies [43]. Although it is unclear what these recommendations are based on, perhaps it is time to develop clear evidence-based guidance to highlight where alternative feasibility study designs might be appropriate and avoid randomised pilot trials being conducted unnecessarily.

To further improve researcher knowledge and understanding of PAFS, continued promotion and endorsement of existing resources, such as the conceptual framework to define PAFS [11], the CONSORT extension for PAFS [24] and the dedicated PAFS website [187] is required. In addition, efforts to develop new resources, including a mini video webinar series developed by the PAFS working group [187] is ongoing. One of the videos in the series that I co-produced specifically focuses on progression criteria, explaining what it is, why it is important and how it should be used. This is important considering some researchers considered progression criteria to be more appropriate to internal, rather than external, pilot trials. These videos are available from the Pilot and Feasibility Studies website (https://pilotandfeasibilitystudies.qmul.ac.uk/).

7.6.3 Investigate generalisability of external randomised pilot trials

Expanding on the previous recommendation, although many pilot trials are considered feasible, definitive trials still fail for various reasons [9]. Although this highlights the need to conduct pilot trials where uncertainties about definitive trial design exist, this might suggest that some external pilot trials do not adequately reflect definitive trial processes.

Since pilot trials are small and often include fewer clinical trial sites, those sites that are most research savvy and enthusiastic tend to be overrepresented in the pilot trial compared to the definitive RCT. The same might be said for intervention delivery, with research teams perhaps able to dedicate more time and support to the smaller number of pilot trial sites which cannot be replicated in the definitive trial when the intervention is rolled out to more sites. This could lead to feasibility outcomes (e.g. around recruitment, data completion and protocol adherence) that are very promising in the pilot trial, but unachievable in the definitive RCT.

Further knowledge and empirical evidence about how well observed processes in a pilot trial reflect those of a definitive trial is needed to ensure that researchers are setting progression criteria that are useful indicators of definitive (not pilot) trial feasibility.

7.6.4 Consider the development of a PAFS repository

Although publication of pilot trial protocols and result publications is improving, many pilot trial publications still go unpublished. This is a particular problem where pilot trials do not demonstrate feasibility [31], and might have introduced publication bias in this DPhil with non-feasible external pilot trials perhaps less likely to be written up for publication, or accepted if they are submitted. Strategies employed by researchers to address this issue include endorsing the notion that an unfeasible pilot trial is not a failed pilot trial [15], and the establishment of dedicated journals for publishing PAFS [29]. Yet many pilot trials still go unreported [31]. One unexplored area for future research is to develop a repository to link PAFS to definitive RCTs so to complete the research pathway and encourage documentation of all PAFS, irrespective of their findings.

This would also allow individual pilot trials to have wider impact i.e. the findings from one pilot trial might inform the design of other trials (not just the intended RCT). To facilitate this, clear progression criteria would be required to ensure that pilot trial findings are transparent and can be interpreted by other researchers to determine whether they are applicable to different contexts. PAFS reports could be uploaded directly to the repository by researchers, and indexed by design (i.e. randomised pilot, non-randomised pilot or feasibility study), clinical area, and feasibility objectives. Researchers could then search the repository to evaluate whether an existing pilot or feasibility study has already addressed an uncertainty they might have in a specific context, avoiding unnecessary duplication of PAFS.

7.6.5 Reduce inefficiencies associated with external randomised pilot trials

The key benefit of an external randomised pilot trial is robust feasibility assessment, with scope to make early changes to trial design to improve feasibility. However, pilot trials can take a long time to design, conduct, analyse and disseminate [30]. My findings indicate that the delay faced between an external pilot and definitive trial can lead to a loss of momentum, and highlights a desire amongst researchers for a faster, and more streamlined route of progression to a definitive trial where pilot trials are feasible. Reduced delays between external pilot and definitive trial might avoid '*trial fatigue*' of research teams, and the potential for the research question to become less pertinent if the healthcare context changes. This is timely given increased focus on policies for streamlined and efficient clinical research in the UK [255].

In Chapter 4 I identified suggestions amongst researchers for reducing this delay and improving efficiency, including: (1) the notion of adaptive pilot trial designs (promoting flexibility to change aspects of the pilot trial e.g. the intervention or a component of the intervention during feasibility assessment), (2) the inclusion of pilot trials in programme grants (with definitive trial funding allocated pending feasibility), and (3) allowing an external pilot trial to transition straight into a definitive RCT where there have been no significant changes to trial design, effectively resembling an internal pilot trial.

This is a significant area for future discussion. A previous qualitative research study presented at ICTMC 2019 highlighted potential conflict amongst funding panel participants (including NIHR, CRUK, CSO and ARUK), with some describing how staged funding could improve external pilot trial efficiency, and others feeling that

despite the appeal this would present significant logistical difficulties [26]. Further conversations between funders of pilot trials, definitive RCTs and researchers are required to outline whether it is ever appropriate for an external pilot trial to seamlessly proceed into a definitive RCT, and if so, under what conditions. This discussion might be informed by the ACCEPT checklist (2013) for deciding whether to include internal pilot data in the main trial dataset without compromising data integrity [256].

Remaining unaddressed questions might include: should researchers a priori outline in their protocol the conditions by which pilot trial data can feed into the main trial to avoid this being a post hoc decision?; what practical considerations are there for clinical trial sites who recruit to both the pilot trial and definitive trial where pilot trial and definitive RCT data is kept separate?; how can research funders facilitate streamlined progression, particularly where different funding sources are used for the pilot and definitive trial?; and what are the ethical implications?

7.6.6 Explore the role of Research Ethics Committee and ethical considerations for randomised pilot trials

The role of the Research Ethics Committee (REC) in reviewing pilot trial ethics applications, and the ethical implications of not establishing clear progression criteria, is an unaddressed perspective in this thesis.

Pilot trials avoid researchers conducting RCTs where they are uncertain about whether it is feasible, which could be regarded as unethical. However, there are also some specific and unique ethical considerations associated with external pilot trials. For example, it is important that the aims and objectives of pilot trials are clear, and participants are made aware how feasibility will be determined, so that they are not misled and do not confuse

the reasons for doing a pilot trial (to assess feasibility) with those of a main trial (to assess effectiveness) [257].

A previous review of 184 ethics applications for PAFS submitted to the Hamilton integrated Research Ethics Board (HiREB), Canada, identified that informed consent documents for PAFS are rarely transparent [258]. Many did not state a clear intention to assess feasibility (42.4%), outline specific feasibility objectives (19.6%) or the criteria for success of the pilot study (1.6%) [258]. It is unclear whether these findings can be generalised to other RECs, or whether standards have improved following publication of more recent guidance for pilot trials e.g. the CONSORT extension for PAFS [24].

Future research should further investigate the role of the REC in ensuring that pilot trial protocols, and participant facing materials, transparently state how feasibility is determined (i.e. progression criteria). Whether the recommendations outlined in this thesis are a useful tool for RECs when assessing pilot trial ethics applications is yet to be determined. This research question formed the basis for a successful UKRI and Mitacs funding award (awarded February 2020) for a Globalink Internship (grant reference NE/T014059/1) which would have added an additional 12-week research extension to this DPhil. Due to the impact of Covid-19 throughout this DPhil this internship did not go ahead, however the proposed study has been given provisional ethical approval by HIREB (reference 13731) and the protocol is detailed in Appendix G1 to inform future research to address this important perspective.

7.6.7 Identify opportunities, and develop resources, for embedding PPI in randomised pilot trials

Finally a perspective that has been considered throughout this thesis but requires further exploration is the role of PPI in pilot trials. The importance of PPI in research is widely acknowledged [228,259,260], and recommendations have been made for how to enhance co-production of PAFS with PPI members [261]. PPI members have previously described their desire to be more involved in PAFS data analysis [261], however involving PPI members in in numerical aspects of trials has historically been challenging, with a lack of resources and guidance identified as a key barrier [262,263].

My findings highlight inconsistencies about whether and how PPI can be involved in discussions around pilot trial progression criteria, with some researchers and PPI members hesitant, and others enthusiastic about this prospect. Further research is needed to explore how PPI members can engage in discussions around pilot trial progression criteria. The development of guidance and resources to support researchers to effectively engage PPI in pilot trials, and to provide PPI members with the knowledge and understanding needed to contribute to pilot trials, is a research priority.

7.7 Conclusion

This thesis has provided a comprehensive understanding of how progression criteria in external randomised pilot trials can inform feasibility assessment of future RCTs, and some of the associated challenges. Initial recommendations to support researchers using progression criteria for external randomised pilot trials have been outlined. I hope that these recommendations will support researchers, funders, editors and peer reviewers to include and encourage the inclusion of clear and useful progression criteria in pilot trials, leading to improved feasibility assessment and reduced research waste. For maximum impact, these recommendations should be considered to inform future development, or update, of established research guidelines for the design, conduct, analysis and reporting of external randomised pilot trials.

Appendices

List of publications related to this DPhil

The following publications are related to the research presented in this DPhil:

Chapter 2

Mellor K, Hopewell S. An investigation of the current use of progression criteria in external randomised pilot studies: a systematic review protocol. *OSF* 2020. doi:10.17605/OSF.IO/BN35K

Mellor K, Eddy S, Peckham N, et al. Progression from external pilot to definitive randomised controlled trial: a methodological review of progression criteria reporting. *BMJ Open* 2021;**11**:e048178. doi:10.1136/bmjopen-2020-048178

Chapter 3

Mellor K, Hejdenberg J, Morgan B, Hopewell S. Progression criteria in external randomised pilot trials: Protocol for a review of Research for Patient Benefit funding applications. *OSF* 2021. doi:10.17605/OSF.IO/89AP7

Mellor K, Harwood J, Hejdenberg J, et al. Inclusion of progression criteria in external randomised pilot trials: a cross sectional study of funding applications submitted to the NIHR Research for Patient Benefit Programme. *Trials* 2022;**23**:931. doi.org/10.1186/s13063-022-06868-8

Chapter 4

Mellor K, Albury C, Hopewell S. Using progression criteria to determine feasibility of external randomised pilot trials: protocol for a qualitative study of stakeholder views. *OSF* 2020. doi:10.17605/OSF.IO/5N2KZ

Mellor K, Dutton S J, Hopewell S, et al. How are progression decisions made following external randomised pilot trials? A qualitative interview study and framework analysis. *Trials* 2022;**23**:132. doi:10.1186/s13063-022-06063-9

Chapter 5

Mellor K, Dutton S J, Hopewell S. Feasibility and progression of a cohort of external randomised pilot trials: A web-based survey study. *OSF* 2021. doi:10.17605/OSF.IO/D28HR

Mellor K, Dutton S J, Hopewell S. Feasibility and progression of a cohort of external randomised pilot trials: A web-based survey. *Trials* 2022. In press.

Chapter 6

Mellor K, Albury C, Dutton S J, et al. Recommendations for progression criteria during external randomised pilot trial design, conduct, analysis and reporting. Under review.

List of presentations related to this DPhil

The following presentations are related to the research presented in this DPhil:

Chapter 2

Mellor K, Dutton S J, Hopewell S. 'Progression from external pilot to definitive randomised controlled trial are not adequately reported: a methodological review of progression criteria reporting', *Society for Clinical Trials*, Virtual meeting, 2021, Contributed session, CP-15, doi:10.1177/17407745211043721

Thabane L. 'Design and conduct of pilot and feasibility trials: focus on unresolved issues', *Society for Clinical Trials*, Virtual meeting, 2021, Invited Talk, SP-25, doi:10.1177/17407745211043721

Chapter 3

Mellor K, Dutton S J, Hopewell S, et al. 'Inclusion of Progression Criteria in External Randomised Pilot Trial Funding Applications Submitted to UK NIHR Research for Patient Benefit', *Society for Clinical Trials*, San Diego, 2022, Poster Presentation, https://www.sctweb.org/meeting/; Recipient of the best poster presentation award E-poster available online: https://tinyurl.com/mp6fmwtk

Chapter 4

Mellor K, Dutton S J, Hopewell S, et al. 'How are progression decisions made following external randomised pilot trials? A qualitative interview study and framework analysis', *Australian Trials Methodology Conference*, Virtual meeting, 2021, Session 3: Contributed talk; Tuesday A: Innovations in clinical trial design

Mellor K. ‘Progression from external pilot to future randomised controlled trial: A qualitative study of stakeholder perspectives and experiences’, *Botnar Institute Student Symposium*, Virtual meeting, 2021, poster presentation

Mellor K, Dutton S J, Hopewell S, et al. ‘How are Progression Decisions Made Following External Randomised Pilot Trials? A Qualitative Interview Study and Framework Analysis’, *Society for Clinical Trials*, San Diego, 2022, Contributed session

Chapter 6

Mellor K. ‘How can pilot trial progression criteria help researchers do better randomised trials?’, *Oxford-MRC DTP Symposium*, Oxford, 2022, Poster Presentation #18, E-poster available online: https://tinyurl.com/mrnk9huy

Mellor K, Albury C, Dutton S J, et al. ‘Recommendations for using progression criteria in external randomised pilot trials to determine feasibility’, *2022 International Clinical Trials Methodology Conference (ICTMC)*, Harrogate, 2022, PS.6C - Challenges in Improving Trials, oral presentation; Runner-up student oral presentation award

Other

Mellor K. ‘Investigating the use of prespecified criteria to inform progression from a randomised pilot study to a definitive RCT: A first year DPhil outline’, *Oxford-MRC DTP Symposium*, Virtual meeting, 2020, '3MRC' (3-Minute Research Competition)

Mellor K. ‘Progression criteria to proceed from pilot to definitive Randomised Controlled Trial’, *Botnar Institute Student Symposium*, Virtual meeting, 2020, oral presentation

Mellor K. ‘Improving the design conduct analysis and reporting of external pilot and feasibility studies’, *Oxford-MRC DTP Welcome event*, Virtual meeting, 2020, Student spotlight - Katie Mellor, oral presentation

Mellor K. ‘The use of progression criteria to inform progression from external pilot to definitive RCT’, *Trial Methodology Research Partnership (TMRP) Annual meeting*, Virtual meeting, 2020, oral presentation

Eldridge S, et al. ‘Good practice in planning, conducting and reporting pilot trials’, *2022 International Clinical Trials Methodology Conference (ICTMC)*, Harrogate, 2022, Educational workshop (W2.4)

List of other dissemination outputs related to this DPhil

The following outputs are related to the research presented in this DPhil:

Chapter 1

Mellor K, 'Trials on trial', *Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS) blog post,* 2021, https://www.ndorms.ox.ac.uk/news/blog/trials-on-trial

A1 CONSORT statement extension to randomised pilot and feasibility trials

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	
	2b	Specific objectives or research questions for pilot trial	
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
	4c	How participants were identified and consented	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	

Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	
Sample size	7a	Rationale for numbers in the pilot trial	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the pilot trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	

Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
	19a	If relevant, other important unintended consequences	
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	
Protocol	24	Where the pilot trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	
	26	Ethical approval or approval by research review committee, confirmed with reference number	

Citation: Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. BMJ. 2016;355.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010, extension to randomised pilot and feasibility trials, Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

A2 Tips for developing and using progression criteria for internal pilot studies

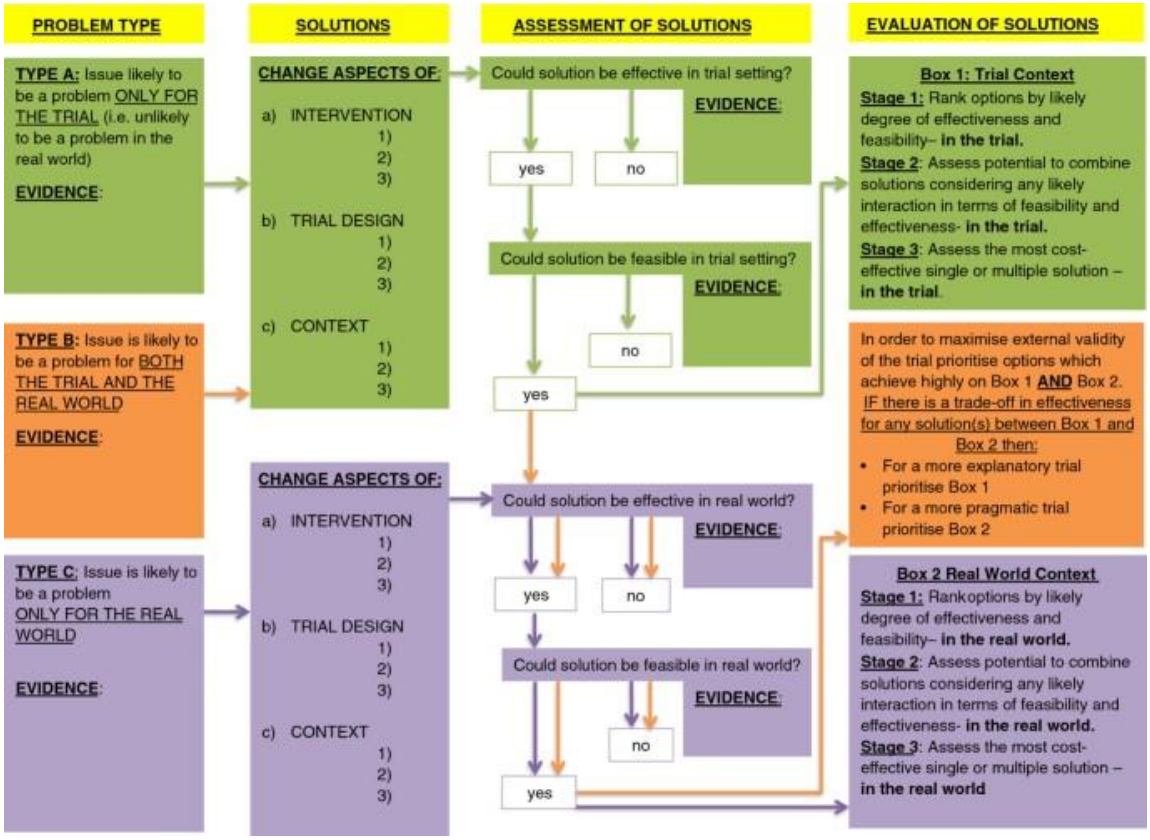
Reproduced from: Box 1 Avery KNL *et al.* Informing efficient randomised controlled trials: Exploration of challenges in developing progression criteria for internal pilot studies. *BMJ Open* 2017;**7**. doi:10.1136/bmjopen-2016-013537, published CC-BY 4.0

Box 1 Ten top tips for developing and using progression criteria for internal pilot studies

1. A traffic light system of green (go), amber (amend) and red (stop) might be preferable to a simple stop/go approach when specifying progression criteria for internal pilot studies;
2. Pre-specified progression criteria agreed with funders need to strike a careful balance between being firm enough to promote ambition in the trial team yet being flexible enough to allow opportunities to remedy early problems;
3. Recruitment progression criteria should be based on rates per centre per unit time (eg, per month) that can be easily extrapolated, rather than specifying that an absolute number should be reached by a specific date, due to the unpredictability of opening sites;
4. When recruitment falls behind, it is essential to explore screening logs to determine whether insufficient participants were approached, insufficient participants passed eligibility criteria or insufficient eligible participants agreed to randomisation;
5. The assessment of intervention adherence, cross-over and outcome event rates should take into account the duration from randomisation to timing of primary outcomes if sufficient data are to be gleaned in time to inform progression;
6. When assessing missing data, it is important to explore the degree of missing data within key outcomes as well as the percentage of participants with missing data;
7. Trial teams should involve both their funders and their Trial Steering Committee in assessing their progression criteria;
8. Pilot study recruitment sites should be representative of sites that recruit into the main study;
9. Triallists may be able to take the opportunity to assess whether changes to existing technologies have occurred since the original study was planned, so that new technologies can be considered with funders, such as using an adaptive design;
10. Pilot studies need to be reported fully. An extension to CONSORT guidelines for pilot and feasibility studies is now available.

A3 A process for Decision-making after Pilot and feasibility Trials (ADePT)

Reproduced from: Figure 2 Bugge C *et al.* A process for Decision-making after Pilot and feasibility Trials (ADePT): Development following a feasibility study of a complex intervention for pelvic organ prolapse. *Trials* 2013;**14**:1. doi:10.1186/1745-6215-14-353, published CC-BY 2.0



B1 Completed PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	N/A
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	27
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	25
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	26
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	27
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	28
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	29
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	29
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	30
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	31
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	31

Section and Topic	Item #	Checklist item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	N/A
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	32
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	33
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	33
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	33
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	34
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	35
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	35
Study characteristics	17	Cite each included study and present its characteristics.	Table B2, appendix B4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	37
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table B2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	67
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table B10, B11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	70
	23b	Discuss any limitations of the evidence included in the review.	73
	23c	Discuss any limitations of the review processes used.	73
	23d	Discuss implications of the results for practice, policy, and future research.	Chapter 7
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	27
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	27
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

B2 Eligibility assessment checklist for full text screening

Trial Descriptor				
Reference:				
PMID:				
Eligibility checklist				
Screening stage	Eligibility check	**Yes (tick and continue)**		**No (if no, do not continue)**
Title/abstract	Published between 2018-2019	Yes		No
Title/abstract	Study design described as a pilot or feasibility study	Yes		No
Title/abstract	In-human health care context	Yes		No
Full text	Randomised trial design	Yes		No
Full text	True pilot RCT design (piloting 1/>1 design component of a future definitive RCT to assess feasibility)	Yes		No
Full text	Reports progression criteria	Yes	No, but reports a recruitment or sample size target	No
Eligibility decision				
Eligible				
Ineligible				
Include in secondary subset				

B3 Data fields and coding strategy used

	Detailed data fields	Coded responses
1	PMID	
2	First author	
3	Country	
4	Journal	*British Medical Journal (BMJ) Open* *Pilot and Feasibility Studies (PAFS)* *Trials* *Public Library of Science (PLoS) One*
5	Funder	Industry Non-industry A combination Unknown
6	Completed/Protocol	Completed Protocol
7	Trial design	Parallel group Cluster Cross-over Factorial Stepped wedge Other
8	Therapeutic Area	Alternative medicine Anaesthesia Cardiology Critical Care Dentistry Dermatology Endocrinology Gastroenterology Geriatrics Hepatology Haematology/Immunology Infectious diseases Musculoskeletal Nephrology Neurology Obstetrics/Gynaecology Oncology Ophthalmology Orthopaedics Otolaryngology (ENT) Paediatrics Pain Palliative care Pharmacology Physiology Psychiatry/Psychology Public Health Radiology Respiratory

	Detailed data fields	Coded responses
		Rheumatology Stress Surgery Trauma Urology Other
9	Intervention type	Drug Surgery/Procedure Counselling/Lifestyle/Physiotherapy Equipment Other
10	Sample size target	
11	[If 7= Cluster] Number of clusters	
12	[If 6=Completed] Recruitment target met?	Yes No Unclear
13	Number of arms	2-arm >2-arms Unclear
14	Single/Multi centre	Single Multi-centre Unclear
15	Do specific objectives or research questions for pilot trial assess feasibility?	Yes No
16	Are primary feasibility objective(s) stated	Yes No
17	Areas of uncertainty (1/multiple)	1 area >1 areas
18	Area/areas of uncertainty?	
19	Where are uncertainties first reported (excluding abstract)?	Research question/s Aim Objectives Outcomes Outcome measures/trial measures Within the text (feasibility associated heading) Within the text (non-specific heading)
20	Any hypothesis testing?	Yes Yes with caution No
21	Trial outcomes address trial objectives?	Yes No Somewhat
22	Are completely defined prespecified assessments or measurements stated, including how and when they are assessed?	Yes No Somewhat
23	Are prespecified criteria (i.e Progression Criteria) used to judge whether, or how, to proceed with future definitive trial stated?	Yes No
24	Are these criteria referred to as ‘Progression Criteria’ (or similar wording)	Yes No

	Detailed data fields	Coded responses
25	Do progression criteria address the trial feasibility outcomes?	All None Some Unclear
26	What is the exact progression criteria wording?	
27	Who decided on progression criteria?	PI Funders TSC DMEC PPI representatives Clinicians Other Not reported
28	Is any rationale/justification for choice of progression criteria reported?	Yes For some criterions only No
29	What format is the progression criteria data?	Quantitative Qualitative A combination/mixed methods Unclear
30	[If 29=Quantitative] Quantitative data format	Distinct threshold Traffic light system or similar Other N/A
31	[If 29=Qualitative] Qualitative data format	Focus groups Interviews Surveys Observation Other N/A
32	Has/will Qualitative data be collected, and does this contribute towards progression criteria?	Yes collected (contributes to PC) Yes collected (DOES NOT contribute to PC) Not collected
33	Is the process of reviewing/analysing PC reported?	Yes No
34	Who is involved in reviewing/assessing progression criteria?	PI Funders TSC DMEC PPI representatives Clinicians Research team (non specific) Other Not reported
35	Are any peer review comments published related to progression criteria?	Yes No Unavailable
36	[If 35=Yes] Specify wording…	
37	[If 35=Yes] Are progression criteria (on the whole) a result of peer review comments (i.e. no PC in earlier manuscript version?)	Yes No Unclear

	Detailed data fields	Coded responses
38	[If 35=Yes] Are progression criteria stated but justification/rationale for specific criteria questioned	Yes No Unclear
39	[If 6=Completed] Did PAFS meet progression criteria	All Some None Unclear
40	[If 6=Completed] Is a statement of intention to proceed to a definitive trial reported?	Proceed Not proceed Conduct further pilot or feasibility assessment No statement reported
41	[If 6=Completed] Is there any justification given for the decision made?	Yes No
42	[If 6=Completed] Is there any comment on data quality e.g. proportion of missing/incomplete data from questionnaires or results	Yes No
43	[If 6=Completed] Is there any comment on refinement of hypotheses?	Yes No
44	[If 6=Completed][If 40=proceed] Are any proposed amendments to definitive trial design reported?	Yes changes No changes Not reported
45	[If 6=Completed][If 40=proceed] Has a funder for the definitive trial been identified?	Yes No Not reported
46	[If 6=Completed][If 45=Yes] Specify…	Industry Non-industry A combination Unknown
47	[If 6=Completed][If 40=proceed] Is a time frame for expectation to progress to the definitive trial been reported?	Yes No Not reported
48	[If 6=Completed][If 47=Yes] Specify…	0-6 months 6-12 months 12-24 months 24 months +
49	[If 6=Completed] Is a published protocol available?	Yes No, but protocol alternative available No
50	[If 6=Completed][If 49=Yes] Have objectives changed since protocol publication?	Yes significantly Yes minor detail No Not reported in protocol
51	[If 7=Completed][If 49=Yes] Have outcomes changed since protocol publication?	Yes significantly Yes minor detail No Not reported in protocol
52	[If 7=Completed][If 49=Yes] Have progression criteria changed since protocol publication?	Yes significantly Yes minor detail No Not reported in protocol

	Detailed data fields	Coded responses
53	[If 7=Completed][If 52=Yes] Is a reason for changing progression criteria given?	Yes No No PC reported in protocol

Items 39-53 were not applicable for trial protocol publications

B4 List of included studies

First author	Year	Journal	Study title	Data set
Ali	2018	BMJ Open	Individual cognitive stimulation therapy for people with intellectual disability and dementia: Protocol of a feasibility randomised controlled trial	Reports progression criteria
Battle	2019	BMJ open	A multicentre randomised feasibility STUdy evaluating the impact of a prognostic model for Management of BLunt chest wall trauma patients: STUMBL Trial	Reports progression criteria
Collings	2019	BMJ Open	INSoles to Ease Pressure (INSTEP) Study: A multicentre, randomised controlled feasibility study to compare the effectiveness of a novel instant optimised insole with a standard insole for people with diabetic neuropathy: A study protocol	Reports progression criteria
Dean	2018	BMJ Open	Community-based rehabilitation training after stroke: Results of a pilot randomised controlled trial (ReTrain) investigating acceptability and feasibility	Reports progression criteria
Dinneen	2019	BMJ Open	NeuroSAFE robot-assisted laparoscopic prostatectomy versus standard robot-assisted laparoscopic prostatectomy for men with localised prostate cancer (NeuroSAFE PROOF): Protocol for a randomised controlled feasibility study	Reports progression criteria
Edwards	2019	BMJ Open	Novel ACT-based eHealth psychoeducational intervention for students with mental distress: A study protocol for a mixed-methodology pilot trial	Reports progression criteria
Froghi	2019	BMJ Open	Ward-based Goal-Directed Fluid Therapy (GDFT) in Acute Pancreatitis (GAP) trial: Study protocol for a feasibility randomised controlled trial	Reports progression criteria
Furlano	2019	BMJ Open	Feasibility of a 6-month pilot randomised controlled trial of resistance training on cognition and brain health in Canadian older adults at-risk for diabetes: Study protocol	Reports progression criteria
Geraghty	2018	BMJ Open	Using an internet intervention to support self-management of low back pain in primary care: Findings from a randomised controlled feasibility trial (SupportBack)	Reports progression criteria

First author	Year	Journal	Study title	Data set
Griffin	2019	BMJ Open	Healthy Dads, Healthy Kids UK, a weight management programme for fathers: Feasibility RCT	Reports progression criteria
Guagliano	2019	BMJ Open	Whole family-based physical activity promotion intervention: The Families Reporting Every Step to Health pilot randomised controlled trial protocol	Reports progression criteria
Harper	2018	BMJ Open	Treatment of fatigue with physical activity and behavioural change support in vasculitis: Study protocol for an open-label randomised controlled feasibility study	Reports progression criteria
Hawley-Hague	2019	BMJ Open	Can smartphone technology be used to support an effective home exercise intervention to prevent falls amongst community dwelling older adults?: The TOGETHER feasibility RCT study protocol	Reports progression criteria
Hughes	2018	BMJ Open	Prediabetes in pregnancy, can early intervention improve outcomes? A feasibility study for a parallel randomised clinical trial	Reports progression criteria
Jolly	2018	BMJ Open	Protocol for a feasibility trial for improving breast feeding initiation and continuation: Assets-based infant feeding help before and after birth (ABA)	Reports progression criteria
Jones	2019	BMJ Open	Walk, Talk and Listen: A pilot randomised controlled trial targeting functional fitness and loneliness in older adults with hearing loss	Reports progression criteria
Keene	2019	BMJ Open	Progressive functional exercise versus best practice advice for adults aged 50 years or over after ankle fracture: Protocol for a pilot randomised controlled trial in the UK - The Ankle Fracture Treatment: Enhancing Rehabilitation (AFTER) study	Reports progression criteria
Lewis	2019	BMJ Open	Cuff Leak Test and Airway Obstruction in Mechanically Ventilated ICU Patients (COMIC): A pilot randomised controlled trial protocol	Reports progression criteria
Limond	2019	BMJ Open	Clinical and cost-effectiveness of teen online problem-solving for adolescents who have survived an acquired brain injury in the UK: Protocol for a randomised, controlled feasibility study (TOPS-UK)	Reports progression criteria
Lockstone	2019	BMJ Open	Non-Invasive Positive airway Pressure thErapy to Reduce Postoperative Lung complications following Upper abdominal Surgery (NIPPER PLUS): protocol for a single-centre, pilot, randomised controlled trial	Reports progression criteria
Lorenzini	2019	BMJ Open	Measuring changes in device use of a head-mounted low vision aid after personalised telerehabilitation: Protocol for a feasibility study	Reports progression criteria

First author	Year	Journal	Study title	Data set
McIntyre	2018	BMJ Open	FLUID trial: A protocol for a hospital-wide open-label cluster crossover pragmatic comparative effectiveness randomised pilot trial	Reports progression criteria
Mcpherson	2019	BMJ Open	Children and teens in charge of their health (catch): A protocol for a feasibility randomised controlled trial of solution-focused coaching to foster healthy lifestyles in childhood disability	Reports progression criteria
Morris	2019	BMJ Open	Dietary Approaches to the Management of type 2 Diabetes (DIAMOND): Protocol for a randomised feasibility trial	Reports progression criteria
Munce	2019	BMJ Open	Ontario Brain Injury Association Peer Support Program: A mixed methods protocol for a pilot randomised controlled trial	Reports progression criteria
Neves	2019	BMJ Open	Protocol for a feasibility study of a cohort embedded randomised controlled trial comparing NE phron S paring T reatment (NEST) for small renal masses	Reports progression criteria
O'Connor	2019	BMJ Open	SAFETEL randomised controlled feasibility trial of a safety planning intervention with follow-up telephone contact to reduce suicidal behaviour: Study protocol	Reports progression criteria
Orkin	2019	BMJ Open	Protocol for a mixed-methods feasibility study for the surviving opioid overdose with naloxone education and resuscitation (SOONER) randomised control trial	Reports progression criteria
Pai	2019	BMJ Open	Protocol for a double-blind, randomised, placebo-controlled pilot study for assessing the feasibility and efficacy of faecal microbiota transplant in a paediatric Crohn's disease population: PediCRaFT Trial	Reports progression criteria
Papathanassoglou	2019	BMJ Open	Relaxation for Critically ill Patient Outcomes and S tress-coping Enhancement (REPOSE): A protocol for a pilot randomised trial of an integrative intervention to improve critically ill patients' delirium and related outcomes	Reports progression criteria
Pennington	2019	BMJ Open	Internet delivery of intensive speech and language therapy for children with cerebral palsy: A pilot randomised controlled trial	Reports progression criteria
Pouw	2018	BMJ Open	Hospital at Home care for older patients with cognitive impairment: A protocol for a randomised controlled feasibility trial	Reports progression criteria
Quraishi	2019	BMJ Open	STOP-Colitis pilot trial protocol: A prospective, open-label, randomised pilot study to assess two possible routes of faecal microbiota transplant delivery in patients with ulcerative colitis	Reports progression criteria

First author	Year	Journal	Study title	Data set
Reddington	2018	BMJ Open	Does early intervention improve outcomes in the physiotherapy management of lumbar radicular syndrome? Results of the POLAR pilot randomised controlled trial	Reports progression criteria
Ribeiro	2019	BMJ Open	Effectiveness of a tailored rehabilitation versus standard strengthening programme for patients with shoulder pain: A protocol for a feasibility randomised controlled trial (the Otago MASTER trial)	Reports progression criteria
Schults	2018	BMJ Open	Normal saline instillation versus no normal saline instillation and lung Recruitment versus no lung recruitment with paediatric Endotracheal Suction: The NARES trial. A study protocol for a pilot, factorial randomised controlled trial	Reports progression criteria
Sharma	2018	BMJ Open	Pain education for patients with non-specific low back pain in Nepal: Protocol of a feasibility randomised clinical trial (PEN-LBP Trial)	Reports progression criteria
Sharma	2019	BMJ Open	Results of a feasibility randomised clinical trial on pain education for low back pain in Nepal: The Pain Education in Nepal-Low Back Pain (PEN-LBP) feasibility trial	Reports progression criteria
Steare	2019	BMJ Open	App to support Recovery in Early Intervention Services (ARIES) study: Protocol of a feasibility randomised controlled trial of a self-management Smartphone application for psychosis	Reports progression criteria
Sugg	2018	BMJ Open	Morita Therapy for depression (Morita Trial): A pilot randomised controlled trial	Reports progression criteria
Thyer	2018	BMJ Open	Randomised controlled feasibility trial of the Active Communication Education programme plus hearing aid provision versus hearing aid provision alone (ACE to HEAR): A study protocol	Reports progression criteria
Wall	2018	BMJ Open	Safety and feasibility evaluation of tourniquets for total knee replacement (SAFE-TKR): Study protocol	Reports progression criteria
Wiangkham	2019	BMJ Open	Pragmatic cluster randomised double-blind pilot and feasibility trial of an active behavioural physiotherapy intervention for acute non-specific neck pain: A mixed-methods protocol	Reports progression criteria
Wootton	2019	BMJ Open	Telehealth and texting intervention to improve HIV care engagement, mental health and substance use outcomes in youth living with HIV: A pilot feasibility and acceptability study protocol	Reports progression criteria

First author	Year	Journal	Study title	Data set
Yeung	2019	BMJ Open	Randomised controlled trial to investigate the effectiveness of thoracic epidural and paravertebral blockade in reducing chronic post-thoracotomy pain (TOPIC): A pilot study to assess feasibility of a large multicentre trial	Reports progression criteria
Abokhrais	2018	PAFS	A pilot randomised double blind controlled trial of the efficacy of purified fatty acids for the treatment of women with endometriosis-associated pain (PurFECT): Study protocol	Reports progression criteria
Artom	2019	PAFS	Cognitive-behavioural therapy for the management of inflammatory bowel disease-fatigue: A feasibility randomised controlled trial	Reports progression criteria
Aunger	2019	PAFS	A novel behavioural INTErvention to REduce Sitting Time in older adults undergoing orthopaedic surgery (INTEREST): Protocol for a randomised controlled feasibility study	Reports progression criteria
Bérubé	2019	PAFS	Feasibility of a tapering opioids prescription program for trauma patients at high risk of chronic consumption (TOPPtrauma): Protocol for a pilot randomized controlled trial	Reports progression criteria
Bick	2019	PAFS	Protocol for a two-arm feasibility RCT to support postnatal maternal weight management and positive lifestyle behaviour in women from an ethnically diverse inner city population: The SWAN feasibility trial	Reports progression criteria
Bjornstad	2019	PAFS	Healthy Parent Carers peer-led group-based health promotion intervention for parent carers of disabled children: Protocol for a feasibility study using a parallel group randomised controlled trial design	Reports progression criteria
Blanton	2019	PAFS	A web-based carepartner-integrated rehabilitation program for persons with stroke: Study protocol for a pilot randomized controlled trial	Reports progression criteria
Bostrøm	2019	PAFS	Clinical comparative effectiveness of acupuncture versus manual therapy treatment of lateral epicondylitis: Feasibility randomized clinical trial	Reports progression criteria
Bourne	2019	PAFS	Electrically assisted cycling for individuals with type 2 diabetes mellitus: Protocol for a pilot randomized controlled trial	Reports progression criteria
Bowyer-Crane	2019	PAFS	A randomised controlled feasibility trial and qualitative evaluation of an early years language development intervention: Study protocol of the 'outcomes of Talking Together evaluation and results' (oTTer) project	Reports progression criteria
Bryant	2018	PAFS	Cluster randomised controlled feasibility study of HENRY: A community-based intervention aimed at reducing obesity rates in preschool children	Reports progression criteria

First author	Year	Journal	Study title	Data set
Bui	2019	PAFS	App-based supplemental exercise during inpatient orthopaedic rehabilitation increases activity levels: A pilot randomised control trial	Reports progression criteria
Carswell	2019	PAFS	Implementing an arts-based intervention for patients with end-stage kidney disease whilst receiving haemodialysis: A feasibility study protocol 11 Medical and Health Sciences 1117 Public Health and Health Services 11 Medical and Health Sciences 1103 Clini	Reports progression criteria
Clark	2019	PAFS	Saline versus albumin fluid for extracorporeal removal with slow low efficiency dialysis (SAFER-SLED): Study protocol for a pilot trial	Reports progression criteria
Coe	2018	PAFS	A protocol for a randomised double-blind placebo-controlled feasibility study to determine whether the daily consumption of flavonoid-rich pure cocoa has the potential to reduce fatigue in people with relapsing and remitting multiple sclerosis (RRMS)	Reports progression criteria
Courtier	2018	PAFS	ACTIVE - A randomised feasibility trial study protocol of a behavioural intervention to reduce fatigue in women undergoing radiotherapy for early breast cancer: Study protocol	Reports progression criteria
Cro	2018	PAFS	Measuring skin necrosis in a randomised controlled feasibility trial of heat preconditioning on wound healing after reconstructive breast surgery: Study protocol and statistical analysis plan for the PREHEAT trial	Reports progression criteria
De Oliveira Braga	2019	PAFS	EMPOWER-PD - A physical therapy intervention to empower the individuals with Parkinson's disease: A study protocol for a feasibility randomized controlled trial	Reports progression criteria
Deary	2018	PAFS	A psychosocial intervention for the management of functional dysphonia: Complex intervention development and pilot randomised trial	Reports progression criteria
Ditai	2019	PAFS	BabyGel pilot: A pilot cluster randomised trial of the provision of alcohol handgel to postpartum mothers to prevent neonatal and young infant infection-related morbidity in the community	Reports progression criteria
Downey	2018	PAFS	Trial of Remote Continuous versus Intermittent NEWS monitoring after major surgery (TRaCINg): Protocol for a feasibility randomised controlled trial	Reports progression criteria
Drew	2019	PAFS	A protocol for a randomised controlled, double-blind feasibility trial investigating fluoxetine treatment in improving memory and learning impairments in patients with mesial temporal lobe epilepsy: Fluoxetine, Learning and Memory in Epilepsy (FLAME trial	Reports progression criteria

First author	Year	Journal	Study title	Data set
Duncan	2018	PAFS	Physical therapy and deep brain stimulation in Parkinson's Disease: Protocol for a pilot randomized controlled trial	Reports progression criteria
Dunn	2019	PAFS	Evaluating Augmented Depression Therapy (ADepT): Study protocol for a pilot randomised controlled trial	Reports progression criteria
Fuller	2018	PAFS	The ACUTE (Ambulance CPAP: Use, Treatment effect and economics) feasibility study: A pilot randomised controlled trial of prehospital CPAP for acute respiratory failure	Reports progression criteria
Golla	2018	PAFS	Home-based balance training using Wii Fit™: A pilot randomised controlled trial with mobile older stroke survivors	Reports progression criteria
Hayes	2019	PAFS	We Can Quit2 (WCQ2): A community-based intervention on smoking cessation for women living in disadvantaged areas of Ireland - Study protocol for a pilot cluster randomised controlled trial	Reports progression criteria
Hilari	2019	PAFS	Adjustment with aphasia after stroke: Study protocol for a pilot feasibility randomised controlled trial for SUpporting wellbeing through PEeR Befriending (SUPERB)	Reports progression criteria
Horne	2019	PAFS	Regaining Confidence after Stroke (RCAS): A feasibility randomised controlled trial (RCT)	Reports progression criteria
Jones	2019	PAFS	Rapid Analgesia for Prehospital hip Disruption (RAPID): Findings from a randomised feasibility study	Reports progression criteria
Kebbe	2019	PAFS	Feasibility, user experiences, and preliminary effect of Conversation Cards for Adolescents© on collaborative goal-setting and behavior change: Protocol for a pilot randomized controlled trial	Reports progression criteria
Kohrt	2018	PAFS	Reducing stigma among healthcare providers to improve mental health services (RESHAPE): Protocol for a pilot cluster randomized controlled trial of a stigma reduction intervention for training primary healthcare workers in Nepal	Reports progression criteria
Lodder	2019	PAFS	Stigma of living as an autism carer: A brief psycho-social support intervention (SOLACE). Study protocol for a randomised controlled feasibility study	Reports progression criteria
Logan	2018	PAFS	Standing Practice In Rehabilitation Early after Stroke (SPIRES): A functional standing frame programme (prolonged standing and repeated sit to stand) to improve function and quality of life and reduce neuromuscular impairment in people with severe sub-acu	Reports progression criteria

First author	Year	Journal	Study title	Data set
Loughnan	2019	PAFS	A single-centre, randomised controlled feasibility pilot trial comparing performance of direct laryngoscopy versus videolaryngoscopy for endotracheal intubation in surgical patients	Reports progression criteria
Malden	2019	PAFS	A feasibility cluster randomised controlled trial of a preschool obesity prevention intervention: ToyBox-Scotland	Reports progression criteria
McGovern	2018	PAFS	Promoting Alcohol Reduction in Non- Treatment Seeking parents (PAReNTS): A protocol for a pilot feasibility cluster randomised controlled trial of alcohol screening and brief interventions to reduce parental alcohol use disorders in vulnerable families	Reports progression criteria
McIntosh	2018	PAFS	On the Road to Recovery psychological therapy versus treatment as usual for forensic mental health patients: Study protocol for a randomized controlled feasibility trial	Reports progression criteria
Mehta	2019	PAFS	A randomised controlled feasibility trial to evaluate local heat preconditioning on wound healing after reconstructive breast surgery: The preHEAT trial	Reports progression criteria
Meiksin	2019	PAFS	Protocol for pilot cluster RCT of project respect: A school-based intervention to prevent dating and relationship violence and address health inequalities among young people	Reports progression criteria
Milbury	2018	PAFS	A research protocol for a pilot randomized controlled trial designed to examine the feasibility of a couple-based mind-body intervention for patients with metastatic lung cancer and their partners	Reports progression criteria
Milbury	2019	PAFS	A research protocol for a pilot, randomized controlled trial designed to examine the feasibility of a dyadic versus individual yoga program for family caregivers of glioma patients undergoing radiotherapy	Reports progression criteria
Moore	2018	PAFS	Prehospital recognition and antibiotics for 999 patients with sepsis: Protocol for a feasibility study	Reports progression criteria
Morgan	2019	PAFS	A pilot randomised controlled trial of physical activity facilitation for older adults: Feasibility study findings	Reports progression criteria
Morton	2018	PAFS	Chlorhexidine vaginal preparation versus standard treatment at caesarean section to reduce endometritis and prevent sepsis - A feasibility study protocol (the PREPS trial)	Reports progression criteria

First author	Year	Journal	Study title	Data set
Murphy	2018	PAFS	Supporting general practitioner-based care for poorly controlled type 2 diabetes mellitus (the DECIDE study): Feasibility study and protocol for a pilot cluster randomised controlled trial	Reports progression criteria
Mutedzi	2019	PAFS	Improving bereavement outcomes in Zimbabwe: Protocol for a feasibility cluster trial of the 9-cell bereavement tool	Reports progression criteria
Myers	2019	PAFS	Accelerometer-based assessment of physical activity within the Fun for Wellness online behavioral intervention: Protocol for a feasibility study	Reports progression criteria
Negm	2018	PAFS	Getting fit for hip and knee replacement: A protocol for the Fit-Joints pilot randomized controlled trial of a multi-modal intervention in frail patients with osteoarthritis	Reports progression criteria
Newlands	2019	PAFS	Pilot randomised controlled trial of Weight Watchers® referral with or without dietitianled group support for weight loss in women treated for breast cancer: The BRIGHT (BReast cancer weIGHT loss) trial	Reports progression criteria
O'Regan	2019	PAFS	An evaluation of an intervention designed to help inactive adults become more active with a peer mentoring component: A protocol for a cluster randomised feasibility trial of the Move for Life programme	Reports progression criteria
Paul	2019	PAFS	Vital sign monitoring with continuous pulse oximetry and wireless clinical notification after surgery (the VIGILANCE pilot study)- A randomized controlled pilot trial	Reports progression criteria
Payne	2018	PAFS	Study protocol for a randomised pilot study of a computer-based, non-pharmacological cognitive intervention for motor slowing and motor fatigue in Parkinson's disease	Reports progression criteria
Perman-Howe	2018	PAFS	The effect of alcohol strength on alcohol consumption: A randomised controlled cross-over pilot trial	Reports progression criteria
Philip	2019	PAFS	A randomised phase II trial to examine feasibility of standardised, early palliative (STEP) care for patients with advanced cancer and their families [ACTRN12617000534381]: A research protocol	Reports progression criteria
Pile	2018	PAFS	A brief early intervention for adolescent depression that targets emotional mental images and memories: Protocol for a feasibility randomised controlled trial (IMAGINE trial)	Reports progression criteria

First author	Year	Journal	Study title	Data set
Ponsford	2018	PAFS	Study protocol for the optimisation, feasibility testing and pilot cluster randomised trial of Positive Choices: A school-based social marketing intervention to promote sexual health, prevent unintended teenage pregnancies and address health inequalities	Reports progression criteria
Purcell	2018	PAFS	Eutectic mixture of local anaesthetics (EMLA®) as a primary dressing on painful chronic leg ulcers: A pilot randomised controlled trial	Reports progression criteria
Qurashi	2019	PAFS	Glycopyrrolate in comparison to hyoscine hydrobromide and placebo in the treatment of hypersalivation induced by clozapine (GOTHIC1): A feasibility study	Reports progression criteria
Rowe	2019	PAFS	A classroom-based intervention targeting working memory, attention and language skills in 4-5 year olds (RECALL): Study protocol for a cluster randomised feasibility trial	Reports progression criteria
Sanfilippo	2019	PAFS	A study protocol for testing the feasibility of a randomised stepped wedge cluster design to investigate a Community Health Intervention through Musical Engagement (CHIME) for perinatal mental health in the Gambia	Reports progression criteria
Sangraula	2018	PAFS	Protocol for a feasibility study of groupbased focused psychosocial support to improve the psychosocial well-being and functioning of adults affected by humanitarian crises in Nepal: Group Problem Management plus (PM+)	Reports progression criteria
Schlaeger	2018	PAFS	Double-blind acupuncture needles: A multi-needle, multi-session randomized feasibility study	Reports progression criteria
Schmitz	2019	PAFS	Impact of endurance exercise and probiotic supplementation on the intestinal microbiota: A cross-over pilot study	Reports progression criteria
Shvedko	2018	PAFS	Physical Activity Intervention for Loneliness (PAIL) in community-dwelling older adults: Protocol for a feasibility study	Reports progression criteria
Slobogean	2019	PAFS	Fixation using alternative implants for the treatment of hip fractures (FAITH-2): Design and rationale for a pilot multi-centre 2 × 2 factorial randomized controlled trial in young femoral neck fracture patients	Reports progression criteria
Snowden	2018	PAFS	Preoperative Behavioural Intervention versus standard care to Reduce Drinking before elective orthopaedic Surgery (PRE-OP BIRDS): Protocol for a multicentre pilot randomised controlled trial	Reports progression criteria
Sosnowski	2018	PAFS	A feasibility study of a randomised controlled trial to examine the impact of the ABCDE bundle on quality of life in ICU survivors	Reports progression criteria

First author	Year	Journal	Study title	Data set
Tan	2019	PAFS	The efficacy of foot orthoses in individuals with patellofemoral osteoarthritis: A randomised feasibility trial	Reports progression criteria
Timko	2018	PAFS	Cognitive remediation therapy (CRT) as a pretreatment intervention for adolescents with anorexia nervosa during medical hospitalization: A pilot randomized controlled trial protocol	Reports progression criteria
Totty	2019	PAFS	Assessing the effectiveness of dialkylcarbamoylchloride (DACC)-coated post-operative dressings versus standard care in the prevention of surgical site infection in clean or clean-contaminated, vascular surgery (the DRESSINg trial): Study protocol for a pi	Reports progression criteria
Volkmer	2018	PAFS	The 'Better Conversations with Primary Progressive Aphasia (BCPPA)' program for people with PPA (Primary Progressive Aphasia): Protocol for a randomised controlled pilot study	Reports progression criteria
Vranceanu	2019	PAFS	Results of a feasibility randomized controlled trial (RCT) of the Toolkit for Optimal Recovery (TOR): A live video program to prevent chronic pain in at-risk adults with orthopedic injuries	Reports progression criteria
Whitehead	2019	PAFS	HATRIC: A study of Pelargonium sidoides root extract EPs®7630 (Kaloba®) for the treatment of acute cough due to lower respiratory tract infection in adults-study protocol for a double blind, placebocontrolled randomised feasibility trial	Reports progression criteria
Wiggins	2018	PAFS	Testing the effectiveness of REACH Pregnancy Circles group antenatal care: Protocol for a randomised controlled pilot trial	Reports progression criteria
Wong	2018	PAFS	Thiamine versus placebo in older heart failure patients: Study protocol for a randomized controlled crossover feasibility trial (THIAMINE-HF)	Reports progression criteria
Wurz	2019	PAFS	Exploring the feasibility and acceptability of a mixed-methods pilot randomized controlled trial testing a 12-week physical activity intervention with adolescent and young adult cancer survivors	Reports progression criteria
Hilton	2018	PLoS ONE	Randomised feasibility trial to compare three standard of care chemotherapy regimens for early stage triple-negative breast cancer (REaCT-TNBC trial)	Reports progression criteria
Karlsson	2019	PLoS ONE	Feasibility of preoperative supervised home-based exercise in older adults undergoing colorectal cancer surgery – A randomized controlled design	Reports progression criteria

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Wiangkham	2019	PLoS ONE	A cluster randomised, double-blind pilot and feasibility trial of an active behavioural physiotherapy intervention for acute whiplash-associated disorder (WAD)II	Reports progression criteria
Ahnfeldt	2019	Trials	FortiColos - A multicentre study using bovine colostrum as a fortifier to human milk in very preterm infants: Study protocol for a randomised controlled pilot trial	Reports progression criteria
Barrett	2018	Trials	Feasibility of a physical activity programme embedded into the daily lives of older adults living in nursing homes: Protocol for a randomised controlled pilot feasibility study	Reports progression criteria
Brennan	2018	Trials	Prevention of striae gravidarum: Study protocol for a pilot randomised controlled trial	Reports progression criteria
Browne	2019	Trials	Probiotics in pregnancy: Protocol of a double-blind randomized controlled pilot trial for pregnant women with depression and anxiety (PIP pilot trial)	Reports progression criteria
Burroughs	2018	Trials	A feasibility study for NOn-Traditional providers to support the management of Elderly People with Anxiety and Depression: The NOTEPAD study Protocol	Reports progression criteria
Cao	2018	Trials	Aerobic exercise-based cardiac rehabilitation in Chinese patients with coronary heart disease: Study protocol for a pilot randomized controlled trial	Reports progression criteria
Chhetri	2019	Trials	Repetitive vascular occlusion stimulus (RVOS) versus standard care to prevent muscle wasting in critically ill patients (ROSProx):a study protocol for a pilot randomised controlled trial	Reports progression criteria
Crawford	2018	Trials	Psychological Support for Personality (PSP) versus treatment as usual: Study protocol for a feasibility randomized controlled trial of a low intensity intervention for people with personality disorder	Reports progression criteria
Deb	2018	Trials	Aggression Following Traumatic brain injury: Effectiveness of Risperidone (AFTER): Study protocol for a feasibility randomised controlled trial	Reports progression criteria
Forster	2018	Trials	An intervention to support stroke survivors and their carers in the longer term (LoTS2Care): Study protocol for a cluster randomised controlled feasibility trial	Reports progression criteria
Froghi	2018	Trials	Cardiac output Optimisation following Liver Transplant (COLT) trial: Study protocol for a feasibility randomised controlled trial	Reports progression criteria

First author	Year	Journal	Study title	Data set
Greenwood	2018	Trials	The U&I study: Study protocol for a feasibility randomised controlled trial of a pre-cognitive behavioural therapy digital 'informed choice' intervention to improve attitudes towards uptake and implementation of CBT for psychosis	Reports progression criteria
He	2018	Trials	Xue-Fu-Zhu-Yu capsule in the treatment of qi stagnation and blood stasis syndrome: a study protocol for a randomised controlled pilot and feasibility trial	Reports progression criteria
Hutchings	2018	Trials	CONTRACT Study - CONservative TReatment of Appendicitis in Children (feasibility): Study protocol for a randomised controlled Trial	Reports progression criteria
Lee	2018	Trials	Effect and safety of acupuncture for Hwa-byung, an anger syndrome: A study protocol of a randomized controlled pilot trial	Reports progression criteria
Linnemayr	2018	Trials	Behavioral economics-based incentives supported by mobile technology on HIV knowledge and testing frequency among Latino/a men who have sex with men and transgender women: Protocol for a randomized pilot study to test intervention feasibility and acceptab	Reports progression criteria
Littlewood	2019	Trials	Protocol for a multi-centre pilot and feasibility randomised controlled trial with a nested qualitative study: Rehabilitation following rotator cuff repair (the RaCeR study)	Reports progression criteria
Macken	2018	Trials	Palliative long-term abdominal drains versus repeated drainage in individuals with untreatable ascites due to advanced cirrhosis: Study protocol for a feasibility randomised controlled trial	Reports progression criteria
Marsh	2018	Trials	A novel integrated dressing to secure peripheral intravenous catheters in an adult acute hospital: A pilot randomised controlled trial	Reports progression criteria
Marsh	2018	Trials	Expert versus generalist inserters for peripheral intravenous catheter insertion: A pilot randomised controlled trial	Reports progression criteria
Mayo-Wilson	2019	Trials	Microenterprise intervention to reduce sexual risk behaviors and increase employment and HIV preventive practices in economically-vulnerable African-American young adults (EMERGE): Protocol for a feasibility randomized clinical trial	Reports progression criteria
Nymberg	2018	Trials	Pilot study on increased adherence to physical activity on prescription (PAP) through mindfulness: Study protocol	Reports progression criteria
Pace	2019	Trials	Cognitively-Based Compassion Training versus cancer health education to improve health-related quality of life in survivors of solid tumor cancers and their informal caregivers: Study protocol for a randomized controlled pilot trial	Reports progression criteria

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Payne Riches	2019	Trials	The Salt Swap intervention to reduce salt intake in people with high blood pressure: Protocol for a feasibility randomised controlled trial	Reports progression criteria
Poolman	2019	Trials	CARer-ADministration of as-needed subcutaneous medication for breakthrough symptoms in homebased dying patients (CARiAD): Study protocol for a UK-based open randomised pilot trial	Reports progression criteria
Pressman	2019	Trials	Conducting a pilot randomized controlled trial of community-based mindfulness-based stress reduction versus usual care for moderate-to-severe migraine: Protocol for the Mindfulness and Migraine Study (M&M)	Reports progression criteria
Pyle	2019	Trials	Study protocol for a randomised controlled trial of CBT vs antipsychotics vs both in 14-18-year-olds: Managing Adolescent first episode Psychosis: A feasibility study (MAPS)	Reports progression criteria
Russell	2018	Trials	Feasibility of an online mindfulness-based program for patients with melanoma: Study protocol for a randomised controlled trial	Reports progression criteria
Selfe	2019	Trials	Acceptability and feasibility of a 12-week yoga vs. educational film program for the management of restless legs syndrome (RLS): Study protocol for a randomized controlled trial	Reports progression criteria
Taylor	2019	Trials	Protocol for a randomised controlled feasibility study examining the efficacy of brief cognitive therapy for the Treatment of Anxiety Disorders in Adolescents (TAD-A)	Reports progression criteria
Van Oostveen	2018	Trials	Prevention of Infections in Cardiac Surgery study (PICS): Study protocol for a pragmatic cluster-randomized factorial crossover pilot trial	Reports progression criteria
Watt	2019	Trials	A counseling intervention to address HIV stigma at entry into antenatal care in Tanzania (Maisha): Study protocol for a pilot randomized controlled trial	Reports progression criteria
Wright	2018	Trials	The clinical and cost effectiveness of adapted dialectical behaviour therapy (DBT) for bipolar mood instability in primary care (ThrIVe-B programme): A feasibility study	Reports progression criteria
Youssef	2019	Trials	Addition of a new three-dimensional adjustable cervical thoracic orthosis to a multi-modal program in the treatment of nonspecific neck pain: Study protocol for a randomised pilot trial	Reports progression criteria
Zeng	2019	Trials	Si-ni-tang (a Chinese herbal formula) for improving immunofunction in sepsis: Study protocol for a pilot randomized controlled trial	Reports progression criteria

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Ainsworth	2019	BMJ Open	Feasibility trial of a digital self-management intervention ' My Breathing Matters' to improve asthma-related quality of life for UK primary care patients with asthma	Comparator subset
Amaefule	2018	BMJ Open	Effectiveness and acceptability of myoinositol nutritional supplement in the prevention of gestational diabetes (EMmY): A protocol for a randomised, placebo-controlled, double-blind pilot trial	Comparator subset
Andrén	2019	BMJ Open	Therapist-guided and parent-guided internet-delivered behaviour therapy for paediatric Tourette's disorder: A pilot randomised controlled trial with long-term follow-up	Comparator subset
Bana	2019	BMJ Open	Implementation of the Symptom Navi © Programme for cancer patients in the Swiss outpatient setting: A study protocol for a cluster randomised pilot study (Symptom Navi© Pilot Study)	Comparator subset
Beishon	2019	BMJ Open	Effects of brain training on brain blood flow (The Cognition and Flow Study - CogFlowS): Protocol for a feasibility randomised controlled trial of cognitive training in dementia	Comparator subset
Black	2018	BMJ Open	The HARMONIC trial: Study protocol for a randomised controlled feasibility trial of Shaping Healthy Minds - A modular transdiagnostic intervention for mood, stressor-related and anxiety disorders in adults	Comparator subset
Bosanquet	2019	BMJ Open	Perineural local anaesthetic catheter after major lower limb amputation trial (PLACEMENT): Results from a randomised controlled feasibility trial	Comparator subset
Brady	2018	BMJ Open	Integrating culturally informed approaches into physiotherapy assessment and treatment of chronic pain: A pilot randomised controlled trial	Comparator subset
Clark	2019	BMJ Open	Prostate cancer androgen receptor splice variant 7 biomarker study - A multicentre randomised feasibility trial of biomarker-guided personalised treatment in patients with advanced prostate cancer (the VARIANT trial) study protocol	Comparator subset
Clarke	2019	BMJ Open	Safety and efficacy of 2% chlorhexidine gluconate aqueous versus 2% chlorhexidine gluconate in 70% isopropyl alcohol for skin disinfection prior to percutaneous central venous catheter insertion in preterm neonates: The ARCTIC randomised-controlled feasib	Comparator subset

First author	Year	Journal	Study title	Data set
Eaton	2019	BMJ Open	Protocol for a pilot randomised controlled trial evaluating feasibility and acceptability of cognitive remediation group therapy compared with mutual aid group therapy for people ageing with HIV-associated neurocognitive disorder (HAND) in Toronto, Canada	Comparator subset
Ellis-Hill	2019	BMJ Open	HeART of Stroke: Randomised controlled, parallel-Arm, feasibility study of a community-based arts and health intervention plus usual care compared with usual care to increase psychological well-being in people following a stroke	Comparator subset
Ewais	2019	BMJ Open	Protocol for a pilot randomised controlled trial of mindfulness-based cognitive therapy in youth with inflammatory bowel disease and depression	Comparator subset
Farragher	2019	BMJ Open	Protocol for a pilot randomised controlled trial of an educational programme for adults on chronic haemodialysis with fatigue (Fatigue-HD)	Comparator subset
Gordon	2019	BMJ Open	Combining cognitive bias modification training (CBM) and transcranial direct current stimulation (tDCS) to treat binge eating disorder: Study protocol of a randomised controlled feasibility trial	Comparator subset
Granic	2019	BMJ Open	Milk and resistance exercise intervention to improve muscle function in community-dwelling older adults at risk of sarcopenia (MIlkMAN): Protocol for a pilot study	Comparator subset
Griffin	2019	BMJ Open	Intramedullary nails versus distal locking plates for fracture of the distal femur: Results from the Trial of Acute Femoral Fracture Fixation (TrAFFix) randomised feasibility study and process evaluation	Comparator subset
Grunfeld	2019	BMJ Open	Feasibility randomised controlled trial of a guided workbook intervention to support work-related goals among cancer survivors in the UK	Comparator subset
Hall	2018	BMJ Open	Protocol investigating the clinical utility of an objective measure of attention, impulsivity and activity (QbTest) for optimising medication management in children and young people with ADHD QbTest Utility for Optimising Treatment in ADHD' (QUOTA): A fea	Comparator subset
Harji	2018	BMJ Open	Feasibility of a multicentre, randomised controlled trial of laparoscopic versus open colorectal surgery in the acute setting: The LaCeS feasibility trial protocol	Comparator subset
He	2019	BMJ Open	Acupuncture for cancer pain: Protocol for a pilot pragmatic randomised controlled trial	Comparator subset

First author	Year	Journal	Study title	Data set
Hei	2018	BMJ Open	Randomised controlled trial of rhinothermy for treatment of the common cold: A feasibility study	Comparator subset
Hobson	2019	BMJ Open	Using telehealth in motor neuron disease to increase access to specialist multidisciplinary care: A UK-based pilot and feasibility study	Comparator subset
Jabbar-Lopez	2019	BMJ Open	Protocol for an outcome assessor-blinded pilot randomised controlled trial of an ion-exchange water softener for the prevention of atopic eczema in neonates, with an embedded mechanistic study: The Softened Water for Eczema Prevention (SOFTER) trial	Comparator subset
Kyte	2018	BMJ Open	Use of an electronic patient-reported outcome measure in the management of patients with advanced chronic kidney disease: The RePROM pilot trial protocol	Comparator subset
Lang	2018	BMJ Open	A randomised controlled trial of a facilitated home-based rehabilitation intervention in patients with heart failure with preserved ejection fraction and their caregivers: The REACH-HFpEF Pilot Study	Comparator subset
Lassere	2018	BMJ Open	Protocol of the randomised placebo controlled pilot trial of the management of acute sciatica (SCIATICA): A feasibility study	Comparator subset
Lee	2018	BMJ Open	Protocol for the trismus trial - Therabite versus wooden spatula in the amelioration of trismus in patients with head and neck cancer: Randomised pilot study	Comparator subset
McKenzie	2019	BMJ Open	SAFE, a new therapeutic intervention for families of children with autism: Study protocol for a feasibility randomised controlled trial	Comparator subset
Mitchell	2019	BMJ Open	Self-aligning prosthetic device for older patients with vascular-related amputations: Protocol for a randomised feasibility study (the STEPFORWARD study)	Comparator subset
Mitchell	2019	BMJ Open	Acceptability and feasibility pilot randomised controlled trial of medical skin camouflage for recovery of women prisoners with self-harm scarring (COVER): The study protocol	Comparator subset
Nampijja	2019	BMJ Open	Randomised controlled pilot feasibility trial of an early intervention programme for young infants with neurodevelopmental impairment in Uganda: A study protocol	Comparator subset
O'Higgins	2019	BMJ Open	Lending an Ear: IPeer2Peer plus Teens Taking Charge online self-management to empower adolescents with arthritis in Ireland: Protocol for a pilot randomised controlled trial	Comparator subset

First author	Year	Journal	Study title	Data set
Palmer	2019	BMJ Open	A novel group parenting intervention to reduce emotional and behavioural difficulties in young autistic children: Protocol for the Autism Spectrum Treatment and Resilience pilot randomised controlled trial	Comparator subset
Patel	2019	BMJ Open	Persistent physical symptoms reduction intervention: A system change and evaluation (PRINCE) - Integrated GP care for persistent physical symptoms: Protocol for a feasibility and cluster randomised waiting list, controlled trial	Comparator subset
Picariello	2018	BMJ Open	Cognitive-behavioural therapy (CBT) for renal fatigue (BReF): A feasibility randomised-controlled trial of CBT for the management of fatigue in haemodialysis (HD) patients	Comparator subset
Pound	2018	BMJ Open	Dexamethasone versus prednisone for children receiving asthma treatment in the paediatric inpatient population: Protocol for a feasibility randomised controlled trial	Comparator subset
Pyrlis	2019	BMJ Open	Feasibility of using a transition diabetes team to commence injectable therapies postdischarge from a tertiary hospital: A pilot, randomised controlled trial	Comparator subset
Quested	2018	BMJ Open	Protocol for a gender-sensitised weight loss and healthy living programme for overweight and obese men delivered in Australian football league settings (Aussie-FIT): A feasibility and pilot randomised controlled trial	Comparator subset
Ridd	2019	BMJ Open	TEST (Trial of Eczema allergy Screening Tests): Protocol for feasibility randomised controlled trial of allergy tests in children with eczema, including economic scoping and nested qualitative study	Comparator subset
Robinson	2019	BMJ Open	Randomised controlled trial of a Calcium Channel or Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker Regime to Reduce Blood Pressure Variability following Ischaemic Stroke (CAARBS): A protocol for a feasibility study	Comparator subset
Scolari	2019	BMJ Open	Rituximab versus steroids and cyclophosphamide for the treatment of primary membranous nephropathy: Protocol of a pilot randomised controlled trial	Comparator subset
Stagg	2019	BMJ Open	IMPACT study on intervening with a manualised package to achieve treatment adherence in people with tuberculosis: Protocol paper for a mixed-methods study, including a pilot randomised controlled trial	Comparator subset
Tarrant	2018	BMJ open	Singing for people with aphasia (SPA): a protocol for a pilot randomised controlled trial of a group singing intervention to improve well-being	Comparator subset

First author	Year	Journal	Study title	Data set
Tönnies	2019	BMJ Open	Mental health specialist video consultations for patients with depression or anxiety disorders in primary care: Protocol for a randomised controlled feasibility trial	Comparator subset
Van Berkel	2019	BMJ Open	ASSERT (Acute Sacral inSufficiEncy fractuRe augmenTation) randomised controlled, feasibility in older people trial: A study protocol	Comparator subset
Blackwell	2018	PAFS	Computerized positive mental imagery training versus cognitive control training versus treatment as usual in inpatient mental health settings: Study protocol for a randomized controlled feasibility trial	Comparator subset
Chang	2018	PAFS	Exoskeleton-assisted gait training to improve gait in individuals with spinal cord injury: A pilot randomized study	Comparator subset
Clemes	2018	PAFS	Stand out in Class: Restructuring the classroom environment to reduce sedentary behaviour in 9-10-yearolds - Study protocol for a pilot cluster randomised controlled trial	Comparator subset
Cocate	2019	PAFS	Calcium and vitamin D supplementation and/or periodontal therapy in the treatment of periodontitis among Brazilian pregnant women: Protocol of a feasibility randomised controlled trial (the IMPROVE trial)	Comparator subset
De Silva	2018	PAFS	Study protocol: A pilot randomized controlled trial to evaluate the acceptability and feasibility of a counseling intervention, delivered by nurses, for those who have attempted self-poisoning in Sri Lanka	Comparator subset
Doody	2019	PAFS	Assessing the feasibility and impact of an adapted resistance training intervention, aimed at improving the multi-dimensional health and functional capacity of frail older adults in residential care settings: Protocol for a feasibility study	Comparator subset
Drotningsvik	2019	PAFS	Fish protein supplementation in older nursing home residents: A randomised, double-blind, pilot study	Comparator subset
Dunn	2019	PAFS	Home management of lower limb lymphoedema with an intermittent pneumatic compression device: A feasibility study	Comparator subset
Goldberg	2019	PAFS	GAPcare: The Geriatric Acute and Post-acute Fall Prevention Intervention-a pilot investigation of an emergency departmentbased fall prevention program for community-dwelling older adults	Comparator subset

First author	Year	Journal	Study title	Data set
Hall	2018	PAFS	A randomised, phase II, unblinded trial of an Exercise and Nutrition-based Rehabilitation programme (ENeRgy) versus standard care in patients with cancer: Feasibility trial protocol	Comparator subset
Hamilton	2018	PAFS	DIAMOND (DIgital Alcohol Management on Demand): A feasibility RCT and embedded process evaluation of a digital health intervention to reduce hazardous and harmful alcohol use recruiting in hospital emergency departments and online	Comparator subset
Harwood	2018	PAFS	A development study and randomised feasibility trial of a tailored intervention to improve activity and reduce falls in older adults with mild cognitive impairment and mild dementia	Comparator subset
Heslehurst	2018	PAFS	GestationaL Obesity Weight management: Implementation of National Guidelines (GLOWING): A pilot cluster randomised controlled trial of a guideline implementation intervention for the management of maternal obesity by midwives	Comparator subset
Holch	2018	PAFS	ERAPID electronic patient self-Reporting of Adverse-events: Patient Information and aDvice: A pilot study protocol in pelvic radiotherapy	Comparator subset
Holliday	2019	PAFS	A feasibility study with embedded pilot randomised controlled trial and process evaluation of electronic cigarettes for smoking cessation in patients with periodontitis	Comparator subset
Husted	2018	PAFS	A cluster randomised feasibility pilot trial evaluating involving community-dwelling older adults in activities in relation to meals in a rehabilitation program; Recruitment, data collection and protocol	Comparator subset
Lannin	2018	PAFS	Intensive therapy after botulinum toxin in adults with spasticity after stroke versus botulinum toxin alone or therapy alone: A pilot, feasibility randomized trial	Comparator subset
Lemetyinen	2018	PAFS	Co-production and evaluation of an elearning resource to improve African-Caribbean families' knowledge about schizophrenia and engagement with services: A pilot randomised controlled trial protocol	Comparator subset
Littlewood	2019	PAFS	Community Pharmacies Mood Intervention Study (CHEMIST): Feasibility and external pilot randomised controlled trial protocol	Comparator subset

First author	Year	Journal	Study title	Data set
Murphy	2019	PAFS	Evaluating 'enhancing pragmatic language skills for young children with social communication impairments' (E-PLAYS): Protocol for a feasibility randomised controlled trial study	Comparator subset
O'Dolan	2018	PAFS	A randomised feasibility study to investigate the impact of education and the addition of prompts on the sedentary behaviour of office workers	Comparator subset
Pallan	2018	PAFS	A cluster-randomised feasibility trial of a children's weight management programme: The Child weigHt mANaGement for Ethnically diverse communities (CHANGE) study	Comparator subset
Patel	2018	PAFS	Motivational interviewing for low mood and adjustment early after stroke: A feasibility randomised trial	Comparator subset
Pereira	2019	PAFS	Gait analysis following single-shot hyaluronic acid supplementation: A pilot randomized double-blinded controlled trial	Comparator subset
Ranakusuma	2018	PAFS	Oral prednisolone for acute otitis media in children: Protocol of a pilot randomised, open-label, controlled study (OPAL study)	Comparator subset
Rankin	2018	PAFS	Synovectomy during total knee arthroplasty: A pilot single-centre randomised controlled trial	Comparator subset
Rogers	2018	PAFS	Cardiac rehabilitation to improve health-related quality of life following trans-catheter aortic valve implantation: A randomised controlled feasibility study RECOVER-TAVI Pilot, ORCA 4, for the Optimal Restoration of Cardiac Activity Group	Comparator subset
Sahota	2019	PAFS	The feasibility and acceptability of a primary school-based programme targeting diet and physical activity: The PhunkyFoods Programme	Comparator subset
Shingler	2019	PAFS	A feasibility randomised controlled trial of short-term fasting prior to CAPOX chemotherapy for stage 2/3 colorectal cancer: SWiFT protocol	Comparator subset
Smith	2019	PAFS	An investigation of methods to improve recall for the patient-reported outcome measurement in COPD patients: A pilot randomised control trial and feasibility study protocol	Comparator subset
Stulz	2018	PAFS	Using a peanut ball during labour versus not using a peanut ball during labour for women using an epidural: Study protocol for a randomised controlled pilot study	Comparator subset

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Taylor	2019	PAFS	IntEgrating Smoking Cessation treatment As part of usual Psychological care for dEpression and anxiety (ESCAPE): Protocol for a randomised and controlled, multicentre, acceptability, feasibility and implementation trial	Comparator subset
Tully	2018	PAFS	Walk with Me: A protocol for a pilot RCT of a peer-led walking programme to increase physical activity in inactive older adults	Comparator subset
Vaag	2019	PAFS	Psychoeducational groups versus waitlist in treatment of attention-deficit hyperactivity/ impulsivity disorder (ADHD) in adults: A protocol for a pilot randomized waitlistcontrolled multicenter trial	Comparator subset
Yaari	2019	PAFS	Early Minds: A pilot randomised controlled trial of a mindfulness program in early learning centres	Comparator subset
Young	2019	PAFS	Telephone-based motivational interviewing versus usual care in primary care to increase physical activity: A randomized pilot study	Comparator subset
de Dios	2019	PLoS ONE	A pilot randomized trial examining the feasibility and acceptability of a culturally tailored and adherence-enhancing intervention for Latino smokers in the U.S.	Comparator subset
Antonini	2018	Trials	Acceptability to patients, carers and clinicians of an mHealth platform for the management of Parkinson's disease (PD-Manager): Study protocol for a pilot randomised controlled trial 11 Medical and Health Sciences 1117 Public Health and Health Services	Comparator subset
Armstrong-Buisseret	2018	Trials	Reduced fetal movement intervention Trial-2 (ReMIT-2): Protocol for a pilot randomised controlled trial of standard care informed by the result of a placental growth factor (PlGF) blood test versus standard care alone in women presenting with reduced feta	Comparator subset
Bell	2018	Trials	Smartphone-based ecological momentary assessment and intervention in a coping-focused intervention for hearing voices (SAVVy): Study protocol for a pilot randomised controlled trial	Comparator subset
Bright	2019	Trials	Internet-based interpersonal psychotherapy for stress, anxiety, and depression in prenatal women: Study protocol for a pilot randomized controlled trial	Comparator subset
Chu	2019	Trials	Tobacco cessation mobile app intervention (Just Kwit! study): Protocol for a pilot randomized controlled pragmatic trial	Comparator subset
de Fonseka	2018	Trials	Zoledronic acid in the management of mesothelioma - a feasibility study (Zol-A Trial): Study protocol for a randomised controlled trial	Comparator subset

First author	Year	Journal	Study title	Data set
De Wit	2018	Trials	Physical exercise and cognitive engagement outcomes for mild neurocognitive disorder: A group-randomized pilot trial	Comparator subset
Dinius	2019	Trials	Piloting and evaluating feasibility of a training program to improve patient safety for inter-professional inpatient care teams - Study protocol of a cluster randomized controlled trial	Comparator subset
Gaete	2019	Trials	Mental Health Prevention in Preschool Children: Study protocol for a feasibility and acceptability randomised controlled trial of a culturally adapted version of the i Can Problem Solve (ICPS) Programme in Chile	Comparator subset
Granbom	2019	Trials	Preventing falls among older fallers: Study protocol for a two-phase pilot study of the multicomponent LIVE LiFE program	Comparator subset
Green	2019	Trials	A pragmatic pilot phase II randomised controlled trial of prothrombin complex concentrates (PCC) versus fresh frozen plasma (FFP) in adult patients who are undergoing heart surgery (PROPHESY)	Comparator subset
Guillaumier	2018	Trials	Electronic nicotine devices to aid smoking cessation by alcohol- and drug-dependent clients: Protocol for a pilot randomised controlled trial	Comparator subset
Hart	2018	Trials	Mechanical suppression of osteolytic bone metastases in advanced breast cancer patients: A randomised controlled study protocol evaluating safety, feasibility and preliminary efficacy of exercise as a targeted medicine	Comparator subset
Howard	2019	Trials	Prevention of Morbidity in Sickle Cell Disease (POMS2a)-overnight auto-adjusting continuous positive airway pressure compared with nocturnal oxygen therapy: a randomised crossover pilot study examining patient preference and safety in adults and children	Comparator subset
Hulsbaek	2019	Trials	Preliminary effect and feasibility of physiotherapy with strength training and protein-rich nutritional supplement in combination with anabolic steroids in cross-continuum rehabilitation of patients with hip fracture: Protocol for a blinded randomized con	Comparator subset
Kerry-Barnard	2018	Trials	'Test n Treat (TnT)'- Rapid testing and same-day, on-site treatment to reduce rates of chlamydia in sexually active further education college students: Study protocol for a cluster randomised feasibility trial	Comparator subset
Koffman	2019	Trials	Managing uncertain recovery for patients nearing the end of life in hospital: A mixed-methods feasibility cluster randomised controlled trial of the AMBER care bundle	Comparator subset

First author	Year	Journal	Study title	Data set
Kümin	2018	Trials	Reducing Implant Infection in Orthopaedics (RIIiO): A pilot study for a randomised controlled trial comparing the influence of forced air versus resistive fabric warming technologies on postoperative infection rates following orthopaedic implant surgery i	Comparator subset
Lee	2018	Trials	The efficacy and safety of the herbal medicine geonchildan for patients with active rheumatoid arthritis: Study protocol for a randomized, double-blind, placebo-controlled, parallel pilot trial	Comparator subset
Leyton	2019	Trials	Video feedback intervention to enhance parental reflective functioning in primary caregivers of inpatient psychiatric children: Protocol for a randomized feasibility trial	Comparator subset
Mauri	2018	Trials	Pressure support ventilation + sigh in acute hypoxemic respiratory failure patients: Study protocol for a pilot randomized controlled trial, the PROTECTION trial	Comparator subset
Mitropoulos	2018	Trials	Investigating the effectiveness and feasibility of exercise on microvascular reactivity and quality of life in systemic sclerosis patients: Study protocol for a feasibility study	Comparator subset
Murchie	2019	Trials	Achieving Self-Directed Integrated Cancer Aftercare (ASICA) in melanoma: Protocol for a randomised patient-focused pilot trial of delivering the ASICA intervention as a means to earlier detection of recurrent and second primary melanoma	Comparator subset
Nishijima	2018	Trials	Traumatic injury clinical trial evaluating tranexamic acid in children (TIC-TOC): Study protocol for a pilot randomized controlled trial	Comparator subset
O'Donoghue	2018	Trials	Balancing ACT: Evaluating the effectiveness of psychoeducation and Acceptance and Commitment Therapy (ACT) groups for people with bipolar disorder: Study protocol for pilot randomised controlled trial	Comparator subset
Øra	2018	Trials	Telerehabilitation for aphasia - Protocol of a pragmatic, exploratory, pilot randomized controlled trial	Comparator subset
Prediger	2019	Trials	Nocebo effects of a simplified package leaflet compared to unstandardised oral information and a standard package leaflet: A pilot randomised controlled trial	Comparator subset
Richards	2018	Trials	Assessing the effectiveness of Enhanced Psychological Care for patients with depressive symptoms attending cardiac rehabilitation compared with treatment as usual (CADENCE): A pilot cluster randomised controlled trial	Comparator subset

First author	Year	Journal	Study title	Data set
Rodgers	2019	Trials	Coping with Uncertainty in Everyday Situations (CUES©) to address intolerance of uncertainty in autistic children: Study protocol for an intervention feasibility trial	Comparator subset
Saal	2019	Trials	Improved participation of older people with joint contractures living in nursing homes: Feasibility of study procedures in a cluster-randomised pilot trial	Comparator subset
Shafayat	2019	Trials	Promoting Independence in Dementia (PRIDE): Protocol for a feasibility randomised controlled trial	Comparator subset
Shi	2019	Trials	Efficacy and safety of acupuncture for patients with chronic urticaria: Study protocol of a randomized, sham-controlled pilot trial	Comparator subset
Steffens	2018	Trials	Feasibility and acceptability of PrE-operative Physical Activity to improve patient outcomes After major cancer surgery: Study protocol for a pilot randomised controlled trial (PEPA Trial)	Comparator subset
Whicher	2019	Trials	Liraglutide and the management of overweight and obesity in people with schizophrenia, schizoaffective disorder and first-episode psychosis: Protocol for a pilot trial	Comparator subset
Wittkowski	2018	Trials	Enhancing maternal and infant wellbeing: study protocol for a feasibility trial of the Baby Triple P Positive Parenting programme for mothers with severe mental health difficulties (the IMAGINE study)	Comparator subset

C1 Completed STROBE 2007 checklist

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	**Recommendation**	**Page No**
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	77
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	N/A
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	78
Objectives	3	State specific objectives, including any prespecified hypotheses	79
Methods			
Study design	4	Present key elements of study design early in the paper	81
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	81
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	81
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	82
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	83
Bias	9	Describe any efforts to address potential sources of bias	83
Study size	10	Explain how the study size was arrived at	81
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	84
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	84
		(*b*) Describe any methods used to examine subgroups and interactions	84
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	85

	Item No	Recommendation	Page No
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	86
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	87
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	87
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	102
Discussion			
Key results	18	Summarise key results with reference to study objectives	103
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	105
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	103
Generalisability	21	Discuss the generalisability (external validity) of the study results	Chapter 7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

C2 Email template to request approval

NIHR/314
Revs to Proposed wording for PI approval for application inclusion in research – final comments (redline accepted where not an issue)
Re successful and rejected applications
16 February 2021

Subject: Request to use information from RfPB application in support of further research

Dear [Applicant name]

RE: [Application reference number and title]

The NIHR Research for Patient Benefit programme is conducting research on submitted funding applications for randomised pilot and feasibility trials in collaboration with third party UK Higher Education Institutions. The purpose of the research is to review the methodological characteristics of funding applications for pilot and feasibility trials, and to assess funding outcomes (Stage 1 and Stage 2) to help improve the design of pilot and feasibility studies.

You are being approached for permission as you were the lead applicant of a RfPB application. We would like your permission to use some of the information from your application form as part of this research and to share the following information with our collaborating third-party UK Higher Education Institutions.

Proposed Research Use

The information we are proposing to use to support research is:

- Parts of the application form (the research plan only – all personal details will be redacted)
- The outcome letters (Stage 2 and/or Stage 1) containing committee feedback (all personal details will be redacted from the letters).

The information will be sent to the relevant HEI via encrypted transfer.

Permission

We need your permission to use the information in your RfPB application to support this research. Our guidance notes for applicants make it clear that the application will be treated as confidential and acknowledge that the text in application belongs to the applicant and the submitting institution by copyright.

Please reply to this email, copying and pasting the three points below and confirming each of the points by stating YES or No to each point.

Please ensure that you consult with any relevant parties (such as those with signing authority within your institution and/or any co-applicants whose information may appear in the application form) before you respond.

1) Sharing the application form

- Please confirm, on behalf of the institution that submitted the application, that RfPB may use the text including any confidential information contained in the application only for the proposed Research Use outlined above. No personal information will be shared. YES/NO

- Please confirm, on behalf of the institution that submitted the application, that RfPB may use and share the text, data or images used in the application only for the proposed Research Use outlined above. YES/NO

And

- Please confirm that RfPB may use and share the text, data or images used in the application that is owned or controlled by a co-applicant or other third party only for the proposed Research Use outlined above. YES/NO

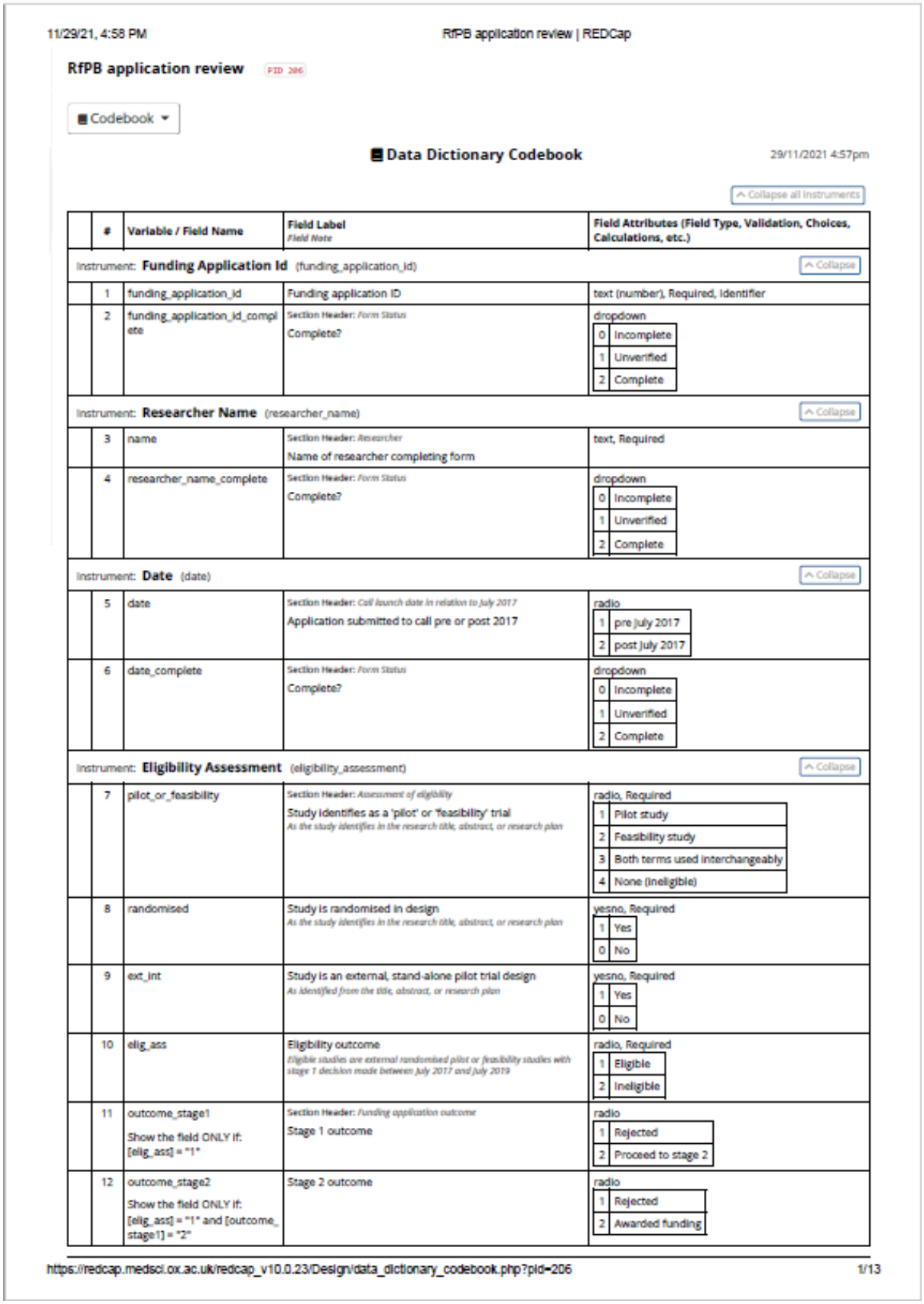
We hope that you will support our endeavours to improve the design of pilot and feasibility studies through this research and would be very grateful for your permission to include your application.

If you have any questions or need clarification regarding this request, please contact me.

Kind regards

The RfPB team/NAME

C3 REDCap Data Dictionary Codebook



11/29/21, 4:58 PM RfPB application review | REDCap

RfPB application review PID 206

Codebook

Data Dictionary Codebook 29/11/2021 4:57pm

Collapse all Instruments

	#	Variable / Field Name	Field Label *Field Note*	Field Attributes (Field Type, Validation, Choices, Calculations, etc.)
Instrument: **Funding Application Id** (funding_application_id)				Collapse
	1	funding_application_id	Funding application ID	text (number), Required, Identifier
	2	funding_application_id_complete	Section Header: *Form Status* Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: **Researcher Name** (researcher_name)				Collapse
	3	name	Section Header: *Researcher* Name of researcher completing form	text, Required
	4	researcher_name_complete	Section Header: *Form Status* Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: **Date** (date)				Collapse
	5	date	Section Header: *Call launch date in relation to July 2017* Application submitted to call pre or post 2017	radio 1 pre July 2017 2 post July 2017
	6	date_complete	Section Header: *Form Status* Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: **Eligibility Assessment** (eligibility_assessment)				Collapse
	7	pilot_or_feasibility	Section Header: *Assessment of eligibility* Study identifies as a 'pilot' or 'feasibility' trial *As the study identifies in the research title, abstract, or research plan*	radio, Required 1 Pilot study 2 Feasibility study 3 Both terms used interchangeably 4 None (ineligible)
	8	randomised	Study is randomised in design *As the study identifies in the research title, abstract, or research plan*	yesno, Required 1 Yes 0 No
	9	ext_int	Study is an external, stand-alone pilot trial design *As identified from the title, abstract, or research plan*	yesno, Required 1 Yes 0 No
	10	elig_ass	Eligibility outcome *Eligible studies are external randomised pilot or feasibility studies with stage 1 decision made between July 2017 and July 2019*	radio, Required 1 Eligible 2 Ineligible
	11	outcome_stage1 Show the field ONLY if: [elig_ass] = "1"	Section Header: *Funding application outcome* Stage 1 outcome	radio 1 Rejected 2 Proceed to stage 2
	12	outcome_stage2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2"	Stage 2 outcome	radio 1 Rejected 2 Awarded funding

https://redcap.medsci.ox.ac.uk/redcap_v10.0.23/Design/data_dictionary_codebook.php?pid=206 1/13

	13	eligibility_assessment_complete	Section Header: *Form Status* Complete?	dropdown 0, Incomplete 1, Unverified 2, Complete
Instrument: **Funding Application Stage 1** (funding_application_stage_1) Collapse				
	14	design Show the field ONLY if: [elig_ass] = "1"	Section Header: *Funding application characteristics as assessed by stage 1 application* Trial design *As the study identifies*	radio 1, Parallel 2, Cluster 3, Factorial 4, Crossover 5, Other
	15	design_other Show the field ONLY if: [elig_ass] = "1" and [design] = "5"	Other specified	text
	16	sample_size Show the field ONLY if: [elig_ass] = "1"	Sample size	text (number)
	17	no_centres Show the field ONLY if: [elig_ass] = "1"	Number of study centres	radio 1, Single 2, Multiple 3, Unclear
	18	no_arms Show the field ONLY if: [elig_ass] = "1"	Number of arms	text (number, Min: 2, Max: 10)

	19	therapeutic_area Show the field ONLY if: [elig_ass] = "1"	Therapeutic area	radio 1 Alternative medicine 2 Anaesthesia 3 Cardiology 4 Critical Care 5 Dentistry 6 Dermatology 7 Endocrinology 8 Gastroenterology and hepatology 9 Geriatrics 10 Haematology / Immunology 11 Infectious diseases 12 Musculoskeletal 13 Nephrology 14 Neurology 15 Obstetrics / Gynaecology 16 Oncology 17 Ophthalmology 18 Otolaryngology (ENT) 19 Paediatrics 20 Pharmacology 21 Physiology 22 Psychiatry / Psychology 23 Radiology 24 Respiratory 25 Rheumatology 26 Surgery 27 Urology 28 Other 29 Trauma 30 Palliative care 31 Primary care
	20	therapeutic_area_other Show the field ONLY if: [elig_ass] = "1" and [therapeutic_area] = "28"	Other specified	text
	21	intervention Show the field ONLY if: [elig_ass] = "1"	Intervention type	radio 1 Drug 2 Surgery or procedure 3 Counselling,lifestyle or physiotherapy 4 Equipment 5 Other 6 Medical device
	22	intervention_other Show the field ONLY if: [elig_ass] = "1" and [intervention] = "5"	Other specified	text
	23	feas_objectives_primary Show the field ONLY if: [elig_ass] = "1"	Primary focus is feasibility (feasibility objectives and outcomes)	yesno 1 Yes 0 No
	24	feas_objectives_rep Show the field ONLY if: [elig_ass] = "1"	Feasibility objectives reported *Objectives explicitly reported in research plan*	yesno 1 Yes 0 No

	25	feas_objectives_txt Show the field ONLY if: [elig_ass] = "1"	Stated feasibility objectives (exact text extract or as taken from research plan)	text
	26	feas_outcomes_rep Show the field ONLY if: [elig_ass] = "1"	Feasibility outcomes reported *Outcomes explicitly reported in research plan*	yesno 1 Yes 0 No
	27	feas_outcomes_txt Show the field ONLY if: [elig_ass] = "1"	Stated feasibility outcomes (exact text extract or as taken from research plan)	text
	28	feas_obj_out Show the field ONLY if: [elig_ass] = "1"	Areas of feasibility uncertainty stated in objectives and/or outcomes	checkbox 1 feas_obj_out___1 Acceptability of intervention or trial (non-participants) 2 feas_obj_out___2 Acceptability of intervention or trial (participants) 3 feas_obj_out___3 Barriers or challenges to intervention implementation 4 feas_obj_out___4 Centre or investigator recruitment, willingness or capacity 5 feas_obj_out___5 Completion or withdrawal 6 feas_obj_out___6 Consent or refusal rate 7 feas_obj_out___7 Data collection tools, measures or assessments 8 feas_obj_out___8 Data completion or missing data 9 feas_obj_out___9 Eligibility 10 feas_obj_out___10 Intervention fidelity 11 feas_obj_out___11 Non/compliance or adherence (non-participants) 12 feas_obj_out___12 Non/compliance or adherence (participants) 13 feas_obj_out___13 Randomsiation 14 feas_obj_out___14 Recruitment 15 feas_obj_out___15 Retention 16 feas_obj_out___16 Safety or adverse events 17 feas_obj_out___17 Determine/estimate definitive trial sample size or collect data to do so e.g. outcome variability 18 feas_obj_out___18 Screening (including referral) 19 feas_obj_out___19 Other 20 feas_obj_out___20 Pilot collection of health economics outcomes 21 feas_obj_out___21 Characteristics of clinical outcomes e.g. to decide on primary outcome
	29	feas_obj_out_oth Show the field ONLY if: [elig_ass] = "1" and [feas_obj_out(19)] = "1"	Other specified	text
	30	qual_research Show the field ONLY if: [elig_ass] = "1"	Qualitative research conducted	yesno 1 Yes 0 No
	31	qual_research_desc Show the field ONLY if: [elig_ass] = "1" and [qual_research] = "1"	Brief description of qualitative research conducted (aims, methods)	text

	32	funding_application_stage_1_complete	Section Header: *Form Status* Complete?	dropdown 0, Incomplete 1, Unverified 2, Complete
Instrument: **Progression Criteria Stage 1** (progression_criteria_stage_1) Collapse				
	33	pc_reporting Show the field ONLY if: [elig_ass] = "1"	Section Header: *Funding application progression criteria as assessed by stage 1 application* Progression criteria reported *Note: Select no if the only target given is a sample size target*	yesno 1, Yes 0, No
	34	pc_wording Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1"	Stated progression criteria wording (exact text extract)	text
	35	pc_format1 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1"	Progression criteria format *Distinct thresholds provide binary single cut-off targets (e.g. >80% recruitment), whereas traffic light systems provide green (go), amber (changes) or red (stop) targets (e.g. < 60% stop, >60% - < 80% changes, >80% go)*	radio 1, Distinct threshold / STOP-GO 2, Traffic light system / STOP-AMEND-GO 3, Other (e.g. non-numerical) 4, Distinct threshold / STOP-GO + 5, Traffic light system / STOP-AMEND-GO +
	36	pc_format1_other Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1" and [pc_format1] = "3"	Other specified	text
	37	pc_format2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1"	Progression criteria format	radio 1, Text 2, Table 3, Other
	38	pc_format2_other Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1" and [pc_format2] = "3"	Other described	text

	39	pc_feas_components Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1"	Specific progression criteria components of feasibility uncertainty	checkbox		
				1	pc_feas_components___1	Acceptability of intervention or trial (non-participants)
				2	pc_feas_components___2	Acceptability of intervention or trial (participants)
				3	pc_feas_components___3	Barriers or challenges to intervention implementation
				4	pc_feas_components___4	Centre or investigator recruitment, willingness or capacity
				5	pc_feas_components___5	Completion or withdrawal
				6	pc_feas_components___6	Consent or refusal rate
				7	pc_feas_components___7	Data collection tools, measures or assessments
				8	pc_feas_components___8	Data completion or missing data
				9	pc_feas_components___9	Eligibility
				10	pc_feas_components___10	Intervention fidelity
				11	pc_feas_components___11	Non/compliance or adherence (non-participants)
				12	pc_feas_components___12	Non/compliance or adherence (participants)
				13	pc_feas_components___13	Randomsiation
				14	pc_feas_components___14	Recruitment
				15	pc_feas_components___15	Retention
				16	pc_feas_components___16	Safety or adverse events
				17	pc_feas_components___17	Determine/estimate definitive trial sample size or collect data to do so e.g. outcome variability
				18	pc_feas_components___18	Screening (including referral)
				19	pc_feas_components___19	Other
				20	pc_feas_components___20	Pilot collection of health economics outcomes
				21	pc_feas_components___21	Characteristics of clinical outcomes e.g. to decide on primary outcome
	40	pc_feas_components_oth Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1" and [pc_feas_components(19)] = "1"	Other described	text		
	41	qual_pc Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1" and [qual_research] = "1"	Qualitative research informs progression criteria	yesno		
				1	Yes	
				0	No	

	42	pc_justification Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1"	justification or rationale for progression criteria reported	radio 1 Yes 2 No 3 For some criteria
	43	pc_justification_wrding Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1" and [pc_justification] = "1, 3"	justification or rationale (exact text extract)	text
	44	pc_who_established Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1"	Reported who was involved in deciding on progression criteria	yesno 1 Yes 0 No
	45	pc_who_est_wrding Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1" and [pc_who_established] = "1"	Who was involved	checkbox 1 pc_who_est_wrding___1 Trial Management Group 2 pc_who_est_wrding___2 Trial Steering Committee or Independent Oversight Committee 3 pc_who_est_wrding___3 Participant representatives or PPI 4 pc_who_est_wrding___4 Funder 5 pc_who_est_wrding___5 Sponsor 6 pc_who_est_wrding___6 Other
	46	pc_who_est_wrd_oth Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1" and [pc_who_established] = "1" and [pc_who_est_wrding(6)] = "1"	Other specified	text
	47	pc_who_assess Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1"	Reported who will be involved in assessing progression criteria	yesno 1 Yes 0 No
	48	pc_who_assess_wrding Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1" and [pc_who_assess] = "1"	Who will be involved	checkbox 1 pc_who_assess_wrding___1 Trial Management Group 2 pc_who_assess_wrding___2 Trial Steering Committee or Independent Oversight Committee 3 pc_who_assess_wrding___3 Participant representatives or PPI 4 pc_who_assess_wrding___4 Funder 5 pc_who_assess_wrding___5 Sponsor 6 pc_who_assess_wrding___6 Other
	49	pc_who_assess_wrd_oth Show the field ONLY if: [elig_ass] = "1" and [pc_reporting] = "1" and [pc_who_assess] = "1" and [pc_who_assess_wrding(6)] = "1"	Other specified	text
	50	progression_criteria_stage_1_complete	Section Header: *Form Status* Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: **Stage 1 Feedback** (stage_1_feedback)				Collapse

	51	feedback_pc Show the field ONLY if: [elig_ass] = "1"	Section Header: *Funding application stage 1 feedback* Stage 1 application feedback mentions progression criteria	yesno 1 Yes 0 No
	52	feedback_pc_sum Show the field ONLY if: [elig_ass] = "1" and [feedback_pc] = "1"	Provide a brief summary of application feedback regarding progression criteria	text
	53	feedback_pc_nopc Show the field ONLY if: [elig_ass] = "1" and [feedback_pc] = "1"	Feedback indicates that progression critiera were not stipulated?	yesno 1 Yes 0 No
	54	feedback_pc_nonum Show the field ONLY if: [elig_ass] = "1" and [feedback_pc] = "1" and [feedback_pc_nopc] = "0"	Feedback requests further detail/clarity e.g. numerical thresholds	yesno 1 Yes 0 No
	55	feedback_pc_whypc Show the field ONLY if: [elig_ass] = "1" and [feedback_pc] = "1" and [feedback_pc_nopc] = "0" and [feedback_pc_nonum] = "0"	Feedback relates to rationale for progression critiera/specific target, or requests a change	yesno 1 Yes 0 No
	56	feedback_other Show the field ONLY if: [elig_ass] = "1"	Any other notable feedback relating to pilot trial design	text
	57	stage_1_feedback_complete	Section Header: *Form Status* Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: **Funding Application Stage 2** (funding_application_stage_2) Collapse				
	58	design2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2"	Section Header: *Funding application characteristics as assessed by stage 2 application* Trial design *As the study identifies*	radio 1 Parallel 2 Cluster 3 Factorial 4 Crossover 5 Other
	59	design_other2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [design2] = "5"	Other specified	text
	60	elig_ass2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [design2] = "5"	Application still eligble at stage 2	yesno 1 Yes 0 No
	61	design_changes2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Any notable changes to trial design between stage 1 and stage 2	text
	62	sample_size2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Sample size	text (number)
	63	no_centres2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Number of study centres	radio 1 Single 2 Multiple 3 Unclear

	64	no_arms2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Number of arms	text (number, Min: 1, Max: 10)
	65	feas_objectives2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Changes to feasibility objectives between stage 1 and stage 2	yesno 1 Yes 0 No
	66	feas_objectives_txt2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [feas_objectives2] = "1" and [elig_ass2] != "0"	Description of changes	text
	67	feas_outcomes2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Changes to feasibility outcomes between stage 1 and stage 2	yesno 1 Yes 0 No
	68	feas_outcomes_txt2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [feas_outcomes2] = "1" and [elig_ass2] != "0"	Description of changes	text
	69	funding_application_stage_2_complete	Section Header: *Form Status* Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: **Progression Criteria Stage 2** (progression_criteria_stage_2) Collapse				
	70	pc_reporting2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Section Header: *Funding application progression criteria as assessed by stage 2 application* Progression criteria reported *Select no if the only target given is a sample size target*	yesno 1 Yes 0 No
	71	pc_changes2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [pc_reporting2] = "1" and [elig_ass2] != "0"	Any notable changes to progression criteria between stage 1 and stage 2	text
	72	pc_wording2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Stated progression criteria wording (exact text extract)	text
	73	pc_format12 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Progression criteria format *Distinct thresholds provide binary single cut-off targets (e.g. >80% recruitment), whereas traffic light systems provide green (go), amber (changes) or red (stop) targets (e.g. < 60% stop, >60% - < 80% changes, >80% go)*	radio 1 Distinct threshold / STOP-GO 2 Traffic light system / STOP-AMEND-GO 3 Other (e.g. non-numerical) 4 Distinct threshold / STOP-GO + 5 Traffic light system / STOP-AMEND-GO +
	74	pc_format1_other2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [pc_format12] = "3" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Other specified	text

	75	pc_format22 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Progression criteria format	radio 1 Text 2 Table 3 Other
	76	pc_format2_other2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [pc_format22] = "3" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Other described	text
	77	pc_feas_components2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Specific progression criteria components of feasibility uncertainty	checkbox

1	pc_feas_components2___1	Acceptability of intervention or trial (non-participants)
2	pc_feas_components2___2	Acceptability of intervention or trial (participants)
3	pc_feas_components2___3	Barriers or challenges to intervention implementation
4	pc_feas_components2___4	Centre or investigator recruitment, willingness or capacity
5	pc_feas_components2___5	Completion or withdrawal
6	pc_feas_components2___6	Consent or refusal rate
7	pc_feas_components2___7	Data collection tools, measures or assessments
8	pc_feas_components2___8	Data completion or missing data
9	pc_feas_components2___9	Eligibility
10	pc_feas_components2___10	Intervention fidelity
11	pc_feas_components2___11	Non/compliance or adherence (non-participants)
12	pc_feas_components2___12	Non/compliance or adherence (participants)
13	pc_feas_components2___13	Randomsiation
14	pc_feas_components2___14	Recruitment
15	pc_feas_components2___15	Retention
16	pc_feas_components2___16	Safety or adverse events
17	pc_feas_components2___17	Determine/estimate definitive trial sample size or collect data to do so e.g. outcome variability
18	pc_feas_components2___18	Screening (including referral)
19	pc_feas_components2___19	Other
20	pc_feas_components2___20	Pilot collection of health economics outcomes
21	pc_feas_components2___21	Characteristics of clinical outcomes e.g. to decide on primary outcome

	78	pc_feas_components_oth2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [pc_feas_components2(19)] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Other described	text
	79	qual_pc2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [qual_research] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Qualitative research informs progression criteria	yesno 1 Yes 0 No
	80	pc_justification2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Justification or rationale for progression criteria reported	radio 1 Yes 2 No 3 For some criteria
	81	pc_justification_wrding2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [pc_justification2] = "1, 3" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Justification or rationale (exact text extract)	text
	82	pc_who_established2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Reported who was involved in deciding on progression criteria	yesno 1 Yes 0 No
	83	pc_who_est_wrding2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [pc_who_established2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Who was involved	checkbox 1 pc_who_est_wrding2___1 Trial Management Group 2 pc_who_est_wrding2___2 Trial Steering Committee or Independent Oversight Committee 3 pc_who_est_wrding2___3 Participant representatives or PPI 4 pc_who_est_wrding2___4 Funder 5 pc_who_est_wrding2___5 Sponsor 6 pc_who_est_wrding2___6 Other
	84	pc_who_est_wrd_oth2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [pc_who_established2] = "1" and [pc_who_est_wrding2(6)] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Other specified	text
	85	pc_who_assess2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Reported who will be involved in assessing progression criteria	yesno 1 Yes 0 No

	86	pc_who_assess_wrding2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [pc_who_assess2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Who will be involved	checkbox 1, pc_who_assess_wrding2___1, Trial Management Group 2, pc_who_assess_wrding2___2, Trial Steering Committee or Independent Oversight Committee 3, pc_who_assess_wrding2___3, Participant representatives or PPI 4, pc_who_assess_wrding2___4, Funder 5, pc_who_assess_wrding2___5, Sponsor 6, pc_who_assess_wrding2___6, Other
	87	pc_who_assess_wrd_oth2 Show the field ONLY if: [elig_ass] = "1" and [pc_reporting2] = "1" and [pc_who_assess2] = "1" and [pc_who_assess_wrding2(6)] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Other specified	text
	88	pc_change_stg2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [pc_reporting2] = "1" and [feedback_pc] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Changes to progression criteria have been made to address stage 1 feedback	yesno 1, Yes 0, No
	89	pc_change_stg2_summary Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [pc_reporting2] = "1" and [pc_change_stg2] = "1" and [feedback_pc] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Summary of changes *Provide a brief summary of changes*	text
	90	progression_criteria_stage_2_complete	Section Header: *Form Status* Complete?	dropdown 0, Incomplete 1, Unverified 2, Complete
Instrument: **Stage 2 Feedback** (stage_2_feedback) Collapse				
	91	feedback_pc2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Section Header: *Funding application stage 2 feedback* Stage 2 application feedback mentions progression criteria	yesno 1, Yes 0, No
	92	feedback_pc_sum2 Show the field ONLY if: [elig_ass] = "1" and [feedback_pc2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Provide a brief summary of application feedback regarding progression criteria	text
	93	feedback_pc_nopc2 Show the field ONLY if: [elig_ass] = "1" and [feedback_pc2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Feedback indicates that progression critiera were not stipulated?	yesno 1, Yes 0, No
	94	feedback_pc_nonum2 Show the field ONLY if: [elig_ass] = "1" and [feedback_pc2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0" and [feedback_pc_nopc2] = "0"	Feedback requests further detail/clarity e.g. numerical thresholds	yesno 1, Yes 0, No

	95	feedback_pc_whypc2 Show the field ONLY if: [elig_ass] = "1" and [feedback_pc2] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0" and [feedback_pc_nopc2] = "0" and [feedback_pc_nonum2] = "0"	Feedback relates to rationale for progression critiera/specific target, or requests a change	yesno 1 Yes 0 No
	96	feedback_other2 Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [elig_ass2] != "0"	Any other notable feedback relating to pilot trial design	text
	97	stage_2_feedback_complete	Section Header: *Form Status* Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument: **Long Term Outcomes** (long_term_outcomes) Collapse				
	98	trial_completed Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [outcome_stage2] = "2" and [elig_ass2] != "0"	Section Header: *RfPB routine post-close monitoring outcomes* External pilot trial has completed	yesno 1 Yes 0 No
	99	def_rct_fund Show the field ONLY if: [elig_ass] = "1" and [trial_completed] = "1" and [outcome_stage1] = "2" and [outcome_stage2] = "2" and [elig_ass2] != "0"	Funding for a future trial has been applied for	radio 1 Yes 2 No 3 Unknown
	100	def_rct_fund_outcome Show the field ONLY if: [elig_ass] = "1" and [trial_completed] = "1" and [def_rct_fund] = "1" and [outcome_stage1] = "2" and [outcome_stage2] = "2" and [elig_ass2] != "0"	Funding application outcome	radio 1 Awarded funding 2 Not awarded funding 3 Unknown
	101	trial_results_pub Show the field ONLY if: [elig_ass] = "1" and [outcome_stage1] = "2" and [outcome_stage2] = "2" and [trial_completed] = "1" and [elig_ass2] != "0"	Pilot trial has been published	radio 1 Yes 2 No 3 Unknown
	102	long_term_outcomes_complete	Section Header: *Form Status* Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete

D1 Completed COREQ 2007 checklist

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

No	Item	Guide questions/description	Page #
Domain 1: Research team and reflexivity			
Personal Characteristics			
1.	Interviewer/facilitator	Which author/s conducted the interview or focus group?	111
2.	Credentials	What were the researcher's credentials? E.g. PhD, MD	111
3.	Occupation	What was their occupation at the time of the study?	111
4.	Gender	Was the researcher male or female?	N/A
5.	Experience and training	What experience or training did the researcher have?	111
Relationship with participants			
6.	Relationship established	Was a relationship established prior to study commencement?	112
7.	Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	112
8.	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	111
Domain 2: study design			
Theoretical framework			
9.	Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	112
Participant selection			
10.	Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	116
11.	Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	119
12.	Sample size	How many participants were in the study?	120
13.	Non-participation	How many people refused to participate or dropped out? Reasons?	133
Setting			
14.	Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	121
15.	Presence of non-participants	Was anyone else present besides the participants and researchers?	N/A
16.	Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	132
Data collection			
17.	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	122

No	Item	Guide questions/description	Page #
18.	Repeat interviews	Were repeat interviews carried out? If yes, how many?	122
19.	Audio/visual recording	Did the research use audio or visual recording to collect the data?	123
20.	Field notes	Were field notes made during and/or after the interview or focus group?	122
21.	Duration	What was the duration of the interviews or focus group?	132
22.	Data saturation	Was data saturation discussed?	121
23.	Transcripts returned	Were transcripts returned to participants for comment and/or correction?	N/A
Domain 3: analysis and findings			
Data analysis			
24.	Number of data coders	How many data coders coded the data?	127
25.	Description of the coding tree	Did authors provide a description of the coding tree?	128
26.	Derivation of themes	Were themes identified in advance or derived from the data?	129
27.	Software	What software, if applicable, was used to manage the data?	127
28.	Participant checking	Did participants provide feedback on the findings?	Table D1
Reporting			
29.	Quotations presented	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. participant number	137
30.	Data and findings consistent	Was there consistency between the data presented and the findings?	137
31.	Clarity of major themes	Were major themes clearly presented in the findings?	135
32.	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	135

D2 Recruitment advertisements

Appendix B. Participant recruitment wording

*Wording to inform participant recruitment for twitter, email and other forms of advertisement are listed below. The email wording **will not change** from that approved below. However, wording to advertise the study e.g. through social media and established research networks or websites might vary dependent on requirements e.g. character/word limits associated.*

1. **Study advertisement wording**

Are you a [insert appropriate description e.g. researcher/trial manager/statistician/participant representative] with external pilot trial experience?

I want to hear about **your experience of using progression criteria** in external randomised pilot trials.

If you are in interested in participating in an online interview as part of a qualitative research study ran by researchers at the University of Oxford, please contact me by email at katie.mellor@ndorms.ox.ac.uk for more information.

2. **Social media wording**

Involved in external pilot RCTs? I want to hear about your experience of using progression criteria. Please contact me for details on how to participate in my qualitative research study.

3. **Email wording** (as will be sent to potential participants identified with PIS attached)

Subject: Do you have experience of external randomised pilot trials?

Dear [name],

Researchers from the Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences at the University of Oxford are investigating the experiences of researchers and participant representatives who have been involved with external randomised pilot trials. Through your participation in this research, I hope to better understand how progression criteria are being used to inform the decision to progress to a definitive randomised controlled trial following an external pilot trial.

I would like to invite you to participate in an online interview, which should take no longer than one hour. Please find attached the participant information sheet for further information. If you are interested in participating, please contact me by email at katie.mellor@ndorms.ox.ac.uk to arrange a date and time that is convenient to you.

This study is being conducted as part of a Medical Research Council funded DPhil at the University of Oxford. Ethical approval has been obtained from the University of Oxford Central University Research Ethics Committee (reference R72039/RE001).

Thank you for taking the time to read this email. I would appreciate it if you please forward this on to any colleagues and participant representatives who have experience of external pilot trials.

If you have any questions or would like further information, please do not hesitate to contact me by email at katie.mellor@ndorms.ox.ac.uk

Kind regards,

Katie Mellor (DPhil Candidate, University of Oxford)

D3 Example participant Information Sheet

Participant Information Sheet for researchers

Miss Katie Mellor, DPhil Candidate
Centre for Statistics in Medicine
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
University of Oxford
Tel: 01865 737 923 | Email: katie.mellor@ndorms.ox.ac.uk

Use of progression criteria in external randomised pilot trials

PARTICIPANT INFORMATION SHEET
Ethics Approval Reference: R72039/RE001
Version 1.0 Date: 26Nov2020

We would like to invite you to take part in this research study conducted by the University of Oxford. Before you decide, please take your time to read through the following information to understand why the research is being done and what it will involve. If there is anything that you do not understand, or if you would like more information, please do not hesitate to contact us.

1. ***What is the purpose of the research?***

External randomised pilot trials aim to assess any uncertainties about a future definitive randomised controlled trial before embarking on it. Changes can then be made to the future trial design if needed, or researchers might decide not to proceed with the future trial altogether. How the progression decision is made following a pilot trial is not always clear. Sometimes specific targets called 'progression criteria' are used to inform this decision. The purpose of this research is to understand how this progression decision is being made, whether progression criteria are being used, how progression criteria are established, applied and analysed, and researchers' experiences of this process including any challenges they faced.

2. ***Why have I been invited to take part?***

You have been invited to take part because you have experience of conducting an external pilot randomised controlled trial.

The inclusion criteria are:

- You are aged 18 years and older
- You are willing and able to give verbal informed consent
- You are either a:
  - Researcher (not limited to a specific job description and can include trialist, medical statistician, methodologist, clinician). You may also be affiliated to a NIHR regional Research Design Service or a funding committee
  - Or you are a participant representative and member of a Trial Steering Committee for an external randomised pilot trial
- You should have knowledge and experience of external randomised pilot trials within your respective role

The exclusion criteria are:

- You are unable or unwilling to attend a video or audio call for interview
- You have none or outdated experience or knowledge of external randomised pilot trial design (i.e. you have not used, reviewed or discussed this methodology within the last 5 years)

Miss Katie Mellor, DPhil Candidate
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3. ***Do I have to take part?***

No. It is up to you to decide if you want to take part in this research. You are free to withdraw from the study at any time, without giving a reason and without penalty, by advising the researchers of this decision. This would not affect your legal rights.

4. ***What does the research involve?***

If you agree to take part in the study, you will be asked for your availability for an online interview. We will contact you via email or phone to do this. At this time, we will explain the procedures, and go through a small number of pre-screening questions to ensure you are eligible. We will then send you a Microsoft Teams invitation for this interview at an agreed time that is suitable for you. You will be sent a web URL that will take you to the virtual interview. You will not need to download the Microsoft Teams app to access the interview. All interviews will be audio recorded.

On the day of the interview, we will talk you though the study procedures and give you the chance to ask questions before we start the recording. The interview will involve answering questions about your experience of external pilot trials, making the decision to proceed, or not proceed, to a future trial following external pilot trial completion, any challenges with this decision, and whether and how you used progression criteria to inform this decision. This should take approximately one hour.

If you are still happy to take part, then you will then be asked to give verbal consent. This will be recorded at the start of the interview. You will also be invited to participate in respondent validation of your interview analysis. This is completely optional. We will invite you to review our analysis of your interview data for factual inaccuracy and discuss whether you feel that the data we have collected has been summarised sufficiently. Please note that transcripts will not be significantly changed as a result of respondent validation.

5. ***Are there any risks in taking part?***

There is a potential risk that any data you provide might be misinterpreted by the researcher. In order to reduce this potential risk, we will invite you to review and provide feedback on the analysis of your interview, a process called 'respondent validation'. This is entirely optional. There is also a risk of inconveniencing you with the burden and time associated with participating in an interview. To minimise this burden, we aim to keep all interviews to one hour in duration. To avoid any risks of COVID-19 transmission, we will follow UK government and University of Oxford guidance and will conduct all interviews online.

6. ***Are there any benefits in taking part?***

There will be no personal benefit to you from taking part in this research. However, this research will add to ongoing research efforts to develop standardised guidance for the use of progression criteria for external randomised pilot trials. Any outputs from this research might be useful in future external randomised pilot trials you are involved with.

7. ***Will my time/travel costs be reimbursed?***

There will be no payment for taking part in this study.

Miss Katie Mellor, DPhil Candidate
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University of Oxford
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8. ***What happens to the data provided?***

The information you provide as part of the study is the **research data**. Any research data from which you can be identified (e.g. your name, job title, institution, and any affiliations), is known as **personal data**. It does not include data where the identity has been removed (anonymous data). We will minimise our use of personal data in the study as much as possible.

All **research data** (including audio recordings and transcripts) will be stored on a secure University of Oxford electronic server. All audio recordings of interviews will be uploaded to the server immediately after interview and deleted from any recording device. Audio recordings will be transcribed by the researchers conducting this study, or by an external transcription service (Prestige Network). Any audio recordings sent to the external transcription service will be sent in a password protected folder via OxFile. Transcripts and recordings will be returned by the same method. Research data, except for audio recordings, will be de-identified and linked to a dummy ID that is not traceable to you.

Personal data will be saved in a password protected file on a secure university of Oxford server. Any personal data collected during the interview including your name, trial names and the names of any other researchers you mention will be redacted from the interview transcript. Personal data (including your contact details and the interview audio recording) will be destroyed by deletion once the study findings are published. The research team will have access to the research data, but only the primary researcher will have access to personal data. All research data and records will be stored for a minimum of 10 years after publication or public release of the work of the research. We would like your permission to use de-identified direct quotes in any research publications.

9. ***What will happen if I don't want to carry on with the study?***

You are free to withdraw from the study at any time without giving any reason and without your legal rights being affected. If you choose to withdraw from the study during the interview, the interview audio recording will be deleted, and you will be withdrawn fully from the study. If you decide after the interview to withdraw, interview data will be included in the final analysis due to the complexities of withdrawing data that has already been audio recorded, anonymised, transcribed, and analysed. However, we will not include any direct quotes from you in any research outputs.

10. ***Who will know that I am taking part in this research?***

All information collected about you will be kept strictly confidential. All such data are kept on firewall and password-protected computers. Designated individuals of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure we are complying with guidelines.

11. ***What will happen to the results of the research?***

The research may be published in a peer review journal. It will also be presented at national or international conferences either as a stand-alone study or as part of the broader research agenda. The research will also be written up as a thesis chapter. The completed thesis will be deposited as open access both in print and online in the University archives, to facilitate its use in future research.

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University of Oxford
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12. *Who has reviewed this study?*

This study has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee (Reference number: R72039/RE001).

13. *Who is organising and funding the research?*

Katie Mellor is a DPhil candidate (DPhil Musculoskeletal Sciences: Biomedical Data Science) at the University of Oxford. The Principal Investigator for this research is her primary supervisor Associate Professor Sally Hopewell. This research is funded through a 3-year Medical Research Council (MRC) doctoral fellowship awarded to Katie Mellor.

14. *Who do I contact if I have a concern about the study or I wish to complain?*

If you have a concern about any aspect of this study, please speak to Katie Mellor +44 (0)1865 737923 or supervisor Associate Professor Sally Hopewell +44 (0)1865 223458, and we will do our best to answer your query. We will acknowledge your concern within 10 working days and give you an indication of how it will be dealt with. If you remain unhappy or wish to make a formal complaint, please contact the Chair of the Medical Sciences Interdivisional Research Ethics Committee (MS IDREC) at the University of Oxford who will seek to resolve the matter as soon as possible: Email: ethics@medsci.ox.ac.uk; Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD.

15. *Data Protection*

The University of Oxford is the data controller with respect to your personal data and, as such, will determine how your personal data is used in the study. The University will process your personal data for the purpose of the research outlined above. Research is a task that we perform in the public interest. Further information about your rights with respect to your personal data is available http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/.

16. *Contact Details*

If you would like to discuss the research with someone beforehand (or if you have questions afterwards), please contact:

Miss Katie Mellor
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Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences
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Participant Information Sheet for participant representatives

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Use of progression criteria in external randomised pilot trials

PARTICIPANT INFORMATION SHEET FOR PARTICIPANT REPRESENTATIVES
Ethics Approval Reference: R72039/RE001
Version 1.1 Date: 16Feb2021

We would like to invite you to take part in this research study conducted by the University of Oxford. Before you decide, please take your time to read through the following information to understand why the research is being done and what it will involve. If there is anything that you do not understand, or if you would like more information, please do not hesitate to contact us.

1. ***What is the purpose of the research?***

External randomised pilot trials aim to assess any uncertainties about a future definitive randomised controlled trial before embarking on it. Changes can then be made to the future trial design if needed, or researchers might decide not to proceed with the future trial altogether. How the progression decision is made following a pilot trial is not always clear. Sometimes specific targets called 'progression criteria' are used to inform this decision. The purpose of this research is to understand how this progression decision is being made, whether progression criteria are being used, how progression criteria are established, applied and analysed, and researchers' experiences of this process including any challenges they faced.

2. ***Why have I been invited to take part?***

You have been invited to take part because you have experience of contributing to an external pilot randomised controlled trial as a participant representative.

The inclusion criteria are:

- You are aged 18 years and older
- You are willing and able to give verbal informed consent
- You are a participant representative for an external randomised pilot trial
- You should have knowledge and experience of external randomised pilot trials within your respective role

The exclusion criteria are:

- You are unable or unwilling to attend a video or audio call for interview
- You have not contributed as a participant representative to an external randomised pilot trial within the last 5 years

3. ***Do I have to take part?***

No. It is up to you to decide if you want to take part in this research. You are free to withdraw from the study at any time, without giving a reason and without penalty, by advising the researchers of this decision. This would not affect your legal rights.

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4. ***What does the research involve?***

If you agree to take part in the study, you will be asked for your availability for an online interview. We will contact you via email or phone to do this. At this time, we will explain the procedures, and go through a small number of pre-screening questions to ensure you are eligible. We will then send you a Microsoft Teams invitation for this interview at an agreed time that is suitable for you. You will be sent a web URL that will take you to the virtual interview. You will not need to download the Microsoft Teams app to access the interview. All interviews will be audio recorded.

On the day of the interview, we will talk you though the study procedures and give you the chance to ask questions before we start the recording. The interview will involve answering questions about your experience of external pilot trials, making the decision to proceed, or not proceed, to a future trial following external pilot trial completion, any challenges with this decision, and whether and how you used progression criteria to inform this decision. This should take approximately one hour.

If you are still happy to take part, then you will then be asked to give verbal consent. This will be recorded at the start of the interview. You will also be invited to participate in respondent validation of your interview analysis. This is completely optional. We will invite you to review our analysis of your interview data for factual inaccuracy and discuss whether you feel that the data we have collected has been summarised sufficiently. Please note that transcripts will not be significantly changed as a result of respondent validation.

5. ***Are there any risks in taking part?***

There is a potential risk that any data you provide might be misinterpreted by the researcher. In order to reduce this potential risk, we will invite you to review and provide feedback on the analysis of your interview, a process called 'respondent validation'. This is entirely optional. There is also a risk of inconveniencing you with the burden and time associated with participating in an interview. To minimise this burden, we aim to keep all interviews to one hour in duration. To avoid any risks of COVID-19 transmission, we will follow UK government and University of Oxford guidance and will conduct all interviews online.

6. ***Are there any benefits in taking part?***

There will be no personal benefit to you from taking part in this research. However, this research will add to ongoing research efforts to develop standardised guidance for the use of progression criteria for external randomised pilot trials. Any outputs from this research might be useful in future external randomised pilot trials you are involved with.

7. ***Will my time/travel costs be reimbursed?***

In appreciation for your time and insights, you will receive a £20 One4All voucher via email after the interview is completed.

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8. ***What happens to the data provided?***

The information you provide as part of the study is the **research data**. Any research data from which you can be identified (e.g. your name, job title, institution, and any affiliations), is known as **personal data**. It does not include data where the identity has been removed (anonymous data). We will minimise our use of personal data in the study as much as possible.

All **research data** (including audio recordings and transcripts) will be stored on a secure University of Oxford electronic server. All audio recordings of interviews will be uploaded to the server immediately after interview and deleted from any recording device. Audio recordings will be transcribed by the researchers conducting this study, or by an external transcription service (Prestige Network). Any audio recordings sent to the external transcription service will be sent in a password protected folder via OxFile. Transcripts and recordings will be returned by the same method. Research data, except for audio recordings, will be de-identified and linked to a dummy ID that is not traceable to you.

Personal data will be saved in a password protected file on a secure university of Oxford server. Any personal data collected during the interview including your name, trial names and the names of any other researchers you mention will be redacted from the interview transcript. Personal data (including your contact details and the interview audio recording) will be destroyed by deletion once the study findings are published. The research team will have access to the research data, but only the primary researcher will have access to personal data. All research data and records will be stored for a minimum of 10 years after publication or public release of the work of the research. We would like your permission to use de-identified direct quotes in any research publications.

9. ***What will happen if I don't want to carry on with the study?***

You are free to withdraw from the study at any time without giving any reason and without your legal rights being affected. If you choose to withdraw from the study during the interview, the interview audio recording will be deleted, and you will be withdrawn fully from the study. If you decide after the interview to withdraw, interview data will be included in the final analysis due to the complexities of withdrawing data that has already been audio recorded, anonymised, transcribed, and analysed. However, we will not include any direct quotes from you in any research outputs.

10. ***Who will know that I am taking part in this research?***

All information collected about you will be kept strictly confidential. All such data are kept on firewall and password-protected computers. Designated individuals of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure we are complying with guidelines.

11. ***What will happen to the results of the research?***

The research may be published in a peer review journal. It will also be presented at national or international conferences either as a stand-alone study or as part of the broader research agenda. The research will also be written up as a thesis chapter. The completed thesis will be deposited as open access both in print and online in the University archives, to facilitate its use in future research.

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12. ***Who has reviewed this study?***

This study has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee (Reference number: R72039/RE001).

13. ***Who is organising and funding the research?***

Katie Mellor is a DPhil candidate (DPhil Musculoskeletal Sciences: Biomedical Data Science) at the University of Oxford. The Principal Investigator for this research is her primary supervisor Associate Professor Sally Hopewell. This research is funded through a 3-year Medical Research Council (MRC) doctoral fellowship awarded to Katie Mellor.

14. ***Who do I contact if I have a concern about the study or I wish to complain?***

If you have a concern about any aspect of this study, please speak to Katie Mellor +44 (0)1865 737923 or supervisor Associate Professor Sally Hopewell +44 (0)1865 223458, and we will do our best to answer your query. We will acknowledge your concern within 10 working days and give you an indication of how it will be dealt with. If you remain unhappy or wish to make a formal complaint, please contact the Chair of the Medical Sciences Interdivisional Research Ethics Committee (MS IDREC) at the University of Oxford who will seek to resolve the matter as soon as possible: Email: ethics@medsci.ox.ac.uk; Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD.

15. ***Data Protection***

The University of Oxford is the data controller with respect to your personal data and, as such, will determine how your personal data is used in the study. The University will process your personal data for the purpose of the research outlined above. Research is a task that we perform in the public interest. Further information about your rights with respect to your personal data is available http://www.admin.ox.ac.uk/councilsec/compliance/gdpr/individualrights/.

16. ***Contact Details***

If you would like to discuss the research with someone beforehand (or if you have questions afterwards), please contact:

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D4 Interview guides

Interview topic guide – Final versions

R72039/RE001

Whilst we will address the questions below during the interview, the qualitative work will remain flexible, allowing participants to guide the conversations and present what is important to them. It is best practice during qualitative interview projects to iteratively develop topics and questions as new ideas are identified from early data collection. Therefore, following best practice, we may add new topics as the interviews progress and data collection continues. The key focus of these interviews will be researchers' experience with, and thoughts about, using progression criteria to inform the decision to progress from a pilot Randomised Controlled Trial (RCT) to a definitive RCT.

INTRODUCTION

Thank you for taking the time to talk to me today.
Have you had sufficient time to read and understand the information that was sent to you?

The aim of this interview is to explore your views of external randomised pilot trials, and how these progress to a future randomised controlled trial. You've been invited to participate in this research because I understand that you have experience of conducting external pilot trials, and I would really like to hear about your experience.

If this is not the case, please let me know at this point. [*confirmation of eligibility*]

Before we start, do you have any questions you would like to ask about this research?

The first part of the interview will involve some shorter questions about you and your current role, and in the second part of the interview we will discuss your experience of pilot trials and progression criteria.

I will be taking some notes so I can keep a track of which questions we have covered.

The interview should last no longer than one hour. To maintain anonymity, once I start recording, I will not refer to you by name.

Start recording

This interview is with participant ___

Could you please confirm that you give your verbal consent to participate in this interview and for it to be audio recorded?
[*Participant to give verbal consent. If not, do not proceed*]

I would like to remind you that any information you provide will be de-identified and stored confidentially in line with the General Data Protection Regulation (GDPR) and Data Protection Act 2018.

Interview topic guide – Final versions

R72039/RE001

Interview guide 1: RESEARCHER

QUESTIONS AND PROMPTS

1. **Can you tell me about your current role in relation to external randomised pilot trials?**
    a. What institution?
    b. For how long?
    c. Involvement with a range or very few clinical trials and pilot trials?
    d. Do you contribute towards a NIHR Research Design Service?
    e. Do you contribute towards any funding committees?
    f. Any journal affiliations e.g. editor, peer reviewer?
2. **Can you tell me about your experience of applying for external pilot trial funding?**
    a. Which funding steams?
    b. How would you describe the application process?
    c. Were there any challenges?
    d. Was funding obtained?
    e. Do you have a lot of experience with these funding applications?
3. **Can you tell me a bit more about the external randomised pilot trial(s) you have been involved with?**
    a. What was the aim of the trial?
    b. Why was the trial done/what were the uncertainties about feasibility?
    c. What were the findings?
        i. Did you decide to proceed/proceed with changes/not proceed etc
4. **What were the feasibility outcomes?**
    a. Why were they important?
    b. Were they typical to other randomised pilot trials you've been involved with?
5. **Did the pilot trial(s) have a qualitative research component?**
    a. What was the aim of the qualitative research?
6. **Did the pilot trial(s) have any Patient and Public Involvement?**
    a. How was PPI used?
7. **Did the pilot trial(s) have any progression criteria?**
    a. You might have used a different term to describe "progression criteria"

    IF NO – USE ALTERNATIVE QUESTIONS
8. **Can you describe the progression criteria used in the pilot trial(s)?**
    a. What feasibility outcomes were progression criteria based on?
    b. What were the specific targets?
    c. Was a traffic light system used?
9. **How did you establish the progression criteria?**
    a. Why were these criteria important to you?
    b. How did you decide on specific targets?
    c. Did you follow any guidance?
    d. Who was involved?
        i. Trial steering committee?

   ii. Trial management group?
   iii. Funders?
   iv. Patient and public representatives (if applicable)?

10. **Did the trial(s) meet the progression criteria?**
    a. All? Some?
11. **How did you assess the progression criteria at the end of the trial(s)?**
    a. Who was involved?
       i. Funders?
       ii. TSC?
       iii. PPI?
12. **How did you decide whether a future trial was feasible?**
    a. How/did progression criteria help you make this decision?
    b. Were there other things you considered in addition to the progression criteria?
    c. Will you make changes to the future/definitive trial?
    b. Who was involved in making this decision?
13. **Were there any challenges in relation to using progression criteria?**
    a. Can you give examples?
    b. Were there any challenges with designing progression criteria?
    c. Were there any challenges with assessing progression criteria?
       i. Where not all targets are met?
    d. Did the progression criteria change during the pilot trial?
    e. If you could run the trial again, would you do anything differently?
14. **What advice would you give to someone who was planning to do an external pilot trial, who not previously used progression criteria?**
    a. Will you use progression criteria in the future?
    b. Why do you think that is important? What is the benefit?
    c. Did that work well for you?
    d. Will you make this change going forward?

ALTERNATIVE QUESTIONS FOR PARTICIPANTS WHO DID NOT USE PROGRESSION CRITERIA

8. **Were you aware of progression criteria but decided not to use it?**
    a. If yes, why?
    b. Did you face any challenges?
9. **How did you decide whether a future trial was feasible?**
    a. What outcomes was this decision based on?
       i. Were there any other things you considered?
    b. Who was involved in making this decision?
       i. Funders?
       ii. TSC?
       iii. PPI?
    c. If feasible, will you make any changes to the future trial?

10. **Would you consider using progression criteria in external pilot trials you are involved with going forward?**
    a. What do you think the benefit would be?
    b. Would you look for support or guidance in using progression criteria?
        i. If so, where would you search?
    c. Who would you involve in discussion around what progression criteria to use?

Interview guide 2: PPI REPRESENATIVE

QUESTIONS AND PROMPTS

1. **Can you please tell me a little about your role as a participant representative?**
    a. What does your role entail?
    b. How long have you been a participant representative for?
    c. How many clinical trials have you contributed to?
    d. How many were external pilot trials?
2. **Can you tell me about the pilot trial/s you have been involved in?**
    a. How did you get involved as a participant representative?
    b. What was the pilot trial trying to find out?
3. **Were there any other participant representatives for the pilot trial?**
4. **Were there any challenges?**
    a. Is this the same for other trials you've contributed to e.g. non pilot trials?
5. **What were the findings of the external pilot trial?**
    a. Did you decide to proceed/proceed with changes/not proceed etc
    b. How was this decision made?
    c. [If proceed] – Will you be involved as a participant representative in the future trial?
6. **What is important to you when deciding whether researchers should do a future trial after this one?**
    a. What do you mean by [……]?
    b. Can you give an example?
    c. Why is this important to you?
7. **Was there any qualitative research e.g. interviewing patients about being in the trial?**
    a. How important is this for pilot trials?
8. **Do you recall discussing progression criteria?**
    a. Is this a familiar term?
    b. You might have used a different term to describe "progression criteria"

    IF NO – USE ALTERNATIVE QUESTIONS
9. **Can you describe the progression criteria that were used?**
    a. What were progression criteria based on?
    b. What were the specific targets?
    c. Was a traffic light system used?
10. **Were you involved in establishing these progression criteria when the trial was being designed at the start?**
    a. Who else was involved?
11. **Were you involved in discussing the progression criteria when the trial finished?**
    a. Did you meet all or some of the progression criteria?
    b. Who else was involved?
    c. Did progression criteria help the team decide whether to do the future trial?
    d. Did you discuss whether the future trial design would change based on what happened in the pilot trial?

12. **How important do you think it is that participant representatives like yourself are involved in this process?**
    a. Establishing progression criteria at the start?
    b. Assessing progression criteria at the end?
    c. Can you give examples to demonstrate what you've mentioned?
13. **Can you tell me whether any part of the process was challenging?**
    a. Can you give examples to demonstrate what you've mentioned?
    b. Was progression criteria a new concept?
    c. Challenges with establishing progression criteria at the start?
    d. Challenges with assessing progression criteria at the end?
14. **Is there anything that you have since reflected on about the progression criteria used, that perhaps you did not think of or say to the research team at the time?**
    a. Can you give examples to demonstrate what you've mentioned?
    b. Would this have changed the progression criteria?

ALTERNATIVE QUESTIONS FOR PARTICIPANTS WHO ARE NOT FAMILIAR WITH PROGRESSION CRITERIA

Explanation: Progression criteria are targets that researchers set at the start of a pilot trial, for example to recruit at least X participants and to retain at least Y. Researchers then look at these targets at the end of the trial to help them decide whether they should do the future trial and if it is likely to work.

9. **How important do you think it is that participant representatives are involved in setting these targets at the start of the trial?**
    a. Can you give examples to demonstrate what you've mentioned?
    b. What do you think the benefits could be?
10. **How important do you think it is that participant representatives are involved in looking at these targets at the end of the trial to say whether or not we should do the future trial?**
    a. Can you give examples to demonstrate what you've mentioned?
    b. What do you think the benefits could be?
11. **Do you think there would be any challenges of being involved in these discussions about progression criteria?**
    a. Before hearing about this research, was progression criteria a new concept?
    b. Can you give examples to demonstrate what you've mentioned?
    c. What challenges might there be in designing the progression criteria?
    d. What challenges might there be in assessing the progression criteria?

D5 Example respondent validation exercise

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RESPONDENT VALIDATION EXERCISE

Thank you for taking the time to speak to me on the 6th of July, I really value your participation in this research. I would like to invite you to participate in a respondent validation (also known as "member checking") exercise. Participating in respondent validation is completely optional.

Below is a short summary of the interview that I have written. If you are willing to participate, could you please read this summary and let me know if this rings true with your experience, whether you think this is a fair summary, and whether you have any further comments you would like to add.

Interview summary

Participant 032 is a trial methodologist with experience of both external and internal pilot trials and conducting trial methodology research in this area. Participant 032 is also an associate editor of a relevant journal.

Participant 032 described the benefit of early and continued communication with funders when designing pilot trials. The participant described how trials may be originally designed as definitive RCTs but are resubmitted as external pilots based on funder recommendation. It is also possible that external pilots that show a main trial is viable may progress directly into a definitive RCT, following discussion with the funder.

Participant 032 described the importance of including as many people as possible when designing a pilot trial and its progression criteria. Participant 032 described that there seems to be a trend over time towards doing RCTs with internal pilot phases, with external pilots more likely to be done where uncertainties are very high. It is important that the broadest range of uncertainties are considered irrespective of internal v external pilot design. Working with a good multidisciplinary team and trials unit can help inform whether an external or internal pilot is more appropriate and input into choice of progression criteria based on trials knowledge, experience and published literature. Participant 032 described that sometimes external pilot trial funding might not allow full trials unit support, although this has not been this participant's direct experience.

Participant 032 described that the traffic light approach to progression criteria promotes flexibility and encourages open and transparent discussions between funders and researchers about feasibility and progression decision making. This approach emphasises that these decisions are not black and white. Participant 032 considers this same approach equally as applicable to both internal or external pilot trials. Participant 032 also described that in addition to formal funder agreed progression criteria there are often additional informal progression criteria that are also monitored throughout a pilot trial.

Participant 032 described that in their opinion it is important to conduct qualitative research alongside pilot trials and triangulate between the qualitative findings and pilot trial findings. Qualitative research can be particularly important in specific settings e.g. where interventions and patient pathways are highly complex. Although a separate qualitative publication is not always needed in addition to a pilot trial results publication, this would be supported if driven forward by a qualitative researcher.

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Finally, participant 032 described that pilot trials can be difficult to discuss with stakeholders who are sometimes unfamiliar with their design and emphasis on feasibility outcomes. Pilot trials are often mis- or poorly reported which can limit their impact and mean that it is challenging to learn broader lessons from individual pilot trials. Although CONSORT guidance is a step towards improving reporting, participant 032 described that guidance for more detailed pilot trial reporting would be beneficial.

Participant 032 has opted into receive a copy of the findings of this research and has given permission to be contacted and invited to participate in any future research related to this DPhil.

Thank you again for your participation and interest in this study.
Best wishes,
Katie

D6 Final analytical framework

CODE	DESCRIPTION	FILES	REFS
1. A PRIORI UNCERTAINTIES ABOUT FEASIBILITY	**CATEGORY: A PRIORI UNCERTAINTIES ABOUT FEASIBILITY**	0	0
Acceptability of trial and-or intervention	Acceptability of the trial and/or intervention to stakeholders e.g. clinical staff, participants	13	20
Clinical benefit or Proof of principle	Is there any clinical benefit?	3	8
Collection of outcome data and-or data completion	Codes to do with outcome data collection e.g. PROMs used etc; Feasibility of data completion or completeness	20	28
Eligibility and screening	Eligibility and screening of participants for the trial	6	6
Est parameters to inform sample size calculations	Estimating parameters or informing sample size calculations for definitive trial	9	13
Fidelity	Intervention fidelity i.e. groups receive the intervention exactly as described in the study protocol	10	15
Health economic or cost assessment	Assessment of cost or health economic analysis	2	2
Maintaining blinding	Maintaining blinding	3	3
Patient experience of pilot trial	Patient experience of the pilot trial is important	5	7
Primary outcome for main trial	To identify the primary outcome for the main trial	5	8
Protocol adherence	Assessment of protocol adherence as one area of feasibility	9	15
Randomisation methods	The randomisation methods used and appropriateness of those methods	2	4
Recruitment	Codes related to pilot trial recruitment	29	89
Retention and or follow up	Codes to do with retaining and/or following up participants in the pilot trial	15	20
Safety or Adverse Events	Uncertainties around safety or adverse events	2	2
Willingness to randomise	Willingness to randomise patients	7	8
2. PILOT TRIAL STAKEHOLDERS	**CATEGORY: PILOT TRIAL STAKEHOLDERS**	0	0

CODE	DESCRIPTION	FILES	REFS
Challenges re pilot trial stakeholders	Challenges between different stakeholders; Challenges specific to certain stakeholders	21	32
Clinical Trials Unit	A clinical trials unit were involved in the pilot trial	7	8
Communication	Communication between stakeholders	22	68
Continuity of stakeholders	Continuity of stakeholders or researchers involved in delivering the pilot trial	9	15
DMEC	Data Monitoring and Ethics Committee	1	1
Enthusiasm and engagement	Enthusiasm and engagement with the pilot trial; Enthusiasm and engagement of specific stakeholders	7	19
Limited experience	Junior or early career researcher; First pilot trial; Inexperienced	20	35
Patient and Public Involvement	Where PPI/Participant representatives contributed; How PPI/Participant representatives contributed to the pilot trial	31	88
Research design service input	RDS input	2	2
Roles and responsibilities	Ideas about whose role something e.g. a specific task is; Ideas about whose responsibility something is; Idea that something is 'not my job role' or 'not what I do'	14	26
Trial Management Group	The role of the Trial Management Group; Who is in the Trial Management Group; What does the Trial Management Group do	8	9
Trial Steering Committee or Trial Oversight committee	The role of the Trial Steering Committee or Oversight Committee; Who is in the Trial Steering/Oversight Committee; What does the Trial Steering/Oversight Committee do	7	7
3. PILOT TRIAL DESIGN AND SET UP	**CATEGORY: PILOT TRIAL DESIGN AND SET UP**	0	0
A different trial design was discussed OR planned OR might have been better OR more appropriate	A different trial might be been better to answer the question e.g. a longer pilot trial, something more flexible, an internal pilot trial, a definitive	17	35

CODE	DESCRIPTION	FILES	REFS
	effectiveness RCT Or external pilot/feasibility design might not have been the most appropriate		
Complicated statistics	Pilot trials have quite complicated statistics	2	4
CONSORT statement	CONSORT statement to inform pilot trial design	3	5
Contextual considerations	Contextual considerations for pilot trial e.g. for the design e.g. for progression criteria used e.g. for how different stakeholders are involved	17	29
Detail and granularity of data	Detail and granularity e.g. for pilot trial data	7	11
Factorial design	Pilot trial following a factorial design	2	4
Informed consent and participant facing documents	Informed consent and participant facing documents for pilot trial	7	8
Obtaining regulatory approvals	Regulatory approvals for the pilot trial e.g. REC, HRA, MHRA, site R&D etc	5	7
Parallels with adaptive trial	Parallels between a pilot trial and an adaptive trial	5	5
Pilot trial background, context, clinical area	Pilot trial background, context and/or clinical area	23	36
Pilot trial funding	Who funded the pilot trial?; Experiences of applying for pilot trial funding	32	187
Pilot trial is within a cohort study	Pilot trial sits within a larger cohort study	3	6
Powered pilot trial	References to the pilot trial being powered	2	2
Pragmatic design	Pilot trial is described as pragmatic in design	3	3
Qualitative research sub study or component	Aim of qualitative research study; Design of qualitative research study e.g. interviews/focus groups with patients, clinical staff	28	60
Sample size	The pilot trial sample size	4	8
Single arm pilot or feasibility trial	Single arm pilot or feasibility study design	2	2
Site Feasibility Questionnaire during set up	Site feasibility questionnaire during site set up	1	1
Terminology	Codes relating to ‘pilot’ and ‘feasibility’ terms and the use of these	22	34

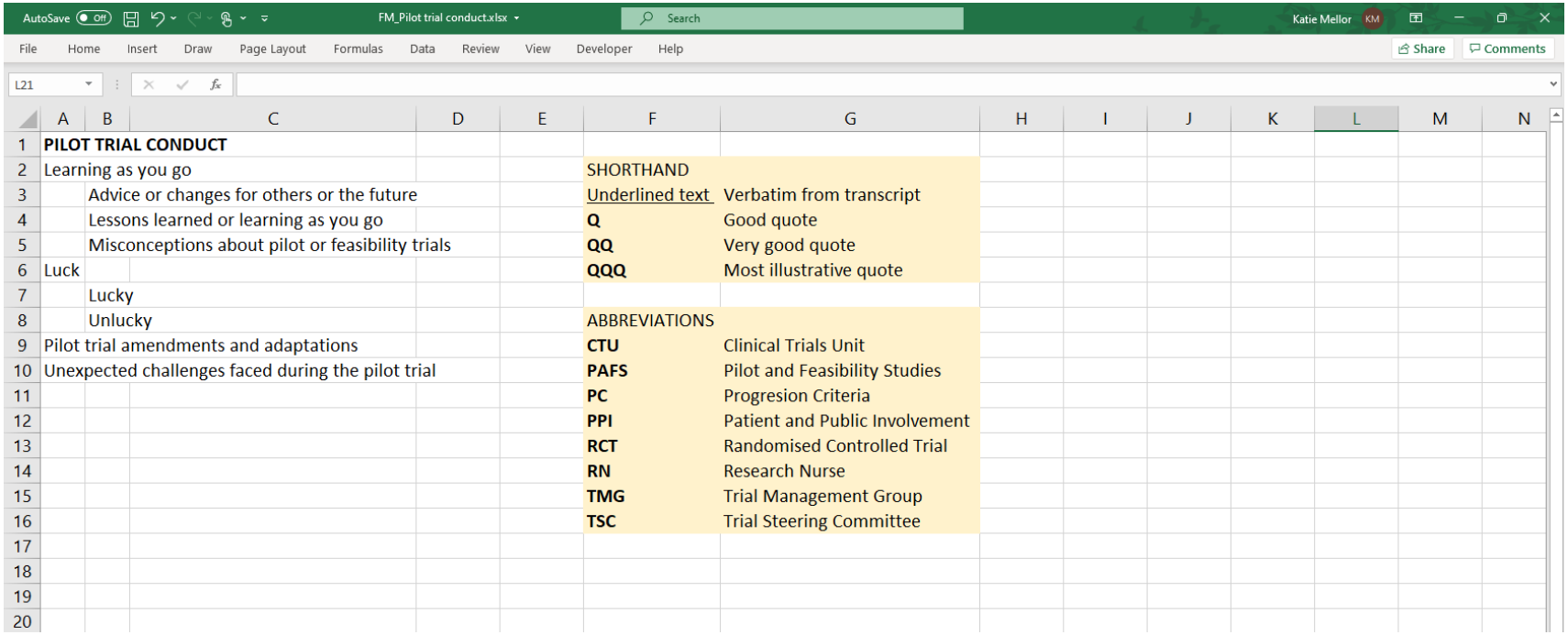
CODE	DESCRIPTION	FILES	REFS
4. PROGRESSION CRITERIA	**CATEGORY: PROGRESSION CRITERIA**	0	0
Applicability to external pilots/more applicable to internal	Progression criteria are more applicable to internal pilot trials (rather than external or stand-alone)	12	18
Established a priori	Progression criteria should be predefined/established a priori and should not be changed during the pilot trial	17	25
Flexible or TRAFFIC LIGHT SYSTEM	Traffic light system or red amber green approach; Flexibility around progression criteria targets; Not finite, not the be all and end all, open to interpretation	22	56
Negative perceptions of progression criteria	For example: You can ignore the progression criteria you set; Progression criteria might not be the best way to make progression decision; Progression criteria might not be the best way to make progression decision	10	19
No formal progression criteria	There was no formal progression criteria	7	12
Positive perceptions of progression criteria	For example: Helpful framework; Ensures transparency and understanding	19	29
Progression criteria should include...	Feasibility outcomes that progression criteria should include	10	13
Progression criteria were unclear or are unknown	Unclear/can't remember specifics re the progression criteria were used	9	11
Rescue plan	Rescue plan for if trial does not go to plan	1	1
Required by funders	Funder requirement	16	22
Strict	Strict targets should be used	12	13
The process for deciding on progression criteria	The process for deciding on progression criteria including who is involved, any guidance that was used, any rationale for progression criteria	22	190
5. PILOT TRIAL CONDUCT	**CATEGORY: PILOT TRIAL CONDUCT**	0	0
Learning as you go	Learning as you go while doing the pilot trial	20	36
Luck	Reference to luck e.g. I was lucky e.g. I was unlucky	4	4

CODE	DESCRIPTION	FILES	REFS
Pilot trial amendments and adaptations	Amendments and adaptations made during the pilot trial e.g. changes to recruitment strategies	17	24
Unexpected challenges faced during the pilot trial	Challenges that were unexpected or unforeseen e.g. uncertainties not included in progression criteria e.g. obtaining regulatory approvals, trial delays, changes to research team	17	32
6. PILOT TRIAL FINDINGS	**CATEGORY: PILOT TRIAL FINDINGS**	0	0
Assessment of the progression criteria	Assessment of the progression criteria targets - were they met or not	15	21
Dissemination including publication	Dissemination of findings including publications related to the pilot trial e.g. protocol paper, results paper	22	39
Hypothesis testing or assessment of efficacy	Pilot trial hypothesis testing or assessment of efficacy	13	21
Perception of a linear process or guaranteed progression	Perception of a linear process or guaranteed progression to future research	7	11
6A FEASIBILITY OF THE FUTURE DEFINITIVE RCT	SUB CATEGORY: Is the future trial feasible? Should we progress to it and if so, how?	0	0
Conflict between findings and progression	Conflict between findings e.g. meeting (or not meeting) the progression criteria and progressing (or not progressing) to a definitive RCT	13	27
Did demonstrate feasibility or has progressed	Pilot trial was found to be feasible and has or will progress	9	11
Did not demonstrate feasibility or will not progress	Pilot trial did not demonstrate feasibility and has or will not progress to future trial	16	22
Experiences of making the progression decision	Whether the decision was complicated, difficult or clear-cut, easy	13	27
External to internal pilot transition	What was an external pilot trial ended up being an internal pilot trial Perceptions about transitioning	10	22
How was or will the progression decision be made	How the decision was/will be made to progress/ whether a future trial is feasible	22	47
Involvement in deciding whether a future trial is feasible	Who is involved in deciding whether the future RCT is feasible e.g. Chief Investigators, Co-I's, Statisticians, the Trial Management Group more broadly, Funders, PPI/Participant representatives, The Trial Steering Committee, Clinical site staff etc	29	115
Other considerations	Other considerations in addition to progression criteria	21	49

CODE	DESCRIPTION	FILES	REFS
7. THE FUTURE DEFINITIVE TRIAL	**CATEGORY: THE FUTURE DEFINITIVE TRIAL**	0	0
Changes to definitive RCT design	Changes that will be made to the definitive RCT design based on the pilot trial findings	13	17
Definitive trial funding	Funding intentions for the future definitive RCT	15	28
Definitive trial will have an internal pilot	Plans for the future definitive trial to have an embedded internal pilot trial	4	6
No intended future definitive trial	There is no intended future definitive trial OR it is unlikely from the off set that there will be a future definitive trial	1	1
8. TIME	**CATEGORY: TIME**	0	0
Changes over time	Things that have changed over time in this field e.g. changes between a pilot trial that was carried out years ago and one that was carried out recently	12	34
Delays	Delays to the pilot trial	10	21
Limited time	Time as a limited resource	14	21
Pilot trials take a long time	Pilot trials take a long time or add a lot of time on to the whole process	13	25
BACKGROUND CODES AND ADMIN		0	0
Confused responses	Any responses to questions that do not make sense or are confused	1	1
Good quotes	Good participant quotes to make a note of	34	143
Other uncoded transcript sections	Uncoded transcript sections/areas	35	88
Participant role, experience, affiliations etc	The role and experience of the researcher in relation to pilot trials and clinical research more broadly	28	141
UNCATEGORISED CODES		0	0

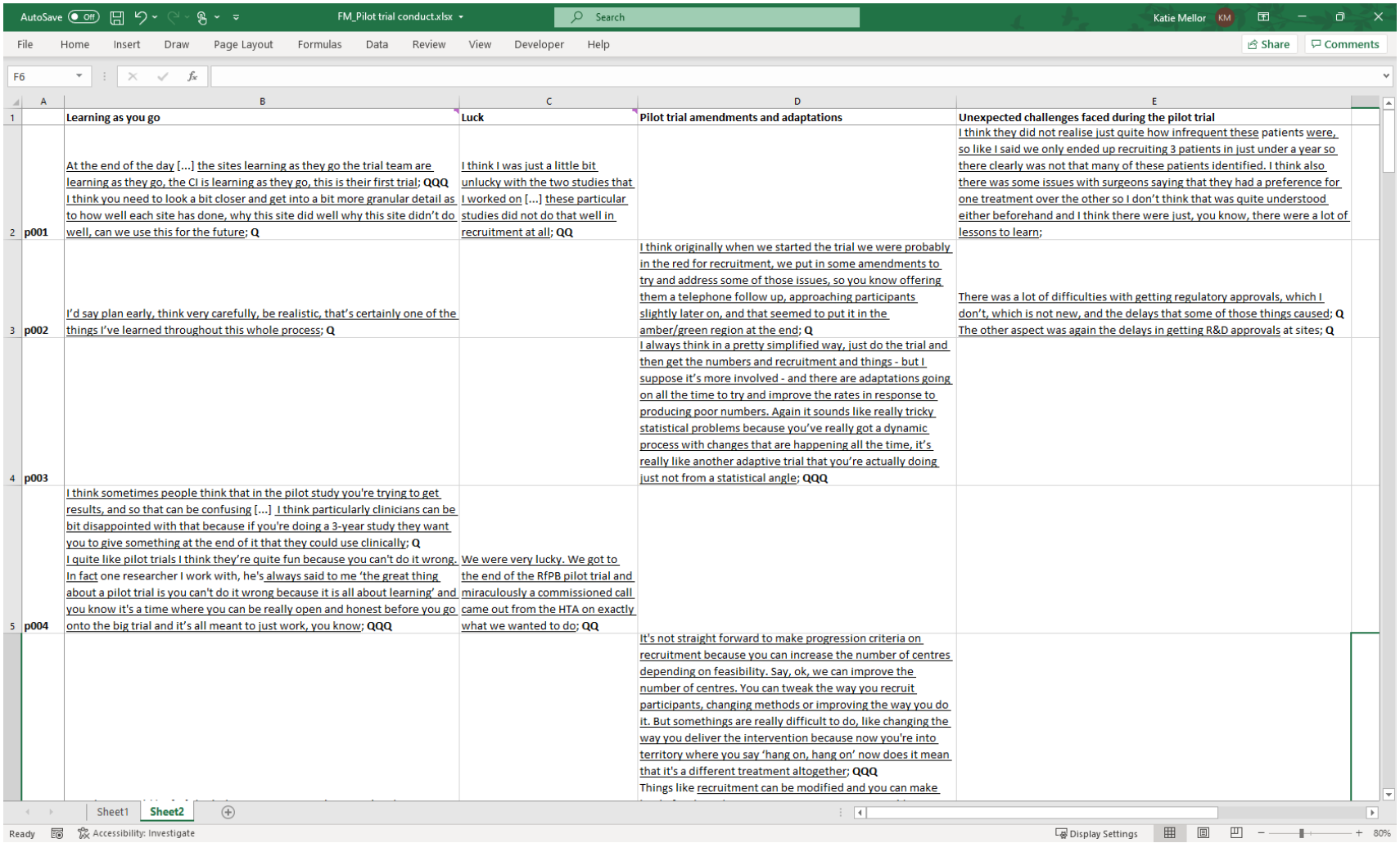
D7 Example framework matrix for the ‘Pilot Trial Conduct’ category

Sheet 1: Description of framework matrix; shorthand used

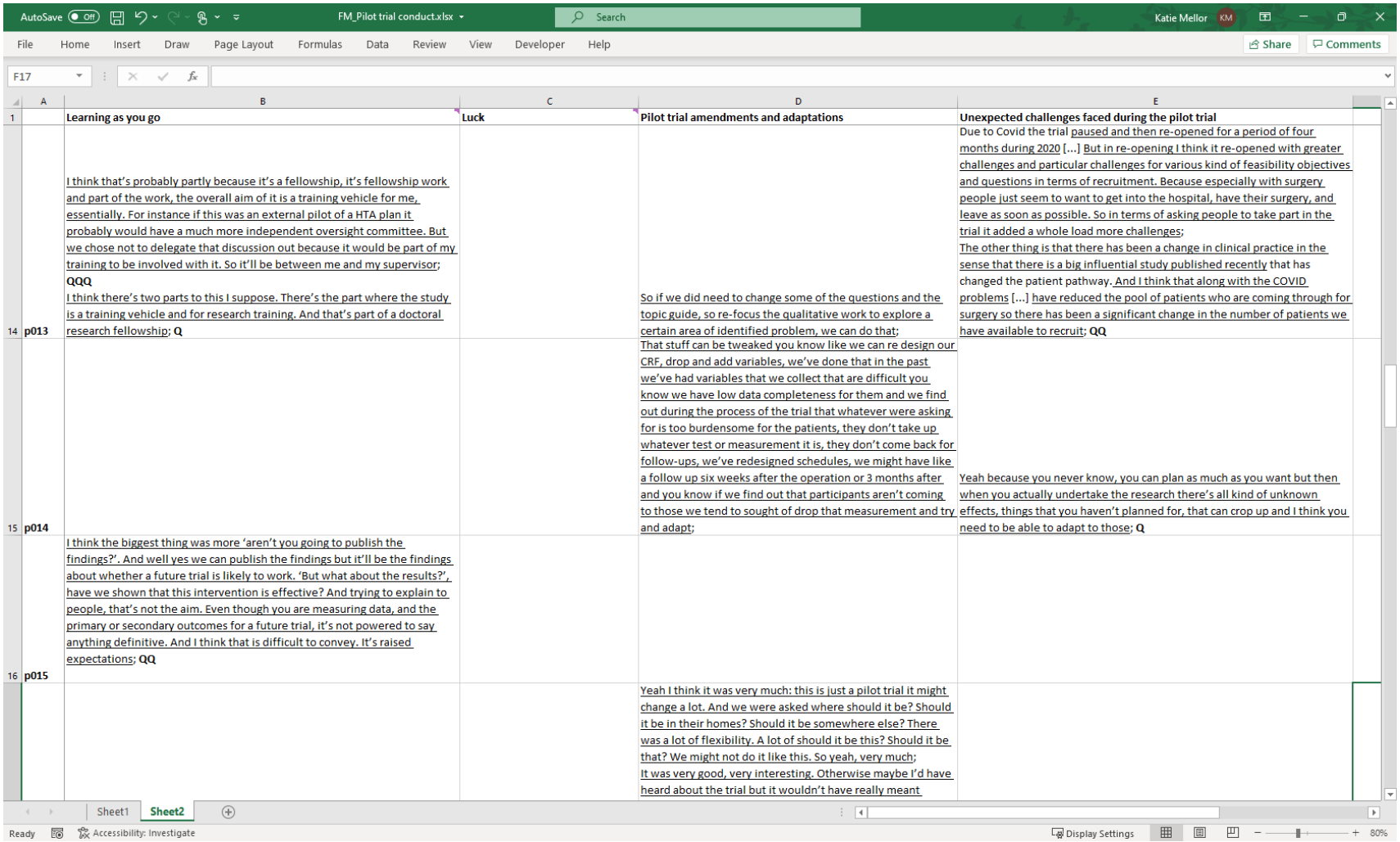


	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	**PILOT TRIAL CONDUCT**													
2	Learning as you go					SHORTHAND								
3		Advice or changes for others or the future				Underlined text	Verbatim from transcript							
4		Lessons learned or learning as you go				**Q**	Good quote							
5		Misconceptions about pilot or feasibility trials				**QQ**	Very good quote							
6	Luck					**QQQ**	Most illustrative quote							
7		Lucky												
8		Unlucky				ABBREVIATIONS								
9	Pilot trial amendments and adaptations					**CTU**	Clinical Trials Unit							
10	Unexpected challenges faced during the pilot trial					**PAFS**	Pilot and Feasibility Studies							
11						**PC**	Progresion Criteria							
12						**PPI**	Patient and Public Involvement							
13						**RCT**	Randomised Controlled Trial							
14						**RN**	Research Nurse							
15						**TMG**	Trial Management Group							
16						**TSC**	Trial Steering Committee							
17														
18														
19														
20														

Sheet 2: Framework matrix, series of snapshots



	A	Learning as you go	Luck	Pilot trial amendments and adaptations	Unexpected challenges faced during the pilot trial
2	p001	At the end of the day [...] the sites learning as they go the trial team are learning as they go, the CI is learning as they go, this is their first trial; QQQ I think you need to look a bit closer and get into a bit more granular detail as to how well each site has done, why this site did well why this site didn't do well, can we use this for the future; Q	I think I was just a little bit unlucky with the two studies that I worked on [...] these particular studies did not do that well in recruitment at all; QQ		I think they did not realise just quite how infrequent these patients were, so like I said we only ended up recruiting 3 patients in just under a year so there clearly was not that many of these patients identified. I think also there was some issues with surgeons saying that they had a preference for one treatment over the other so I don't think that was quite understood either beforehand and I think there were just, you know, there were a lot of lessons to learn;
3	p002	I'd say plan early, think very carefully, be realistic, that's certainly one of the things I've learned throughout this whole process; Q		I think originally when we started the trial we were probably in the red for recruitment, we put in some amendments to try and address some of those issues, so you know offering them a telephone follow up, approaching participants slightly later on, and that seemed to put it in the amber/green region at the end; Q	There was a lot of difficulties with getting regulatory approvals, which I don't, which is not new, and the delays that some of those things caused; Q The other aspect was again the delays in getting R&D approvals at sites; Q
4	p003			I always think in a pretty simplified way, just do the trial and then get the numbers and recruitment and things - but I suppose it's more involved - and there are adaptations going on all the time to try and improve the rates in response to producing poor numbers. Again it sounds like really tricky statistical problems because you've really got a dynamic process with changes that are happening all the time, it's really like another adaptive trial that you're actually doing just not from a statistical angle; QQQ	
5	p004	I think sometimes people think that in the pilot study you're trying to get results, and so that can be confusing [...] I think particularly clinicians can be bit disappointed with that because if you're doing a 3-year study they want you to give something at the end of it that they could use clinically; Q I quite like pilot trials I think they're quite fun because you can't do it wrong. In fact one researcher I work with, he's always said to me 'the great thing about a pilot trial is you can't do it wrong because it is all about learning' and you know it's a time where you can be really open and honest before you go onto the big trial and it's all meant to just work, you know; QQQ	We were very lucky. We got to the end of the RfPB pilot trial and miraculously a commissioned call came out from the HTA on exactly what we wanted to do; QQ		
				It's not straight forward to make progression criteria on recruitment because you can increase the number of centres depending on feasibility. Say, ok, we can improve the number of centres. You can tweak the way you recruit participants, changing methods or improving the way you do it. But somethings are really difficult to do, like changing the way you deliver the intervention because now you're into territory where you say 'hang on, hang on' now does it mean that it's a different treatment altogether; QQQ Things like recruitment can be modified and you can make	



	A	B	C	D	E
1		**Learning as you go**	**Luck**	**Pilot trial amendments and adaptations**	**Unexpected challenges faced during the pilot trial**
14	**p013**	I think that's probably partly because it's a fellowship, it's fellowship work and part of the work, the overall aim of it is a training vehicle for me, essentially. For instance if this was an external pilot of a HTA plan it probably would have a much more independent oversight committee. But we chose not to delegate that discussion out because it would be part of my training to be involved with it. So it'll be between me and my supervisor; **QQQ** I think there's two parts to this I suppose. There's the part where the study is a training vehicle and for research training. And that's part of a doctoral research fellowship; **Q**		So if we did need to change some of the questions and the topic guide, so re-focus the qualitative work to explore a certain area of identified problem, we can do that;	Due to Covid the trial paused and then re-opened for a period of four months during 2020 [...] But in re-opening I think it re-opened with greater challenges and particular challenges for various kind of feasibility objectives and questions in terms of recruitment. Because especially with surgery people just seem to want to get into the hospital, have their surgery, and leave as soon as possible. So in terms of asking people to take part in the trial it added a whole load more challenges; The other thing is that there has been a change in clinical practice in the sense that there is a big influential study published recently that has changed the patient pathway. And I think that along with the COVID problems [...] have reduced the pool of patients who are coming through for surgery so there has been a significant change in the number of patients we have available to recruit; **QQ**
15	**p014**			That stuff can be tweaked you know like we can re design our CRF, drop and add variables, we've done that in the past we've had variables that we collect that are difficult you know we have low data completeness for them and we find out during the process of the trial that whatever were asking for is too burdensome for the patients, they don't take up whatever test or measurement it is, they don't come back for follow-ups, we've redesigned schedules, we might have like a follow up six weeks after the operation or 3 months after and you know if we find out that participants aren't coming to those we tend to sought of drop that measurement and try and adapt;	Yeah because you never know, you can plan as much as you want but then when you actually undertake the research there's all kind of unknown effects, things that you haven't planned for, that can crop up and I think you need to be able to adapt to those; **Q**
16	**p015**	I think the biggest thing was more 'aren't you going to publish the findings?'. And well yes we can publish the findings but it'll be the findings about whether a future trial is likely to work. 'But what about the results?', have we shown that this intervention is effective? And trying to explain to people, that's not the aim. Even though you are measuring data, and the primary or secondary outcomes for a future trial, it's not powered to say anything definitive. And I think that is difficult to convey. It's raised expectations; **QQ**			
				Yeah I think it was very much: this is just a pilot trial it might change a lot. And we were asked where should it be? Should it be in their homes? Should it be somewhere else? There was a lot of flexibility. A lot of should it be this? Should it be that? We might not do it like this. So yeah, very much; It was very good, very interesting. Otherwise maybe I'd have heard about the trial but it wouldn't have really meant	

D8 Reflexivity journal extracts

A3.1 A journal entry relating to my prior assumptions at the point of protocol pre-registration

Date	Activity	Journal entry
27-Nov-20	OSF preregistration	As part of the protocol pre-registration there was a space to add positionality reflections. I stated the following: My prior assumptions are that since there is currently no guidance in this area, current practice with regards to using progression criteria varies between different research teams. Reflecting on my own experience of working in different clinical trial teams, I also assume that different researchers have different ideas of what should constitute progression criteria based on their experience and role in the trial. I also think, based on the competitive nature of academia, that choice of progression criteria could be directly or indirectly influenced by the desire to show that a pilot trial is feasible in order to justify funding applications for larger definitive research trials.

A3.2 A series of journal entries relating to interview, transcription and coding of the first interview

Date	Activity	Journal entry
16-Dec-20	Pre-interview P001	Pre first interview – Reminders to self: . Remember to take notes so I can go back to previous questions . Remember to use probes and ensure the questions are open and not closed . Remember 'in your experience as a ….' . Remember to not assume I know what something means - ask for clarifications, examples etc . Use participants' own words to relay back Although I have met this participant before, I have not looked in detail at the trials that participant 1 works on since I wouldn't know about trials that other participants work on going forward. Following the interview I should arrange a meeting with Charlotte to discuss how everything went. Reminder to ask to borrow Charlotte's Dictaphone as a spare for future interviews.
16-Dec-20	Post-interview P001	First interview went really well. I think it was clear that the different roles in research teams will be a key thing to explore. It was interesting how much P001 (a trial statistician) valued qualitative research in the pilot trials they work on. It was clear that group consensus and discussion was important to P001 and relationships both between the research team and site and within the research team itself. I also noticed frustration about the situation where a pilot trial finishes, if it does not progress, it is *just finished*. Again demonstrating the importance of communication because this is not an unfamiliar outcome for pilot trials.
04-Jan-21	Transcription P001	Transcription of P001 took a lot longer than thought, I had put 4hrs in my calendar to do this, but it took most of the day. However, it was a very helpful experience and was difficult to not think even just at the transcription stage about higher level concepts and themes (analytical). I think it will be good to do a few more as learning opportunity and then ask Prestige Network to do some. When transcribing I noticed that one of my questions might have been leading… I said 'it might depend

		on context' in the question and 'context' was referred to in the answer. Reminder to be aware of, and try to avoid this going forward.
05-Jan-21	Coding P001	NVivo was user friendly. I auto coded questions by heading so must use the same question structure going forward in other transcripts. I felt like I should code everything (line by line) at this stage but was not sure whether some codes included text extracts that are far too big (note to ask Charlotte opinion on this). I also realise after this process that I need to sometimes include the interview questions asked in my coding to ensure I am clear about what responses are in relation to.

A3.3 A series of journal entries relating to interesting discussion points

Date	Activity	Journal entry
11-Feb-21	Coding P010	I developed lots of new codes based on this interview that describe the challenges of conducting pilot trials. A big discussion point was around the limited funding available from RfPB that means often CTUs often cannot support pilot trials. This could be a problem when transitioning from pilot to a definitive trial – for example, a CTU might come onboard at the definitive trial stage and notice things that perhaps could have been done better in the pilot. I keep noticing that trial statisticians with lots of trial experiences seem to be less comfortable with setting prespecified progression criteria for external pilot trials because there is no available data to set specific numerical targets. I need to keep an eye on this and see whether trial statisticians with less experience e.g. those who are early career researchers feel the same way?
09-Mar-21	Call with Charlotte	I called Charlotte after some confusion around eligibility of a participant representative I interviewed this morning. After talking to Charlotte I realise that often coming at this study from a background in trials I can be very strict on eligibility. Actually this study has very minimal potential to harm and if someone tells me they are eligible and they have confirmed that they read the PIS, that is all I can ask of them. If they start talking about other things (e.g. other trial designs) then that is OK, it is a finding in itself if someone doesn't quite understand the design of a pilot or feasibility trial OR has not been involved in progression criteria. I need to appreciate that this is a finding and this is OK.
26-Apr-21	Meeting with Charlotte	Discussing development of my themes with Charlotte realising how much my thoughts towards PC have changed since doing the qual study. At first I thought PC were really important to ensure we are being transparent and only doing definitive trials that are feasible. But I did not consider back then how much researchers themselves probably do not want to do a trial that is not feasible and invest time and energy into something that is unlikely to work. However researchers don't only want a trial that is feasible, but also want one that will demonstrate efficacy. This is not the point of a pilot trial, but I can completely see why researchers want that reassurance. I am starting to wonder whether way we interpret the findings of external pilot trials fits into the current framework we have for progression criteria based largely on internal pilot trials? I am not sure... I spoke to Charlotte about the importance of recognising that my thinking is changing but not allowing this to bias any future interviews and ensuring that my analysis should mirror the data I am collecting.
18-Jun-21	Developing themes	As I am writing up the themes I have developed for the first draft of this chapter I am wondering whether there is a cross cutting theme about research inefficiency or waste, and whether this fits nicely under my higher level theme or whether there is scope to further improve the wording so this reflects this findings I have developed. My thinking is that there can be research inefficiency in the following: 1. Researchers can't do pilot trials as they want to because there is not enough funding available (per trial) so they do a scaled

		back version e.g. not doing qual research, not collecting outcomes as they would intend to for a future trial (?) 2. People are doing pilot trials perhaps when they don't need to or when an alternative design would be better e.g. doing them because funder told them to / because they are a junior CI 3. Pilot trials that are feasible and done well aren't progressing further for other reasons (i.e. too many pilot trials compared to available funding and resources for definitive trials - a *bottleneck*) I am not sure now whether this is another sub theme or in fact ties in nicely with the Higher Level them and I should update the wording of this to highlight further

A3.4 A journal entry relating to ongoing recruitment to the study

Date	Activity	Journal entry
15-Feb-21	Recruitment	On Friday I tweeted about the qualitative study and invited people to contact me if they would like to participate. This was very well received and I had ~30 retweets and was contacted by a number of people, one of which I am meeting this morning. This person asked me if a 'feasibility trial' is eligible, so I said that I am following definitions for pilot/feasibility based on Eldridge et al 2016 conceptual framework but appreciate that the terms are used interchangeably. I asked whether the aim of the study is to *'assess the feasibility of a future RCT and involves piloting all or part of it?'* - the answer to this was yes so I thought appropriate to interview. This person is PI for a trial that has not yet completed so questions will be focused on how PC was established, and the plans (if any) for how it will be assessed at the end.
24-May-21	Recruitment	In a recent interview one participant asked whether I had interviewed a specific researcher who has done research that might be of interest to the study. It would be really interesting to speak to people who have done research in this area and have published influential papers or methodological work on Pilot and Feasibility Trials outside of the Pilot and Feasibility Studies working group that I am part of. I realise that working so closely with the PAFS group, although we are from a range of institutions, might have influenced some of my perceptions of the best way to do things. *Post reflection note: After speaking about this with Charlotte in catch up meeting I have emailed MS IDREC team with request for an amendment to ethics approval so I can contact corresponding authors of influential papers in this field to invite them to participate.*

E1 Completed CROSS 2021 checklist

Checklist for Reporting Of Survey Studies (CROSS)

Section/topic	Item	Item description	Reported on page #
Title and abstract			
Title and abstract	1a	State the word "survey" along with a commonly used term in title or abstract to introduce the study's design.	178
	1b	Provide an informative summary in the abstract, covering background, objectives, methods, findings/results, interpretation/discussion, and conclusions.	N/A
Introduction			
Background	2	Provide a background about the rationale of study, what has been previously done, and why this survey is needed.	179
Purpose/aim	3	Identify specific purposes, aims, goals, or objectives of the study.	180
Methods			
Study design	4	Specify the study design in the methods section with a commonly used term (e.g., cross-sectional or longitudinal).	181
Data collection methods	5a	Describe the questionnaire (e.g., number of sections, number of questions, number and names of instruments used).	184
	5b	Describe all questionnaire instruments that were used in the survey to measure particular concepts. Report target population, reported validity and reliability information, scoring/classification procedure, and reference links (if any).	184
	5c	Provide information on pretesting of the questionnaire, if performed (in the article or in an online supplement). Report the method of pretesting, number of times questionnaire was pre-tested, number and demographics of participants used for pretesting, and the level of similarity of demographics between pre-testing participants and sample population.	186
	5d	Questionnaire if possible, should be fully provided (in the article, or as appendices or as an online supplement).	186
Sample characteristics	6a	Describe the study population (i.e., background, locations, eligibility criteria for participant inclusion in survey, exclusion criteria).	183
	6b	Describe the sampling techniques used (e.g., single stage or multistage sampling, simple random sampling, stratified sampling, cluster sampling, convenience sampling). Specify the locations of sample participants whenever clustered sampling was applied.	183
	6c	Provide information on sample size, along with details of sample size calculation.	183
	6d	Describe how representative the sample is of the study population (or target population if possible), particularly for population-based surveys.	N/A
Survey administration	7a	Provide information on modes of questionnaire administration, including the type and number of contacts, the location where the survey was conducted (e.g., outpatient room or by use of online tools, such as SurveyMonkey).	184
	7b	Provide information of survey's time frame, such as periods of recruitment, exposure, and follow-up days.	185

Section/topic	Item	Item description	Reported on page #
	7c	Provide information on the entry process: –>For non-web-based surveys, provide approaches to minimize human error in data entry. –>For web-based surveys, provide approaches to prevent "multiple participation" of participants.	187
Study preparation	8	Describe any preparation process before conducting the survey (e.g., interviewers' training process, advertising the survey).	184
Ethical considerations	9a	Provide information on ethical approval for the survey if obtained, including informed consent, institutional review board [IRB] approval, Helsinki declaration, and good clinical practice [GCP] declaration (as appropriate).	181
	9b	Provide information about survey anonymity and confidentiality and describe what mechanisms were used to protect unauthorized access.	181
Statistical analysis	10a	Describe statistical methods and analytical approach. Report the statistical software that was used for data analysis.	188
	10b	Report any modification of variables used in the analysis, along with reference (if available).	N/A
	10c	Report details about how missing data was handled. Include rate of missing items, missing data mechanism (i.e., missing completely at random [MCAR], missing at random [MAR] or missing not at random [MNAR]) and methods used to deal with missing data (e.g., multiple imputation).	N/A
	10d	State how non-response error was addressed.	N/A
	10e	For longitudinal surveys, state how loss to follow-up was addressed.	N/A
	10f	Indicate whether any methods such as weighting of items or propensity scores have been used to adjust for non-representativeness of the sample.	N/A
	10g	Describe any sensitivity analysis conducted.	N/A
Results			
Respondent characteristics	11a	Report numbers of individuals at each stage of the study. Consider using a flow diagram, if possible.	191
	11b	Provide reasons for non-participation at each stage, if possible.	N/A
	11c	Report response rate, present the definition of response rate or the formula used to calculate response rate.	191
	11d	Provide information to define how unique visitors are determined. Report number of unique visitors along with relevant proportions (e.g., view proportion, participation proportion, completion proportion).	N/A
Descriptive results	12	Provide characteristics of study participants, as well as information on potential confounders and assessed outcomes.	N/A
Main findings	13a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates along with 95% confidence intervals and p-values.	192
	13b	For multivariable analysis, provide information on the model building process, model fit statistics, and model assumptions (as appropriate).	N/A

Section/topic	Item	Item description	Reported on page #
	13c	Provide details about any sensitivity analysis performed. If there are considerable amount of missing data, report sensitivity analyses comparing the results of complete cases with that of the imputed dataset (if possible).	N/A
Discussion			
Limitations	14	Discuss the limitations of the study, considering sources of potential biases and imprecisions, such as non-representativeness of sample, study design, important uncontrolled confounders.	217
Interpretations	15	Give a cautious overall interpretation of results, based on potential biases and imprecisions and suggest areas for future research.	215
Generalizability	16	Discuss the external validity of the results.	Chapter 7
Other sections			
Role of funding source	17	State whether any funding organization has had any roles in the survey's design, implementation, and analysis.	N/A
Conflict of interest	18	Declare any potential conflict of interest.	N/A
Acknowledgements	19	Provide names of organizations/persons that are acknowledged along with their contribution to the research.	N/A

E2 Survey outline

Progression of external pilot trials

Welcome

We appreciate your interest in participating in this online survey.

You have been invited to participate as we have identified that you are the corresponding author of a publication for an external randomised pilot or feasibility trial.

Please read through the information in the follwoing link before agreeing to participate (if you wish to) by ticking the 'Yes, I agree to take part' box below.

https://static.onlinesurveys.ac.uk/media/account/333/survey/820002/question/study_information.pdf

Please note that you may only participate in this survey if you are 18 years of age or over. ** Required*

- ○ I certify that I am 18 years of age or over

If you have read the information above and agree to participate with the understanding that the data you submit will be processed accordingly, please tick the box below to start the survey. ** Required*

- ○ Yes, I agree to take part

1 / 8

Page 2

Which of the following best describes the current pilot trial stage?

- ○ Trial planning & design
- ○ Set up
- ○ Conduct
- ○ Analysis
- ○ Reporting/Dissemination

Are the pilot trial findings published?

- ○ Yes
- ○ No

Do you plan to publish the pilot trial findings in the future?

- ○ Yes
- ○ No

Why do you not plan on publishing the pilot trial findings?

Has the pilot trial recruitment period been extended beyond the original proposed timeframe?

- ○ Yes
- ○ No

Page 2

What were the pilot trial findings in relation to the feasibility of a future definitive trial?

- ○ Future definitive trial is feasible
- ○ Future definitive trial is feasible with changes to design
- ○ Future definitive trial is not feasible
- ○ Feasibility of the future definitive trial is unclear

Please briefly describe any proposed changes to the future definitive trial design

Please briefly specify why feasibility is unclear

Do you intend to do any further feasibility assessment?

- ○ Yes
- ○ No

To what extent was the pre-specified progression criteria met?

- ○ Met all criteria
- ○ Met some criteria
- ○ Met none of the criteria

3 / 8

- Other

Please specify

How helpful were progression criteria in informing the assessment of definitive trial feasibility?

- Very helpful
- Somewhat helpful
- Not helpful
- They were not a consideration

Did other factors (in addition to progression criteria) inform the assessment of definitive trial feasibility?

- Yes
- No

Please specify

Do you intend to conduct a future definitive trial?

- Yes
- No

Has funding for the definitive trial been applied for?

- Yes
- No

Please specify definitive trial funding source

Was definitive trial funding awarded?

- Yes, funding was awarded
- Application outcome is not yet known
- No, funding was not awarded

What best describes the current stage of the definitive trial?

- Trial planning & design
- Set up
- Conduct
- Analysis
- Reporting/Dissemination

Have the definitive trial findings been published?

- Yes

○ No

What influenced your decision not to conduct a definitive trial?

Is there anything else you would like to share regarding the findings of your pilot trial?

Is there anything else you would like to share regarding whether your pilot trial did or did not progress to a future definitive trial?

Prize draw

As a thank you for your time we invite you to enter a prize draw for a £50 One4All e-voucher. The winner will be drawn at random once the survey closes on the 14th of February 2022.

By entering the prize draw you are consenting for your email to be shared with the One4All company directly to process the e-voucher if you are successful. One4All will hold this email address for 13 months and will only hold this data for the purpose of issuing and managing the digital gift card in line with the General Data Protection Regulation.

I would like to enter the prize draw to win a £50 One4All e-voucher

- ○ Yes, I would like to enter the prize draw
- ○ No, I would not like to enter the prize draw

Please confirm the email address you would like to enter

Final page

Thank you for taking the time to complete this survey.

If you have experienced any issues, please contact the Principal Researcher directly: Katie Mellor (katie.mellor@ndorms.ox.ac.uk; +44 (0)1865 737923).

E3 Email invitation to participate wording

Survey follow up study
Email wording

Note: Mail merge will be used to personalise emails to address recipients by name and include details of the trial publication.

Subject: Online survey to explore progression of external pilot trials

Dear <Participant name>

RE: <Publication title>

We are researchers based at the University of Oxford, conducting research on the progression of external randomised pilot trials. The purpose of our research is to explore the findings and outcomes of external randomised pilot trials that have been published, to help inform the development of future guidance for external randomised pilot trials as part of an MRC funded DPhil study.

You are being approached directly as you are the corresponding author for an external randomised pilot trial <protocol/results publication> that we previously identified when conducting a review. We have obtained your email address directly from the publication.

We are interested to know what the findings of your pilot trial were, and whether it progressed onto further research. The survey should take approximately 5-10 minutes to complete and will close on <DD-MMM-YYYY>.

The survey can be accessed via this link: <insert link>

We hope that you will support our endeavours to improve the design of pilot and feasibility trials through completion of this survey. Although we are interested in the outcomes of individual pilot trials, we will de-identify all data following our analysis so that any outputs from this research will not be attributable to any individuals.

If you have any questions, please do not hesitate to contact me.

Kind regards,

Miss Katie Mellor

University Direct Line: 01865 737 923

University e-mail: katie.mellor@ndorms.ox.ac.uk

E4 Pre survey information

Miss Katie Mellor, DPhil Candidate
Centre for Statistics in Medicine
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Progression of external randomised pilot trials: A web-based survey of trialists

Pre survey information

General Information

The aim of this study is to explore the outcomes of external randomised pilot trials that were previously identified through a review.

We appreciate your interest in participating in this online survey. You have been invited to participate as we have identified that you are the corresponding author of a publication for an external randomised pilot or feasibility trial. Please read through this information before agreeing to participate (if you wish to) by ticking the 'yes' box below.

You may ask any questions before deciding to take part by contacting the researcher (details below).

The Principal Researcher is Miss Katie Mellor, who is attached to the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences at the University of Oxford. This project is being completed under the supervision of Professor Sally Hopewell.

You will be asked to complete a short web-based survey. This should take about 5-10 minutes. No background knowledge is required. This survey will explore the findings of your pilot trial including whether it was feasible and progressed to further research, and how you made these decisions. This data will not be shared with any third parties and will only be used by researchers at the University of Oxford.

Do I have to take part?

No. Please note that participation is voluntary. If you do decide to take part, you may withdraw at any point for any reason before submitting your answers by pressing the 'Exit' button/ closing the browser. All questions are optional. Once you have submitted the survey your answers cannot be amended or deleted. However, if you wish to withdraw following survey or realise that you have provided incorrect answers you can contact the study team and we can exclude your responses from our analysis.

How will my data be used?

We have obtained your email address through the public domain as corresponding author of a research publication. We will keep this so that we can link publications together to help us find out what happened to individual pilot trials. However, we will maintain anonymity of all respondents in all research outputs. We will not collect any further personal data and your IP address will not be stored. We will take all reasonable measures to ensure that data remain confidential.

The responses you provide will be stored in a password-protected electronic file on University of Oxford secure servers and will be included in a DPhil thesis and may be presented at conferences and published in academic journals. Your email address will be deleted as soon as it is no longer required for the research. Research data will be stored for 10 years after publication or public release of the work of the research.

Miss Katie Mellor, DPhil Candidate
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Who will have access to my data?

The University of Oxford is the data controller with respect to your personal data and, as such, will determine how your personal data is used in the study. The University will process your personal data for the purpose of the research outlined above. Research is a task that we perform in the public interest. Further information about your rights with respect to your personal data is available from https://compliance.admin.ox.ac.uk/individual-rights.

The data you provide will not be shared outside of the University of Oxford.

Who has reviewed this study?

This project has been reviewed by, and received ethics clearance through, a subcommittee of the University of Oxford Central University Research Ethics Committee [R78375/RE001].

Who do I contact if I have a concern or I wish to complain?

If you have a concern about any aspect of this study, please speak to Katie Mellor (katie.mellor@ndorms.ox.ac.uk; +44 (0)1865 737923) or her supervisor, Sally Hopewell (+44 (0)1865 223458), and we will do our best to answer your query. We will acknowledge your concern within 10 working days and give you an indication of how it will be dealt with. If you remain unhappy or wish to make a formal complaint, please contact the Chair of the Research Ethics Committee at the University of Oxford who will seek to resolve the matter as soon as possible:

Medical Sciences Interdivisional Research Ethics Committee; Email: ethics@medsci.ox.ac.uk; Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD

F1 Initial recommendations presented at stakeholder workshops in July 2022

Katie Mellor, DPhil Candidate

Thesis: The role of progression criteria in the design, conduct, analysis and reporting of external randomised pilot trials

Summary infographic

Recommendations for progression criteria design

1.1 Consider from the earliest opportunity

Researchers should consider progression criteria from the onset when designing their pilot trial. Early consideration of progression criteria presents a valuable opportunity for researchers to think about where their uncertainties lie and what problems that they might face, potentially saving time and effort in the long run. Where researchers have not had the opportunity to agree progression criteria prior to submission of their pilot trial funding application, they should instead include preliminary proposed progression criteria with clear plans for finalising criteria prior to starting their pilot trial.

1.2 Frame around feasibility objectives and outcomes

Researchers should consider whether progression criteria are needed for each of their feasibility objectives. Too often progression criteria only focus on recruitment and retention and do not account for other feasibility issues that might also be pertinent to the success of the definitive RCT. However, not all data collected during the external pilot trial needs to inform progression criteria, some might instead help refine the trial design. Framing progression criteria around feasibility objectives and outcomes should also promote the use of clear, unambiguous terminology and transparent feasibility assessment.

1.3 Consider both quantitative and qualitative data

Although it has become standard practice to use numerical targets for progression criteria, researchers should be mindful that this might not always be appropriate. Although quantifiable targets might seemingly add transparency and clarity to progression criteria assessment, they should be avoided where they are not meaningful. Mixed method approaches to PAFS data collection have been recommended [1,2], and feasibility questions that might be best addressed using qualitative research methods have been outlined [3]. Researchers might therefore opt to have a combination of numerical and non-numerical progression criteria. An example is presented below in Figure 1 [4].

Table 2

MyComrade progression criteria

	Go—proceed with RCT	Amend—proceed with changes	Stop—do not proceed unless changes are possible
1. Feasibility of practice recruitment Can 16 practices be recruited to take part in 3 months (8 practices in NI and 8 in ROI)?	If ≥ 14 practices are recruited to take part in 3 months	If ≥ 14 practices are recruited, but it takes longer than predicted (e.g. 3–6 months)	Unable to recruit practices
2. Feasibility of patient recruitment Can 20 patients per practice (total N = 320) be recruited?	If 20 patients are recruited in one month per practice; a total of 320 (100%)	If 10–19 patients are recruited in one month per practice; a total of 160–319 (50 to < 100%)	If < 10 patients are recruited in one month per practice; a total of < 159 (50%)
3. Feasibility of practice retention Can ≥ 14 practices be retained in the study until completion?	≥ 14 (88%) retained	≥ 12 (75%) retained	< 12 retained
4. Feasibility of patient retention Can at least 80% of recruited patients be retained in the study until completion?	≥ 256 (80%) retained	224–255 (70–80%) retained	< 224 retained
5. Intervention implementation	Delivery of intervention judged strongly feasible by qualitative data	Delivery of intervention judged feasible by qualitative data	Delivery of intervention judged possibly feasible by qualitative data

Figure 1 Example progression criteria including both quantitative and qualitative data

Reproduced from Hynes et al (2022) Pilot Feasibility Stud 8:1–16, published CC-BY 4.0

1.4 Provide justification for any numerical targets

Researchers should provide justification for any stated numerical progression criteria targets to indicate how they were derived. Rationale need not be statistical as pilot trials are usually underpowered for hypothesis testing, but some rationale for criteria should be given (e.g. clinical assumptions; pragmatically derived; based on previous feasibility or observational work; developed using consensus methods). Investigators should be aware that small pilot trial sample sizes might mean that any estimates of rates are subject to considerable uncertainty [5].

1.5 Develop guidelines rather than rules

Progression criteria are best viewed as guidelines rather than strict rules. Researchers should therefore develop progression criteria that will help identify and explore potential challenges with their trial design to inform the development of actionable solutions.

For example, it is becoming increasingly common for investigators to use a traffic light approach for progression criteria. This approach is also recommended and widely used in RCTs with internal pilot trial phases [6,7]. There are no agreed hard and fast rules for the meanings attributed to each colour, but typically measures below a lower (red) threshold indicate that the pilot trial is not feasible [stop], above a higher (green) threshold that it is feasible [go], and between the two (amber) that it might be feasible if appropriate changes can be made [amend] [8].

1.6 Seek input and sense check

Researchers should try to involve other stakeholders to develop, or agree, progression criteria so that targets are more meaningful and less prone to bias. A Research Design Service (RDS) or Clinical Trials Unit (CTU) can input into the methodological considerations of progression criteria, and clinical colleagues can help ensure that progression criteria make sense for different clinical contexts, recognising that pilot trial sites are not always reflective of the sites used in the main trial. Researchers might also want to involve PPI representatives to sense check their progression criteria. For internal pilot trials researchers are advised to agree their progression criteria with their Trial Steering Committee (TSC) in advance [6]. This recommendation might also be applicable to external pilot trials that have an independent TSC.

Recommendations for progression criteria during pilot trial conduct

2.1 Revisit regularly throughout the pilot trial

Researchers might find it useful to revisit their progression criteria targets regularly throughout their pilot trial. This might be particularly important when any changes to the pilot trial design are made, so that researchers can determine whether these changes have improved the trial design (i.e. whether indicators of feasibility are trending towards green progression criteria). Criteria that fall within the 'red' domain might also signify that urgent attention is needed to identify, outline and pilot actionable solutions in response to problems that are being faced.

There might be instances where changes to the pilot trial design might directly or indirectly affect the applicability of the progression criteria. In these instances, researchers might re-define their progression criteria, following consultation with any stakeholders who initially input into their development, to ensure that they are still usable indicators of trial feasibility. Where any changes to progression criteria are made, reasons for these changes should be fully reported in pilot trial publications.

Recommendations for progression criteria analysis

3.1 Avoid considering criteria in isolation

Most pilot trials will have multiple progression criteria, so researchers should consider their method of multi-criteria assessment. Researchers might opt to take a holistic approach to feasibility assessment and consider criteria in relation to each other, the implications for the future definitive trial, and whether any solutions to poorly performing criteria have been identified to come to an overall conclusion of feasibility. Outlining clear, actionable solutions where progression criteria are not met (e.g. are within red or amber ranges) is an important, but often overlooked, component of feasibility assessment. This is in line with recommendations for evaluating the feasibility of internal pilot trials which suggests that definitive trial funders acknowledge the importance of considering supplementary data e.g. a 'rescue plan' that outlines any problems encountered and how they were addressed [6]. An alternative approach suggested for multi-criteria assessment is to determine overall progression based on the worst-performing criterion (e.g. if one criterion is not met then the trial is not feasible) [9].

3.2 Engage in discussion

Just as it is important to engage different stakeholders in developing progression criteria, it is important to engage stakeholders at the end of the pilot trial when determining feasibility. At this stage it might be particularly useful to speak to people outside of the immediate trial team, e.g. healthcare professionals who were implementing the intervention or trial processes, to gain a comprehensive understanding about what might have worked well and what might require improvement in the definitive trial. For example, a behavioural science approach might be conducted to identify specific challenges and potential solutions [10].

3.3 Go beyond the progression criteria

Since progression criteria are developed during the early pilot trial design stage, they do not account for unforeseen events and challenges researchers might face whilst conducting the pilot trial. Researchers should account for these factors and draw on any relevant external evidence generated outside of their pilot trial when drawing conclusions about feasibility and progression.

3.4 Consider both feasibility (problem solving) and progression (decision making)

Researchers should consider both feasibility assessment (problem-solving) and progression decision (decision-making) as complimentary but distinct phases. There might be instances where pilot trials are considered feasible but do not progress for other reasons that are external to the pilot trial design (e.g. funding might not be available, the healthcare context might have changed, the intervention might now be superseded, or the CI might not intend to pursue the definitive trial at this time). It is important to be transparent about both whether the pilot trial is considered feasible, and whether researchers intend to progress to further research. Doing so might further evidence wider challenges with pilot trial progression for the research community to address, or even present the opportunity for other research groups to advance completed pilot trials that were feasible but might not otherwise progress.

Recommendations for progression criteria reporting

4.1 Suggestions for what information to report

Clear and transparent reporting of progression criteria ensures that trial feasibility is assessed with integrity and rigour. Clear reporting also enhances the wider usability of pilot trial findings. For example researchers can adequately determine whether progression criteria for one pilot trial might be applicable to another if information about how those criteria were developed is provided. This should encourage better research practice and avoid researchers providing generic criteria upon request.

To improve transparency of progression criteria reporting, I propose that the following information detailed in Table 1 is included in external randomised pilot trial publications. The suggested items for protocol publications might also be applicable to researchers who are developing funding applications for external randomised pilot trials.

Table 1 Suggested reporting items and rationale

Suggested item	Rationale	Protocol	Result
METHODS			
Completely defined pre-specified progression criteria, including how and when they are assessed	To ensure the pilot trial meets its (feasibility) objectives, specific measures or assessments should be defined to address each separate objective or research question (1). A range of methods can be used to address the objectives in a pilot trial. These methods are often based on descriptive statistics such as means and percentages but might also be narrative descriptions (2). It is these feasibility objectives and measures that progression criteria should be based on. Providing information about what the progression criteria are, and the method of assessment, ensures that findings can be verified based on the description of the analyses used. Not every objective and outcome measure might have associated progression criteria, for example some data might be collected to refine the trial processes rather than as an indication of feasibility. Although it has become standard practice to provide numerical targets for progression criteria, researchers should be mindful that this might not always be appropriate, for example where researchers want to account for qualitative data in their progression decision. Furthermore, investigators should also be aware that estimates of rates in pilot trials may be subject to considerable uncertainty, so it is best to be cautious about setting definitive thresholds that could be missed simply due to chance variation. Instead it is becoming increasingly common for investigators to use a traffic light system for criteria used to judge feasibility, whereby measures (e.g. recruitment rates) below a lower threshold indicate that the trial is not feasible as it is and there are likely problems that require urgent attention, above a higher threshold that it is feasible, and between the two that it might be feasible but that there are potential problems to investigate (3).	✓	✓
Brief description of the involvement (role) of different stakeholders in developing, or agreeing, progression criteria	There is potential for bias when progression criteria are developed in isolation as different stakeholders might have competing interests to demonstrate feasibility to justify progression to further research funding. For this reason multiple stakeholders may be involved in developing, or agreeing, progression criteria. For example progression criteria might be developed with input from a Clinical Trials Unit or a Research Design Service and agreed with research funders and an independent Trial Steering Committee.	✓	*

Katie Mellor, DPhil Candidate

Thesis: The role of progression criteria in the design, conduct, analysis and reporting of external randomised pilot trials

The information contained in this document is confidential and should not be published or redistributed

Suggested item	Rationale	Protocol	Result
Rationale for progression criteria, including any data or clinical assumptions supporting any targets provided	It should be stated how progression criteria were derived to ensure transparent feasibility assessment. Rationale need not be statistical as pilot trials are usually underpowered for hypothesis testing, but some rationale for criteria should be given (e.g. clinical assumptions; pragmatically derived; based on previous feasibility or observational work; developed using consensus methods). Reporting this information might also enhance the wider usability of pilot trial findings (e.g. progression criteria developed for one pilot trial might inform progression criteria used in another).	✓	✓
Method of multi-criteria assessment	Many pilot trials will have multiple progression criteria, so researchers should indicate a proposed method of multi-criteria assessment in their pilot trial protocol. Researchers might opt to take a holistic approach to feasibility assessment and view progression criteria as guidelines rather than strict thresholds. In this approach, they might instead consider whether targets were met, the implications for the future definitive trial, and whether any solutions to poorly performing criteria have been identified to come to an overall conclusion of feasibility. Alternatively, researchers might opt to take a more structured approach to multi-criteria assessment and determine overall progression based on the worst-performing criterion (e.g. if one criterion is not met then the trial is not feasible) (4).	✓	*
RESULTS			
Any changes to progression criteria after the pilot trial commenced, with reasons	An assessment or measure might change during a pilot trial because the change enables investigators to glean more information about the operation of the intervention or for reasons of acceptability or practicability (5). These changes might directly or indirectly impact on the applicability of the pre-specified progression criteria. For example, progression criteria might be linked to a specific measurement instrument that might change during the conduct of the pilot trial, and so the progression criteria itself might require alteration to reflect the pilot trial amendment. In the interests of full reporting and because of the usefulness of such information to the overall assessment of feasibility, all such changes to progression criteria should be reported.		✓
For each progression criteria, results in terms of whether criteria indicate	Results for each progression criteria should be provided to demonstrate whether the criteria indicated feasibility. Where numerical targets including a traffic light approach was used researchers should indicate whether progression criteria were above the upper threshold		✓

Suggested item	Rationale	Protocol	Result
feasibility and if applicable, whether numerical targets were met	(green), below the lower threshold (red), or between the two (amber). Where progression criteria do not have numerical targets, a clear statement to reflect whether the findings indicate feasibility is sufficient.		
For each progression criteria, implications for the future definitive trial, including any proposed amendments	To progress from a pilot trial to a future definitive RCT, it is important to understand how the implications of the findings in the pilot carry over to the future definitive RCT (6). For clarity, researchers should state for each progression criteria what implications their findings have for their definitive trial design. For example, if progression criteria have not been met but there are proposed changes to the future definitive RCT that have been identified from the pilot trial, these should be stated. This aligns with the revised Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare (CReDECI 2) which recommends that researchers provide a description of how intervention piloting has impacted a definitive intervention, including any changes made (7).		✓
Overall statement of trial feasibility assessment	Researchers should provide an overall statement of feasibility based on their pilot trial findings. This is important because sometimes progression criteria do not adequately reflect trial feasibility. For example, a pilot trial might be feasible (based on assessment of progression criteria) but might not progress for other reasons such as unanticipated challenges faced, or external evidence that has been gathered outside of the pilot trial. This statement might be different to any subsequent statements in the discussion and conclusion about intended progression to a future definitive RCT (6), as sometimes pilot trials might be feasible but might not progress for other reasons.		✓

*Items might be omitted from pilot trial results publications if the pilot trial protocol is published and can be referenced

1 CONSORT 2010 statement: extension to randomised pilot and feasibility trials, Item 6a
2 CONSORT 2010 statement: extension to randomised pilot and feasibility trials, Item 12a
3 CONSORT 2010 statement: extension to randomised pilot and feasibility trials, Item 6c
4 Lewis M, Bromley K, Sutton CJ, et al. Determining sample size for progression criteria for pragmatic pilot RCTs: the hypothesis test strikes back! Pilot Feasibility Stud 2021;7:40. doi:10.1186/s40814-021-00770-x
5 CONSORT 2010 statement: extension to randomised pilot and feasibility trials, Item 6b
6 CONSORT 2010 statement: extension to randomised pilot and feasibility trials, Item 22a
7 Möhler R, Köpke S, Meyer G. Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: Revised guideline (CReDECI 2). Trials 2015;16:1–9. doi:10.1186/s13063-015-0709-y

4.2 Consider reporting in a table format for clarity and conciseness

To promote clarity and conciseness, researchers might opt to report progression criteria in a table format in their pilot trial publications. This is particularly useful for completed trials to report the progression criteria set, the corresponding finding and the implications for the future RCT design. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) is a transparent approach to grading the quality of evidence to inform healthcare recommendations. GRADE recommends using Summary of Findings (SoF) tables to provide a concise summary of the key information that underpins recommendations. This format of evidence synthesis strikes a balance between simplicity (i.e. the presentation of evidence or information) and completeness (i.e. reporting transparency) [11]. Presenting pilot trial findings in a similar format is one-way that researchers can organise and present their pilot trial findings [12–15]. One example is presented below in Figure 2 [12].

Objectives	Criteria for success	Considerations
To evaluate the feasibility of procedures (e.g. randomisation, recruitment, collecting data, management and follow-up)	The trial would be considered feasible if it was run smoothly without serious problems or obstructions that were able to stop the study.	All research procedures were feasible but the following issues should be considered:
◦ Randomisation		➢ No issue regarding the randomisation (i.e. no report regarding participants' disagreement with treatment allocation).
◦ Recruitment		➢ Ideally, double blinding should be kept in order to maintain the quality of the trial but more assessors need to be provided for every clinic in order to reduce the risk factor of journey issues (patients did not want to travel to other physiotherapy clinics) if a future trial is to be sufficiently funded.
		➢ Increase the number of recruited physiotherapy clinics/ insurance companies in order to increase the recruitment rate.
		➢ An increase in the number of assessors may be considered. Setting assessment centres did not work in this trial due to participants' journey issues. It would be ideal to have an assessor in each clinic to enable the baseline assessment to take place local to each clinic prior to the first treatment session. That would then stop the patient needing to make the separate journey for the assessment or travelling to different physiotherapy clinics.
◦ Collecting data		➢ Information for cost-effectiveness analysis should be considered in another way (set up an electronic system by collaborating with an insurance company or a physiotherapy company in order to record relevant information rather than giving a diary pocket book to participants).
		➢ Collecting level of education (less than post-secondary), headache at inception and low back pain, which are the significant predictors of persistent WAD.
◦ Management		➢ No difficulty with the management for the trial.
◦ Follow-up		➢ Face-to-face follow-up may be an issue because participants get back to their normal life and they may not want to come to a clinic owing to their work commitments. Telephone follow-up may be an interesting option for a future trial.
To evaluate recruitment rates, refusal rates and retention in the private sector in the UK	The trial would be considered feasible if • ≥ 50% of eligible patients were recruited • At least 3 participants a week per intervention arm were recruited • ≥ 80% of all recruited participants completed the follow-up at 3 months	Overall, the trial was feasible as: • 70% of eligible patients were recruited • An average of one (1.27) person was recruited per week (excluding temporary stopping of the trial). This point was an issue to modify in the future trial. An increase in the number of recruited physiotherapy clinics may be an option. • ~93% of recruited participants completed 3-month follow-up
To evaluate dropout rates of participants in the private sector in the UK	The trial would be considered feasible if ≤ 20% of all recruited participants dropped out	2/8 (25%) participants were lost to follow-up at 3 months. Therefore, the overall dropout in this trial was ~7%.
To estimate the required sample for a definitive trial	The trial would be considered feasible if it was feasible to achieve the sample size for a cluster RCT based upon recruitment data	The required sample size for a cluster RCT is 238 patients using 24 physiotherapy clinics based on power = 90%, significance level = 0.05, difference of NDI = 4 and cluster size = 10.

To evaluate the feasibility of data collection for cost-effectiveness analysis	The trial would be considered feasible if the following components of the cost-effective analysis were collected with minimal missing data:
	• General information (e.g. current work status and salary)
	• Direct medical costs
	  • Medical costs (e.g. physiotherapy, general practice and complementary medicine)
	  • Resource uses (e.g. diagnosis tests)
	• Indirect medical costs
	  • Participant journey costs
	  • Training costs for physiotherapists in the experimental arm
		Only 2 participants returned their diary pocket book. Another strategy for collecting information for cost-effectiveness analysis should be considered in another way for a future trial. Setting up an electronic recording system by collaborating with an insurance company or a physiotherapy company may be a good option in order to collect relevant information.

WAD, whiplash-associated disorder; RCT, randomised controlled trial; NDI, neck disability index.

https://doi.org/10.1371/journal.pone.0215803.t008

Figure 2 Example table to report progression criteria findings and implications for definitive RCT

Reproduced from Wiangkham et al (2019) PLoS One 14:e0215803, published CC-BY 4.0

References

1 Donald G. A brief summary of pilot and feasibility studies: Exploring terminology, aims, and methods. *Eur J Integr Med* 2018;24:65–70. doi:10.1016/j.eujim.2018.10.017

2 Yardley L, Ainsworth B, Arden-Close E, *et al.* The person-based approach to enhancing the acceptability and feasibility of interventions. *Pilot Feasibility Stud* 2015;1. doi:10.1186/s40814-015-0033-z

3 O'Cathain A, Hoddinott P, Lewin S, *et al.* Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: Guidance for researchers. *Pilot Feasibility Stud* 2015;1:1–13. doi:10.1186/s40814-015-0026-y

4 Hynes L, Murphy AW, Hart N, *et al.* The MultimorbiditY COllaborative Medication Review And DEcision Making (MyComrade) study: a protocol for a cross-border pilot cluster randomised controlled trial. *Pilot Feasibility Stud* 2022;8:1–16. doi:10.1186/S40814-022-01018-Y/TABLES/3

5 Netz Y, Lidor R, Ziv G. Small samples and increased variability-discussing the need for restricted types of randomization in exercise interventions in old age. *Eur Rev Aging Phys Act* 2019;16:1–8. doi:10.1186/S11556-019-0224-3/TABLES/4

6 Avery KNL, Williamson PR, Gamble C, *et al.* Informing efficient randomised controlled trials: Exploration of challenges in developing progression criteria for internal pilot studies. *BMJ Open* 2017;7. doi:10.1136/bmjopen-2016-013537

7 Herbert E, Julious SA, Goodacre S. Progression criteria in trials with an internal pilot: an audit of publicly funded randomised controlled trials. *Trials* 2019;20:1–9. doi:10.1186/s13063-019-3578-y

8 Eldridge SM, Chan CL, Campbell MJ, *et al.* CONSORT 2010 statement: Extension to randomised pilot and feasibility trials. *BMJ* 2016;355:i5239. doi:10.1136/bmj.i5239

9 Lewis M, Bromley K, Sutton CJ, *et al.* Determining sample size for progression criteria for pragmatic pilot RCTs: the hypothesis test strikes back! *Pilot Feasibility Stud* 2021;7:40. doi:10.1186/s40814-021-00770-x

10 Gillies K, Brehaut J, Coffey T, *et al.* How can behavioural science help us design better trials? *Trials* 2021;22:1–7. doi:10.1186/S13063-021-05853-X/FIGURES/1

11 Guyatt G, Oxman AD, Akl EA, *et al.* GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94. doi:10.1016/j.jclinepi.2010.04.026

12 Wiangkham T, Duda J, Sayeed Haque M, *et al.* A cluster randomised, double-blind pilot and feasibility trial of an active behavioural physiotherapy intervention for acute whiplash-associated disorder (WAD)II. *PLoS One* 2019;14:e0215803. doi:10.1371/journal.pone.0215803

13 Purcell A, Buckley T, King J, *et al.* Eutectic mixture of local anaesthetics (EMLA®) as a primary dressing on painful chronic leg ulcers: A pilot randomised controlled trial. *Pilot Feasibility Stud* 2018;4:123. doi:10.1186/s40814-018-0312-6

14 Newlands RSN, Ntessalen M, Clark J, *et al.* Pilot randomised controlled trial of Weight Watchers® referral with or without dietitianled group support for weight loss in women treated for breast cancer: The BRIGHT (BReast cancer welGHT loss) trial. *Pilot Feasibility Stud* 2019;5:24. doi:10.1186/s40814-019-0405-x

15 Sharma S, Jensen MP, Moseley GL, *et al.* Results of a feasibility randomised clinical trial on pain education for low back pain in Nepal: The Pain Education in Nepal-Low Back Pain (PEN-LBP) feasibility trial. *BMJ Open* 2019;9:e026874. doi:10.1136/bmjopen-2018-026874

F2 Workshop invitations and information provided

Stakeholder consultation meeting invitations_v1.0_09 May 2022

Stakeholder consultation meeting invitation – IN PERSON

Subject:

Invitation to attend a consultation workshop to discuss draft recommendations for external randomised pilot trial progression criteria

Main text:

You are invited to attend a stakeholder consultation workshop to review and improve draft recommendations for using progression criteria in external randomised pilot trials

Researchers at the University of Oxford have been investigating how trialists plan to determine external randomised pilot trial feasibility using progression criteria.

We have studied progression criteria in external randomised pilot trial funding applications, interviewed trialists about how they use progression criteria in practice, reviewed progression criteria reporting in external randomised pilot trial publications and surveyed trialists to identify and explore barriers to pilot trial progression. Based on our findings, we have developed a set of recommendations that can be used by researchers when designing external randomised pilot trials to improve the assessment of external pilot trial feasibility.

We would now like to involve the wider research community in reviewing and providing feedback on these draft recommendations. Do they capture what good external randomised pilot trial feasibility assessment looks like from your perspective? Will they be of practical use to you? Is there anything we have missed out? How can we improve them?

Consultation workshop

We are holding a consultation workshop on Tuesday the 12th of July 2022 at the Botnar Research Centre, starting at 10:00 and finishing at 12:30 with lunch provided.

To register your interest in attending, please follow this link:
https://form.jotform.com/221242162589354

Draft recommendations and an agenda will be circulated in advance of the meeting.

We hope you can attend! If you have any questions about the workshop, please contact Katie Mellor (DPhil Candidate) at the University of Oxford:

Email: katie.mellor@ndorms.ox.ac.uk

Telephone: 01865 737 923

Stakeholder consultation meeting invitation – VIRTUAL

Subject:

Invitation to attend a consultation workshop to discuss draft recommendations for external randomised pilot trial progression criteria

Main text:

You are invited to attend a stakeholder consultation workshop to review and improve draft recommendations for using progression criteria in external randomised pilot trials

Researchers at the University of Oxford have been investigating how trialists plan to determine external randomised pilot trial feasibility using progression criteria.

We have studied progression criteria in external randomised pilot trial funding applications, interviewed trialists about how they use progression criteria in practice, reviewed progression criteria reporting in external randomised pilot trial publications and surveyed trialists to identify and explore barriers to pilot trial progression. Using these findings, we have developed a set of recommendations that can be used by researchers when designing external randomised pilot trials to improve the assessment of external pilot trial feasibility.

We would now like to involve the wider research community in reviewing and providing feedback on these draft recommendations. Do they capture what good external randomised pilot trial feasibility assessment looks like from your perspective? Will they be of practical use to you? Is there anything we have missed out? How can we improve them?

Consultation workshop

We are holding a virtual consultation workshop on Thursday the 14th of July 2022 on MS Teams, starting at 10:00 and finishing at 12:00.

To register your interest in attending, please follow this link:
https://form.jotform.com/221242555416349

Draft recommendations and an agenda will be circulated in advance of the meeting.

We hope you can attend! If you have any questions about the workshop, please contact Katie Mellor (DPhil Candidate) at the University of Oxford:

Email: katie.mellor@ndorms.ox.ac.uk

Telephone: 01865 737 923

F3 Email to confirm ethical review is not required

Katie Mellor

From: MSD Ethics
Sent: 05 May 2022 19:01
To: Katie Mellor
Cc: Sally Hopewell
Subject: RE: Question about MSIDREC approval

Dear Katie,

Thank you for your email. From the information you have provided, this does not sound like research requiring ethical review, but a public engagement exercise.

Best wishes
Helen

From: Katie Mellor <katie.mellor@ndorms.ox.ac.uk>
Sent: 05 May 2022 17:12
To: MSD Ethics <ethics@medsci.ox.ac.uk>
Cc: Sally Hopewell <sally.hopewell@csm.ox.ac.uk>
Subject: Question about MSIDREC approval

Dear MSIDREC,

I am a DPhil student based in NDORMS. My research has focused around developing recommendations for researchers for using progression criteria to determine whether pilot trials are feasible.

I have used various research methods to explore this aspect of pilot trials and develop recommendations including: a methodological review, a study of research funding applications (MSIDREC reference: R74410_RE001), qualitative interviews (MSIDREC reference: R72039_RE001), and a survey (MSIDREC reference: R78375_RE001).

I am now seeking to hold a stakeholder engagement workshop (with researchers and research funders who have been involved in aspects of the DPhil) where I will explore stakeholders' opinions on these recommendations so I can ensure that they are useful and fit for purpose. A similar approach to obtaining feedback through workshops has been used to develop recommendations presented in the following publications:
https://www.sciencedirect.com/science/article/pii/S2451865419302248
https://bmjopen.bmj.com/content/7/2/e013537

I have reviewed the Research Support website to determine whether this would constitute a research activity. I believe that this would not be considered research and does not require ethical approval because I am not aiming to generate new data or findings. I think that this is more of an involvement activity, like patient and public involvement, although seeking researcher input (as the "consumer" of my proposed recommendations) rather than patients and the public.

I am writing to confirm whether you agree with my assessment that this activity would not be considered research, and to confirm that MSIDREC approval for any workshop of this nature is not required?

Thank you for your help.

Kind regards,
Katie

1

G1 Protocol for a cross-sectional study of progression criteria stipulated in external randomised pilot trial ethics applications

The following protocol was correct as of the 15th of November 2021 and informed the HiREB application which was provisionally approved.

PROTOCOL - UKRI Mitacs Globalink Exchange Scheme study

RESEARCH TEAM

Katie Mellor; Katie.mellor@ndorms.ox.ac.uk
Mohammed I Khan; Khanm107@mcmaster.ca
Sally Hopewell; Sally.hopewell@csm.ox.ac.uk
Lehana Thabane; ThabanL@mcmaster.ca

TITLE

Exploring the use of progression criteria in external randomised pilot trial protocols submitted for ethical approval: A document analysis of Hamilton integrated Research Ethics Board applications

BACKGROUND

External randomised pilot trials (or pilot RCTs) aim to investigate areas of uncertainty about an intended future definitive Randomised Controlled Trial (RCT). The primary aims and objectives of a pilot trial should focus on assessment of feasibility. These recommendations are described in the 2016 Consolidated Standards of Reporting Trials (CONSORT) extension for reporting randomised pilot and feasibility trials [1]. How the feasibility objectives will be assessed to come to a conclusion about trial feasibility should be built into the pilot trial design from the earliest opportunity. Assessment of trial feasibility can be informed by prespecified progression criteria, based on the pilot trial objectives, to guide interpretation of the pilot trial findings. These prespecified progression criteria can inform the decision to proceed to a future definitive RCT, proceed with amendments, undertake further feasibility work, or not proceed at all.

Pilot trials can increase the likelihood of definitive RCT success. It can be argued that conducting a definitive large scale RCT where uncertainties about trial design remain is both unethical and can lead to resources being wasted. However, it is also unethical if the aims and objectives of a pilot trial are unclear, as this could potentially mislead participants to confuse the reasons for

doing a pilot trial (to assess feasibility) with those of a main trial (to assess effectiveness) [2]. Therefore, it is a priority of research ethics committees to ensure that pilot trial protocols clearly state that the primary aims and objectives are to assess feasibility of a future definitive trial, and include details of how feasibility will be determined (i.e. progression criteria).

A previous review found that the transparency of informed consent in informed consent documents for pilot or feasibility studies submitted to the Hamilton integrated Research Ethics Board (HiREB), between January 2004 and March 2020, is inadequate [3,4]. To expand on these findings, we intend to review pilot trial ethics applications submitted since 2016 (the year that CONSORT guidance for pilot trials was published) [1] to explore the inclusion of progression criteria in pilot trial protocols. The findings of this research will be triangulated with other research that our group has conducted to inform the development of guidance for the development and assessment of progression criteria in external randomised pilot trials.

RESEARCH DESIGN

A document analysis of pilot trial protocols submitted to the Hamilton integrated Research Ethics Board, Canada.

Document analysis is described as a systematic procedure for reviewing or evaluating documents in order to elicit meaning, gain understanding, and develop knowledge [5]. In this study the documents are the protocols that inform the HiREB application.

RESEARCH QUESTIONS

1. Do pilot trial protocols submitted to the HiREB as part of an ethics application include clear progression criteria?
2. What are the characteristics of included progression criteria e.g. what uncertainties about feasibility inform progression criteria, how are they formatted and how were they developed?
3. Do progression criteria often change between the first submitted protocol version and the final submitted protocol version?

AIM AND OBJECTIVES

This research aims to determine how researchers plan to assess pilot trial objectives (i.e. progression criteria) in pilot trial protocols submitted to the HiREB as part of research ethics applications.

The primary objective is to describe whether clear progression criteria are included in pilot trial protocols submitted to the HiREB.

The secondary objectives are to determine whether and how progression criteria relate to the feasibility objectives and outcomes, to document and describe any rationale provided for stated criteria for progression and to determine whether progression criteria have changed between the initial submitted protocol and revised final submitted protocol version.

METHODS

1. Document sources and sampling

Document sources

Included documents are the pilot trial protocols submitted as part of the HiREB application. A waiver of consent will be sought from HiREB so the research team can access the redacted study protocols of eligible ethics applications.

Eligibility criteria

Application protocols will be included if they meet the following eligibility criteria:

1. Were submitted to the HiREB electronic database (eREB)
2. Were submitted since October 2016 (i.e. not prior to the date of publication of the CONSORT extension)
3. Are randomised in design
4. Are feasibility studies conducted in preparation for a future definitive RCT

Database search and screening

The HiREB electronic database (eREB) will be searched for applications with "pilot", "feasibility" or both terms in the application title or description, that were submitted following October 2016 up until the time of database search. Those that are randomised in design and have the primary aim of assessing the feasibility of a definitive RCT, will be included.

Sample size

All studies that meet the eligibility criteria will be included.

2. Data collection and management

Data collection

Data will be collected into a data abstraction sheet in Microsoft Excel (Office 16). Appendix 1 details a full data abstraction list.

Essential features of each document will be recorded so that the document sample can be sufficiently described. These include: Year of submission, sample size, randomised design, number of treatment groups, therapeutic area, intervention, and outcome of HiREB review i.e. whether ethical approval was granted.

We will collect data on the pilot trial feasibility objectives and outcomes (i.e. areas of uncertainty being assessed) and whether progression criteria are reported. Where progression criteria are reported, we will document whether criteria reflect the stated feasibility objectives and outcomes, the criteria format (e.g. stop-go, stop-amend-go), any stated justification or rationale for criteria, whether the protocol details how progression criteria were decided

(including who was involved), and how progression criteria will be assessed (including who will be involved). We will also document whether stated progression criteria changed between the initial submitted protocol version and the final, approved protocol.

3. Data analysis

Descriptive statistics produced using Stata (version. 16.0; StataCorp) will be produced to describe the number of protocols that stipulate progression criteria to determine progression to a definitive study (primary outcome). Descriptive statistics will be supplemented by narrative synthesis to describe the characteristics of stated progression criteria.

Content analysis will be used to identify areas of uncertainty about trial design (e.g. recruitment, data collection tools, acceptability of trial and/or intervention) that inform feasibility objectives and outcomes, and those areas that inform progression criteria. Content analysis will also be used to describe different approaches to developing progression criteria, and intentions for assessing progression criteria to form conclusions about feasibility where this information is given. Finally, content analysis will also explore any aspects of progression criteria that change between the initial submitted protocol and the final, approved protocol version.

DATA MANAGEMENT

All source data are the property of HiREB. All protocols will be redacted and de-identified by HiREB before inclusion in this study. The anonymity of specific trials will be maintained in all research outputs. A de-identified document archive of protocols submitted as part of the included HiREB applications will be maintained on password protected Oxford University servers, accessed through a VPN and stored on an encrypted laptop. KM will be based in Canada at McMaster University at the time of conducting this research.

Ethical and regulatory considerations

This study requires ethical approval and the Hamilton Health Sciences research ethics board will be approached for this approval. This study will conform to the Declaration of Helsinki.

Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. Protocols will be de-identified before inclusion in this study and given a unique study number. No personal data of researchers who have submitted the HiREB application will be shared. All documents will be stored securely and only accessible by the research team and authorised personnel.

Funding

This research is funded through a UKRI-Mitacs Globalink Doctoral Exchange programme awarded to KM. Funding has been awarded for a 12-week period. A Gantt chart is detailed in Appendix 2.

Impact and dissemination

This study will provide an up-to-date assessment of the inclusion of progression criteria in pilot trial protocols submitted as part of ethics applications to the HiREB. The findings will be triangulated with ongoing research to inform the development of guidance for progression criteria in external pilot trials. These findings will also allow us to consider whether there is a need to develop additional recommendations for ethics committees who are reviewing pilot trial ethics applications. The findings from this research will be published in peer reviewed journals and presented at conferences either as a standalone study or as part of the wider DPhil research.

Publication policy

All investigators will be involved in reviewing drafts of the manuscripts, abstracts and any other publications arising from the study. KM will lead on publication outputs. Authorship will be determined in accordance with the ICMJE guidelines, and any other contributors will be acknowledged.

Archiving

All research data will be stored on a University of Oxford protected server. In adherence with the MRC Retention framework for research data and records, research data and related material will be archived and retained for a minimum of 10 years after the study has been completed.

REFERENCES

1. Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: Extension to randomised pilot and feasibility trials. BMJ 2016;355:i5239. doi:10.1136/bmj.i5239
2. Sim J. Distinctive aspects of consent in pilot and feasibility studies. J Eval Clin Pract 2021;27:657–64. doi:10.1111/jep.13556
3. Khan MI, Holek M, Bdair F, et al. Assessing the transparency of informed consent in feasibility and pilot studies: a single-centre quality assurance study protocol. BMJ Open 2020;10:e036226. doi:10.1136/bmjopen-2019-036226
4. Khan MIUU, Mbuagbaw L, Holek M, et al. Transparency of informed consent in pilot and feasibility studies is inadequate: a single-center quality assurance study. Pilot Feasibility Stud 2021 71 2021;7:1–10.https://doi.org/10.1186/s40814-021-00828-w (accessed 19 Apr 2021).
5. Bowen G. Document Analysis as a Qualitative Research Method Article in Qualitative. Published Online First: 2009. doi:10.3316/QRJ0902027

APPENDIX 1 Data abstraction list

Data point	Prespecified coding
Study ID	(Numerical)
Year of submission	(Numerical)
Number of arms	2 >2
Randomisation design	Parallel Cluster Other
Sample size	(Numerical)
Therapeutic area	Cardiology Critical Care Dentistry Endocrinology Gastroenterology/Hepatology Geriatrics Haematology/Immunology Musculoskeletal Neurology Obstetrics/Gynaecology Oncology Ophthalmology Otolaryngology Paediatrics Psychiatry/Psychology Radiology Respiratory Rheumatology Surgery Trauma Palliative care Primary care Other
Intervention type	Drug Surgery or procedure Counselling, lifestyle or physiotherapy Equipment Medical Device Other
Application outcome	Ethical approval granted Ethical approval not granted
Feasibility objectives	(Verbatim)
Feasibility outcomes	(Verbatim)
Inclusion of progression criteria	Yes No
Progression criteria	(Verbatim)
Progression criteria format	Stop-go Stop-amend-go Other

Data point	Prespecified coding
Justification or rationale for progression criteria given	Yes Somewhat/for some criteria No
How were progression criteria decided/developed	(Verbatim)
Who was involved?	Trial Management Group Trial Steering Committee Patient and Public Involvement/ Participant representatives Funders Other
Who will assess progression criteria?	Trial Management Group Trial Steering Committee Patient and Public Involvement/ Participant representatives Funders Other
Any further detail provided re progression criteria assessment (e.g. how decisions around feasibility will be made if only some criteria are met?)	(Verbatim)
Changes to progression criteria between the initial submitted protocol and the final, approved protocol	Yes No
Description of changes	(Verbatim)

APPENDIX 2 Gantt chart

Gantt Chart - Globalink 12 week internship													
Milestones													
Study group meetings (monthly)													
Deliverables													
Protocol development													
Discussions with HiREB and application for ethics approval													
Obtain document sample													
Data collection													
Data analysis													
Write up of findings													
Study group dissemination meeting													
Weeks	**Prior to internship**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**

Note exact dates to be confirmed, anticipated start mid-April 2021

References

1 Akobeng AK. Understanding randomised controlled trials. *Arch Dis Child* 2005;**90**:840–4. doi:10.1136/ADC.2004.058222

2 Theme 6: the cost of randomised trials, trends and determinants - Clinical trial metadata: defining and extracting metadata on the design, conduct, results and costs of 125 randomised clinical trials funded by the National Institute for Health Research Health Technology Assessment programme - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK274324/ (accessed 1 Dec 2021).

3 Ioannidis JPA. Clinical trials: What a waste. *BMJ* 2014;**349**. doi:10.1136/BMJ.G7089

4 Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. *BMJ* 1997;**315**:640–5. doi:10.1136/bmj.315.7109.640

5 Manzoli L, Flacco ME, D'Addario M, *et al.* Non-publication and delayed publication of randomized trials on vaccines: survey. *BMJ* 2014;**348**. doi:10.1136/BMJ.G3058

6 Chapman SJ, Shelton B, Mahmood H, *et al.* Discontinuation and non-publication of surgical randomised controlled trials: observational study. *BMJ* 2014;**349**. doi:10.1136/BMJ.G6870

7 Kasenda B, Von Elm E, You J, *et al.* Prevalence, Characteristics, and Publication of Discontinued Randomized Trials. *JAMA* 2014;**311**:1045–52.

doi:10.1001/JAMA.2014.1361

8 Walters SJ, Dos Anjos Henriques-Cadby IB, Bortolami O, *et al.* Recruitment and retention of participants in randomised controlled trials: A review of trials funded and published by the United Kingdom Health Technology Assessment Programme. *BMJ Open* 2017;**7**:e015276. doi:10.1136/bmjopen-2016-015276

9 Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. *Contemp Clin Trials Commun* 2018;**11**:156. doi:10.1016/J.CONCTC.2018.08.001

10 Speich B, Gryaznov Id D, Busse Id JW, *et al.* Nonregistration, discontinuation, and nonpublication of randomized trials: A repeated metaresearch analysis. *PLOS Med* 2022;**19**:e1003980. doi:10.1371/JOURNAL.PMED.1003980

11 Eldridge SM, Lancaster GA, Campbell MJ, *et al.* Defining Feasibility and Pilot Studies in Preparation for Randomised Controlled Trials: Development of a Conceptual Framework. *PLoS One* 2016;**11**:e0150205. doi:10.1371/journal.pone.0150205

12 Gloy V, Speich B, Griessbach A, *et al.* Scoping review and characteristics of publicly available checklists for assessing clinical trial feasibility. *BMC Med Res Methodol 2022 221* 2022;**22**:1–8. doi:10.1186/S12874-022-01617-6

13 Arain M, Campbell MJ, Cooper CL, *et al.* What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Med Res Methodol* 2010;**10**:67. doi:10.1186/1471-2288-10-67

14 Abbott JH. The Distinction Between Randomized Clinical Trials (RCTs) and

Preliminary Feasibility and Pilot Studies: What They Are and Are Not. *J Orthop Sport Phys Ther* 2014;**44**:555–8. doi:10.2519/jospt.2014.0110

15 Thabane L, Ma J, Chu R, *et al.* A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol* 2010;**10**:1. doi:10.1186/1471-2288-10-1

16 Craig P, Dieppe P, Macintyre S, *et al.* Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008;:a1655. doi:10.1136/bmj.a1655

17 NIHR. Guidance on applying for feasibility studies. v1.0 Jul 2017. https://www.nihr.ac.uk/documents/nihr-research-for-patient-benefit-rfpb-programme-guidance-on-applying-for-feasibility-studies/20474 (accessed 13 Nov 2019).

18 Whitehead AL, Sully BGO, Campbell MJ. Pilot and feasibility studies: Is there a difference from each other and from a randomised controlled trial? *Contemp Clin Trials* 2014;**38**:130–3. doi:10.1016/j.cct.2014.04.001

19 Levati S, Campbell P, Frost R, *et al.* Optimisation of complex health interventions prior to a randomised controlled trial: A scoping review of strategies used. *Pilot Feasibility Stud* 2016;**2**. doi:10.1186/s40814-016-0058-y

20 Bowen DJ, Kreuter M, Spring B, *et al.* How we design feasibility studies. *Am J Prev Med* 2009;**36**:452–7. doi:10.1016/j.amepre.2009.02.002

21 Wittes J, Brittain E. The role of internal pilot studies in increasing the efficiency of clinical trials. *Stat Med* 1990;**9**:65–72.http://doi.wiley.com/10.1002/sim.4780090113 (accessed 6 Aug 2020).

22 Avery KNL, Williamson PR, Gamble C, *et al.* Informing efficient randomised controlled trials: Exploration of challenges in developing progression criteria for internal pilot studies. *BMJ Open* 2017;**7**. doi:10.1136/bmjopen-2016-013537

23 NIHR. HTA Programme supporting information (REALMS), Version 2.2. 2021.https://www.nihr.ac.uk/documents/hta-programme-supporting-information-realms/27265 (accessed 15 Jun 2022).

24 Eldridge SM, Chan CL, Campbell MJ, *et al.* CONSORT 2010 statement: Extension to randomised pilot and feasibility trials. *BMJ* 2016;**355**:i5239. doi:10.1136/bmj.i5239

25 QMUL. Pilot and feasibility studies. https://pilotandfeasibilitystudies.qmul.ac.uk/introduction/ (accessed 5 Jun 2020).

26 Fairhurst K, Avery K, O'Cathain A, *et al.* PS5A - O1 When to do an external or internal pilot study : findings from an interview study with research funders. In: *Trials. Meeting abstracts from the 5th International Clinical Trials Methodology Conference (ICTMC 2019)*. Brighton: : BMC 2019. doi:10.1186/s13063-019-3688-6

27 Cook JA, Beard DJ, Cook JR, *et al.* The curious case of an internal pilot in a multicentre randomised trial-time for a rethink? *Pilot Feasibility Stud* 2016;**2**:2–4. doi:10.1186/s40814-016-0113-8

28 Conn VS, Algase DL, Rawl SM, *et al.* Publishing Pilot Intervention Work. *West J Nurs Res* 2010;**32**:994–1010. doi:10.1177/0193945910367229

29 Lancaster GA. Pilot and feasibility studies come of age! *Pilot Feasibility Stud*

2015;**1**:1. doi:10.1186/2055-5784-1-1

30 Morgan B, Hejdenberg J, Hinrichs-Krapels S, *et al.* Do feasibility studies contribute to, or avoid, waste in research? *PLoS One* 2018;**13**:1–8. doi:10.1371/journal.pone.0195951

31 Morgan B, Hejdenberg J, Kuleszewicz K, *et al.* Are some feasibility studies more feasible than others? A review of the outcomes of feasibility studies on the ISRCTN registry. *Pilot Feasibility Stud 2021 71* 2021;**7**:1–8. doi:10.1186/S40814-021-00931-Y

32 Fairhurst K, Blazeby JM, Potter S, *et al.* Value of surgical pilot and feasibility study protocols. *Br J Surg* 2019;**106**:968–78. doi:10.1002/bjs.11167

33 Story DA. Feasibility and pilot studies: dropping the fig leaf. *Anaesthesia* 2020;**75**:152–4. doi:10.1111/anae.14865

34 Campbell MJ, Lancaster GA, Eldridge SM. A randomised controlled trial is not a pilot trial simply because it uses a surrogate endpoint. *Pilot Feasibility Stud* 2018;**4**:10–3. doi:10.1186/s40814-018-0324-2

35 CONSORT. Consort - Endorsers. http://www.consort-statement.org/about-consort/endorsers1 (accessed 6 Jul 2022).

36 Turner L, Shamseer L, Altman DG, *et al.* Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review. *Syst Rev* 2012;**1**. doi:10.1186/2046-4053-1-60

37 Khan MIU, Brar HK, Sun CY, *et al.* The reporting of pilot and feasibility studies

in the top dental specialty journals is suboptimal. *Pilot Feasibility Stud 2022 81* 2022;**8**:1–8. doi:10.1186/S40814-022-01182-1

38 Charlesworth M, Klein AA, White SM. A bibliometric analysis of the conversion and reporting of pilot studies published in six anaesthesia journals. *Anaesthesia* 2019;:1–7. doi:10.1111/anae.14817

39 Isiguzo G, Zunza M, Chirehwa M, *et al.* Quality of abstracts of pilot trials in heart failure: A systematic survey. *Contemp Clin Trials Commun* 2018;**4**:107. doi:10.1186/s40814-018-0302-8

40 Horne E, Lancaster GA, Matson R, *et al.* Pilot trials in physical activity journals: a review of reporting and editorial policy. *Pilot Feasibility Stud* 2018;**4**:1–13. doi:10.1186/s40814-018-0317-1

41 Thabane L, Lancaster G. A guide to the reporting of protocols of pilot and feasibility trials. *Pilot feasibility Stud* 2019;**5**:37. doi:10.1186/s40814-019-0423-8

42 Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract* 2004;**10**:307–12. doi:10.1111/j..2002.384.doc.x

43 Shanyinde M, Pickering RM, Weatherall M. Questions asked and answered in pilot and feasibility randomized controlled trials. *BMC Med Res Methodol* 2011;**11**:117. doi:10.1186/1471-2288-11-117

44 Westlund E, Stuart EA. The Nonuse, Misuse, and Proper Use of Pilot Studies in Experimental Evaluation Research. *Am J Eval* 2017;**38**:246–61. doi:10.1177/1098214016651489

45 Bruckenthal P, Broderick JE. Assessing Treatment Fidelity in Pilot Studies Assist in Designing Clinical Trials. *Adv Nurs Sci* 2007;**30**:E72–84. doi:10.1097/00012272-200701000-00015

46 Jones TA, Olds TS, Currow DC, *et al.* Feasibility and Pilot Studies in Palliative Care Research: A Systematic Review. *J Pain Symptom Manage* 2017;**54**:139-151.e4. doi:10.1016/j.jpainsymman.2017.02.015

47 Gannon B. The Feasibility Study: A Health Economics Perspective. *Glob Reg Heal Technol Assess Ital North Eur Spanish* 2017;**4**:grhta.5000254. doi:10.5301/grhta.5000254

48 Browne RH. On the use of a pilot sample for sample size determination. *Stat Med* 1995;**14**:1933–40. doi:10.1002/sim.4780141709

49 Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharm Stat* 2005;**4**:287–91. doi:10.1002/pst.185

50 Teare MD, Dimairo M, Shephard N, *et al.* Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study. *Trials* 2014;**15**:264. doi:10.1186/1745-6215-15-264

51 Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol* 2012;**65**:301–8. doi:10.1016/j.jclinepi.2011.07.011

52 Cocks K, Torgerson DJ. Sample size calculations for pilot randomized trials: A confidence interval approach. *J Clin Epidemiol* 2013;**66**:197–201. doi:10.1016/j.jclinepi.2012.09.002

53 Stallard N. Optimal sample sizes for phase II clinical trials and pilot studies. *Stat Med* 2012;**31**:1031–42. doi:10.1002/sim.4357

54 Whitehead AL, Julious SA, Cooper CL, *et al.* Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. *Stat Methods Med Res* 2015;**25**:1057–73. doi:10.1177/0962280215588241

55 Hertzog MA. Considerations in Determining Sample Size for Pilot Studies. *Wiley Period Inc Res Nurs Heal* 2008;:180–191. doi:10.1002/nur.20247

56 Tickle-degnen L. Nuts and bolts of conducting feasibility studies. *Am J Occup Ther* 2013;**67**:1–7. doi:10.5014/ajot.2013.006270

57 NIHR. Guide to ... Feasibility and pilot studies : a guide for NIHR Research Design Service advisors. 2015. http://www.rds-eastmidlands.nihr.ac.uk/resources/Guide to Supporting Feasibility and Pilot Studies MAY 2016 FIANAL.pdf

58 Lee EC, Whitehead AL, Jacques RM, *et al.* The statistical interpretation of pilot trials: Should significance thresholds be reconsidered? *BMC Med Res Methodol* 2014;**14**. doi:10.1186/1471-2288-14-41

59 Kraemer HC, Mintz J, Noda A, *et al.* Caution regarding the use of pilot studies to guide power calculations for study proposals. Arch. Gen. Psychiatry. 2006;**63**:484–9. doi:10.1001/archpsyc.63.5.484

60 Cooper CL, Whitehead A, Pottrill E, *et al.* Are pilot trials useful for predicting randomisation and attrition rates in definitive studies: A review of publicly funded trials. *Clin Trials* 2018;**15**:189–96. doi:10.1177/1740774517752113

61 Sim J. Should treatment effects be estimated in pilot and feasibility studies? *Pilot Feasibility Stud* 2019;**5**:1–7. doi:10.1186/s40814-019-0493-7

62 Wilson DT, Walwyn REA, Brown J, *et al.* Statistical challenges in assessing potential efficacy of complex interventions in pilot or feasibility studies. *Stat Methods Med Res* 2015;**25**:997–1009. doi:10.1177/0962280215589507

63 Blatch-Jones AJ, Pek W, Kirkpatrick E, *et al.* Role of feasibility and pilot studies in randomised controlled trials: A crosssectional study. *BMJ Open* 2018;**8**:22233. doi:10.1136/bmjopen-2018-022233

64 Kistin C, Silverstein M. Pilot studies: A critical but potentially misused component of interventional research. *JAMA - J Am Med Assoc* 2015;**314**:1561–2. doi:10.1001/jama.2015.10962

65 Eldridge SM, Costelloe CE, Kahan BC, *et al.* How big should the pilot study for my cluster randomised trial be? *Stat Methods Med Res* 2016;**25**:1039–56. doi:10.1177/0962280215588242

66 Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. *J Psychiatr Res* 2011;**45**:626–9. doi:10.1016/j.jpsychires.2010.10.008

67 Bell ML, Whitehead AL, Julious SA. Guidance for using pilot studies to inform the design of intervention trials with continuous outcomes. *Clin Epidemiol* 2018;**10**:153–7. doi:10.2147/CLEP.S146397

68 Pilot Studies: Common Uses and Misuses | NCCIH. https://www.nccih.nih.gov/grants/pilot-studies-common-uses-and-misuses

(accessed 10 Jul 2020).

69 Mbuagbaw L, Kosa SD, Lawson DO, *et al.* The reporting of progression criteria in protocols of pilot trials designed to assess the feasibility of main trials is insufficient: a meta-epidemiological study. *Pilot feasibility Stud* 2019;**5**:120. doi:10.1186/s40814-019-0500-z

70 Hallingberg B, Turley R, Segrott J, *et al.* Exploratory studies to decide whether and how to proceed with full-scale evaluations of public health interventions: a systematic review of guidance. *Pilot Feasibility Stud* 2018;**4**:104. doi:10.1186/s40814-018-0290-8

71 Lewis M, Bromley K, Sutton CJ, *et al.* Determining sample size for progression criteria for pragmatic pilot RCTs: the hypothesis test strikes back! *Pilot Feasibility Stud* 2021;**7**:40. doi:10.1186/s40814-021-00770-x

72 Teresi JA, Yu X, Stewart AL, *et al.* Guidelines for Designing and Evaluating Feasibility Pilot Studies. *Med Care* 2021;**00**:1–9. doi:10.1097/MLR.0000000000001664

73 Arnold DM, Burns KEA, Adhikari NKJ, *et al.* The design and interpretation of pilot trials in clinical research in critical care. *Crit Care Med* 2009;**37**:69–74. doi:10.1097/CCM.0b013e3181920e33

74 Feeley N, Cossette S, Côté J, *et al.* The importance of piloting an RCT intervention. *Can J Nurs Res* 2009;**41**:85–99.http://www.ncbi.nlm.nih.gov/pubmed/19650515 (accessed 23 Oct 2019).

75 O'Cathain A, Hoddinott P, Lewin S, *et al.* Maximising the impact of qualitative

research in feasibility studies for randomised controlled trials: Guidance for researchers. *Pilot Feasibility Stud* 2015;**1**:1–13. doi:10.1186/s40814-015-0026-y

76 Hassan ZA, Schattner P, Mazza D. Doing A Pilot Study: Why Is It Essential? *Malaysian Fam physician Off J Acad Fam Physicians Malaysia* 2006;**1**:70–3.http://www.ncbi.nlm.nih.gov/pubmed/27570591

77 NIHR. HTA Tips for Applicants, v1.0. 2019.https://www.nihr.ac.uk/documents/hta-tips-for-applicants/12130 (accessed 15 Jun 2022).

78 Moore GF, Audrey S, Barker M, *et al.* Process evaluation of complex interventions: Medical Research Council guidance. *BMJ* 2015;**350**. doi:10.1136/BMJ.H1258

79 Bryant M, Dharni N, Dickerson J, *et al.* Use of progression criteria to support monitoring and commissioning decision making of public health services: Lessons from Better Start Bradford. *BMC Public Health* 2019;**19**:1–9. doi:10.1186/s12889-019-7149-7

80 Potter M, Gordon S, Hamer P. The Nominal Group Technique: A useful consensus methodology in physiotherapy research. *New Zeal J Physiother* 2004;**32**.

81 Young H, Goodliffe S, Madhani M, *et al.* Co-producing Progression Criteria for Feasibility Studies: A Partnership between Patient Contributors, Clinicians and Researchers. *Int J Environ Res Public Health* 2019;**16**:3756. doi:10.3390/ijerph16193756

82 Bugge C, Williams B, Hagen S, *et al.* A process for Decision-making after Pilot

and feasibility Trials (ADePT): Development following a feasibility study of a complex intervention for pelvic organ prolapse. *Trials* 2013;**14**:1. doi:10.1186/1745-6215-14-353

83 Hagen NA, Biondo PD, Brasher PMA, *et al.* Formal Feasibility Studies in Palliative Care: Why They Are Important and How to Conduct Them. *J Pain Symptom Manage* 2011;**42**:278–89. doi:10.1016/j.jpainsymman.2010.11.015

84 O'Cathain A, Thomas KJ, Drabble SJ, *et al.* Maximising the value of combining qualitative research and randomised controlled trials in health research: The QUAlitative Research in Trials (QUART) study - A mixed methods study. *Health Technol Assess (Rockv)* 2014;**18**:1–197. doi:10.3310/hta18380

85 O'Cathain A, Thomas KJ, Drabble SJ, *et al.* What can qualitative research do for randomised controlled trials? A systematic mapping review. *BMJ Open* 2013;**3**. doi:10.1136/bmjopen-2013-002889

86 Fletcher A, Jamal F, Moore G, *et al.* Realist complex intervention science: Applying realist principles across all phases of the Medical Research Council framework for developing and evaluating complex interventions. *Evaluation* 2016;**22**:286–303. doi:10.1177/1356389016652743

87 Mathison S. Why Triangulate? *Educ Res* 1988;**17**:13–7. doi:10.3102/0013189X017002013

88 O'Cathain A, Murphy E, Nicholl J. Why, and how, mixed methods research is undertaken in health services research in England: A mixed methods study. *BMC Health Serv Res* 2007;**7**:1–11. doi:10.1186/1472-6963-7-85/TABLES/7

89 Lancaster GA, Thabane L. Guidelines for reporting non-randomised pilot and feasibility studies. *Pilot Feasibility Stud* 2019;**5**:1–6. doi:10.1186/s40814-019-0499-1

90 Mbuagbaw L, Lawson DO, Puljak L, *et al.* A tutorial on methodological studies: the what, when, how and why. *BMC Med Res Methodol* 2020;**20**:226. doi:10.1186/s12874-020-01107-7

91 Mellor K, Hopewell S. An investigation of the current use of progression criteria in external randomised pilot studies: a systematic review protocol. *OSF* Published Online First: 7 May 2020. doi:10.17605/OSF.IO/BN35K

92 Lawson DO, Puljak L, Pieper D, *et al.* Reporting of methodological studies in health research: a protocol for the development of the MethodologIcal STudy reportIng Checklist (MISTIC). *BMJ Open* 2020;**10**:e040478. doi:10.1136/BMJOPEN-2020-040478

93 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**. doi:10.1136/BMJ.N71

94 Mohammad D, Murad H, Murad MH, *et al.* Guidelines for reporting meta-epidemiological methodology research. *BMJ Evidence-Based Med* 2017;**22**:139–42. doi:10.1136/EBMED-2017-110713

95 Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: Updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;**340**:698–702. doi:10.1136/bmj.c332

96 Pilot and Feasibility Studies | Research. https://pilotfeasibilitystudies.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research (accessed 10 Jul 2020).

97 Authors | BMJ Open. https://bmjopen.bmj.com/pages/authors/#submission_guidelines (accessed 10 Jul 2020).

98 Trials | Research. https://trialsjournal.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research (accessed 10 Jul 2020).

99 PLOS ONE: accelerating the publication of peer-reviewed science. https://journals.plos.org/plosone/s/submission-guidelines#loc-guidelines-for-specific-study-types (accessed 10 Jul 2020).

100 Stata Statistical Software: Release 15. StataCorp. 2017.

101 Sperandei S. Understanding logistic regression analysis. *Biochem Medica* 2014;**24**:12–8. doi:10.11613/BM.2014.003

102 Babyak MA. What You See May Not Be What You Get: A Brief, Nontechnical Introduction to Overfitting in Regression-Type Models. *Psychosom Med* 2004;**66**:411–21. doi:0033-3174/04/6603-0411

103 Bursac Z, Gauss CH, Williams DK, *et al.* Purposeful selection of variables in logistic regression. *Source Code Biol Med* 2008;**3**:17. doi:10.1186/1751-0473-3-17

104 Hayes C, Ciblis A, Darker C, *et al.* We Can Quit2 (WCQ2): A community-based intervention on smoking cessation for women living in disadvantaged areas of

Ireland - Study protocol for a pilot cluster randomised controlled trial. *Pilot Feasibility Stud* 2019;**5**:138. doi:10.1186/s40814-019-0511-9

105 Pouw MA, Calf AH, Van Munster BC, *et al.* Hospital at Home care for older patients with cognitive impairment: A protocol for a randomised controlled feasibility trial. *BMJ Open* 2018;**8**:e020332. doi:10.1136/bmjopen-2017-020332

106 Battle C, Hutchings HA, Driscoll T, *et al.* A multicentre randomised feasibility STUdy evaluating the impact of a prognostic model for Management of BLunt chest wall trauma patients: STUMBL Trial. *BMJ Open* 2019;**9**:e029187. doi:10.1136/bmjopen-2019-029187

107 Ribeiro DC, Jafarian Tangrood Z, Sole G, *et al.* Effectiveness of a tailored rehabilitation versus standard strengthening programme for patients with shoulder pain: A protocol for a feasibility randomised controlled trial (the Otago MASTER trial). *BMJ Open* 2019;**9**:e028261. doi:10.1136/bmjopen-2018-028261

108 Timko CA, Goulazian TJ, Fitzpatrick KK, *et al.* Cognitive remediation therapy (CRT) as a pretreatment intervention for adolescents with anorexia nervosa during medical hospitalization: A pilot randomized controlled trial protocol. *Pilot Feasibility Stud* 2018;**4**:87. doi:10.1186/s40814-018-0277-5

109 De Oliveira Braga H, Gregório EC, Myra RS, *et al.* EMPOWER-PD - A physical therapy intervention to empower the individuals with Parkinson's disease: A study protocol for a feasibility randomized controlled trial. *Pilot Feasibility Stud* 2019;**5**:19. doi:10.1186/s40814-019-0394-9

110 McIntyre L, Taljaard M, McArdle T, *et al.* FLUID trial: A protocol for a hospital-wide open-label cluster crossover pragmatic comparative effectiveness

randomised pilot trial. *BMJ Open* 2018;**8**:e022780. doi:10.1136/bmjopen-2018-022780

111 Qurashi I, Chu S, Drake R, *et al.* Glycopyrrolate in comparison to hyoscine hydrobromide and placebo in the treatment of hypersalivation induced by clozapine (GOTHIC1): A feasibility study. *Pilot Feasibility Stud* 2019;**5**:79. doi:10.1186/s40814-019-0462-1

112 Abokhrais IM, Saunders PTK, Denison FC, *et al.* A pilot randomised double blind controlled trial of the efficacy of purified fatty acids for the treatment of women with endometriosis-associated pain (PurFECT): Study protocol. *Pilot Feasibility Stud* 2018;**4**:83. doi:10.1186/s40814-018-0274-8

113 Philip J, Collins A, Le B, *et al.* A randomised phase II trial to examine feasibility of standardised, early palliative (STEP) care for patients with advanced cancer and their families [ACTRN12617000534381]: A research protocol. *Pilot Feasibility Stud* 2019;**5**:44. doi:10.1186/s40814-019-0424-7

114 Mayo-Wilson LJ, Glass NE, Ssewamala FM, *et al.* Microenterprise intervention to reduce sexual risk behaviors and increase employment and HIV preventive practices in economically-vulnerable African-American young adults (EMERGE): Protocol for a feasibility randomized clinical trial. *Trials* 2019;**20**:439. doi:10.1186/s13063-019-3529-7

115 Payne Riches S, Piernas C, Aveyard P, *et al.* The Salt Swap intervention to reduce salt intake in people with high blood pressure: Protocol for a feasibility randomised controlled trial. *Trials* 2019;**20**:584. doi:10.1186/s13063-019-3691-y

116 Logan A, Freeman J, Kent B, *et al.* Standing Practice In Rehabilitation Early after

Stroke (SPIRES): A functional standing frame programme (prolonged standing and repeated sit to stand) to improve function and quality of life and reduce neuromuscular impairment in people with severe sub-acu. *Pilot Feasibility Stud* 2018;**4**:66. doi:10.1186/s40814-018-0254-z

117 Browne PD, Bolte A, Claassen E, *et al.* Probiotics in pregnancy: Protocol of a double-blind randomized controlled pilot trial for pregnant women with depression and anxiety (PIP pilot trial). *Trials* 2019;**20**:440. doi:10.1186/s13063-019-3389-1

118 Mcpherson AC, Biddiss E, Chen L, *et al.* Children and teens in charge of their health (catch): A protocol for a feasibility randomised controlled trial of solution-focused coaching to foster healthy lifestyles in childhood disability. *BMJ Open* 2019;**9**:e025119. doi:10.1136/bmjopen-2018-025119

119 Drew CJG, Postans M, Petralia C, *et al.* A protocol for a randomised controlled, double-blind feasibility trial investigating fluoxetine treatment in improving memory and learning impairments in patients with mesial temporal lobe epilepsy: Fluoxetine, Learning and Memory in Epilepsy (FLAME trial. *Pilot Feasibility Stud* 2019;**5**:87. doi:10.1186/s40814-019-0474-x

120 Rowe A, Titterington J, Taggart L. A classroom-based intervention targeting working memory, attention and language skills in 4-5 year olds (RECALL): Study protocol for a cluster randomised feasibility trial. *Pilot Feasibility Stud* 2019;**5**:82. doi:10.1186/s40814-019-0468-8

121 Whitehead A, Simpson C, Willcox M, *et al.* HATRIC: A study of Pelargonium sidoides root extract EPs®7630 (Kaloba®) for the treatment of acute cough due to

lower respiratory tract infection in adults-study protocol for a double blind, placebocontrolled randomised feasibility trial. *Pilot Feasibility Stud* 2019;**5**:98. doi:10.1186/s40814-019-0478-6

122 Steare T, O'Hanlon P, Eskinazi M, *et al.* App to support Recovery in Early Intervention Services (ARIES) study: Protocol of a feasibility randomised controlled trial of a self-management Smartphone application for psychosis. *BMJ Open* 2019;**9**:e025823. doi:10.1136/bmjopen-2018-025823

123 Hilari K, Behn N, Marshall J, *et al.* Adjustment with aphasia after stroke: Study protocol for a pilot feasibility randomised controlled trial for SUpporting wellbeing through PEeR Befriending (SUPERB). *Pilot Feasibility Stud* 2019;**5**:14. doi:10.1186/s40814-019-0397-6

124 Deary V, McColl E, Carding P, *et al.* A psychosocial intervention for the management of functional dysphonia: Complex intervention development and pilot randomised trial. *Pilot Feasibility Stud* 2018;**4**:46. doi:10.1186/s40814-018-0240-5

125 Wall PD, Ahmed I, Metcalfe A, *et al.* Safety and feasibility evaluation of tourniquets for total knee replacement (SAFE-TKR): Study protocol. *BMJ Open* 2018;**8**:e022067. doi:10.1136/bmjopen-2018-022067

126 Cooper C, O'Cathain A, Hind D, *et al.* Conducting qualitative research within Clinical Trials Units: Avoiding potential pitfalls. *Contemp Clin Trials* 2014;**38**:338–43. doi:10.1016/j.cct.2014.06.002

127 Sidani S, Braden CJ. *Design, evaluation, and translation of nursing interventions*. John Wiley & Sons 2011.

128 Perepletchikova F, Kazdin AE. Treatment integrity and therapeutic change: Issues and research recommendations. *Clin Psychol Sci Pract* 2005;**12**:365–83.

129 Julious S, Tan SB, Machin D. *An Introduction to Statistics in Early Phase Trials - Steven Julious, Say Beng Tan, David Machin - Google Books*. Wiley-Blackwell 2010.

130 Altman DG, Bland JM. Measurement in Medicine: The Analysis of Method Comparison Studies. *J R Stat Soc Ser D (The Stat* 1983;**32**:307–17. doi:10.2307/2987937

131 Baltussen R, Niessen L. Priority setting of health interventions: The need for multi-criteria decision analysis. *Cost Eff Resour Alloc* 2006;**4**:14. doi:10.1186/1478-7547-4-14

132 Polit DF, Beck CT. *Nursing research: Principles and methods*. Lippincott Williams & Wilkins 2004.

133 Kohrt BA, Jordans MJD, Turner EL, *et al.* Reducing stigma among healthcare providers to improve mental health services (RESHAPE): Protocol for a pilot cluster randomized controlled trial of a stigma reduction intervention for training primary healthcare workers in Nepal. *Pilot Feasibility Stud* 2018;**4**:36. doi:10.1186/s40814-018-0234-3

134 Jones JK, Evans BA, Fegan G, *et al.* Rapid Analgesia for Prehospital hip Disruption (RAPID): Findings from a randomised feasibility study. *Pilot Feasibility Stud* 2019;**5**:77. doi:10.1186/s40814-019-0454-1

135 Moore C, Bulger J, Morgan M, *et al.* Prehospital recognition and antibiotics for

999 patients with sepsis: Protocol for a feasibility study. *Pilot Feasibility Stud* 2018;**4**:64. doi:10.1186/s40814-018-0258-8

136 Quraishi MNN, Yalchin M, Blackwell C, *et al.* STOP-Colitis pilot trial protocol: A prospective, open-label, randomised pilot study to assess two possible routes of faecal microbiota transplant delivery in patients with ulcerative colitis. *BMJ Open* 2019;**9**:e030659. doi:10.1136/bmjopen-2019-030659

137 McGovern R, Stamp E, Javanbakht M, *et al.* Promoting Alcohol Reduction in Non- Treatment Seeking parents (PAReNTS): A protocol for a pilot feasibility cluster randomised controlled trial of alcohol screening and brief interventions to reduce parental alcohol use disorders in vulnerable families. *Pilot Feasibility Stud* 2018;**4**:111. doi:10.1186/s40814-018-0305-5

138 Loudon K, Treweek S, Sullivan F, *et al.* The PRECIS-2 tool: Designing trials that are fit for purpose. *BMJ* 2015;**350**. doi:10.1136/bmj.h2147

139 Purcell A, Buckley T, King J, *et al.* Eutectic mixture of local anaesthetics (EMLA®) as a primary dressing on painful chronic leg ulcers: A pilot randomised controlled trial. *Pilot Feasibility Stud* 2018;**4**:123. doi:10.1186/s40814-018-0312-6

140 Newlands RSN, Ntessalen M, Clark J, *et al.* Pilot randomised controlled trial of Weight Watchers® referral with or without dietitianled group support for weight loss in women treated for breast cancer: The BRIGHT (BReast cancer weIGHT loss) trial. *Pilot Feasibility Stud* 2019;**5**:24. doi:10.1186/s40814-019-0405-x

141 Sharma S, Jensen MP, Moseley GL, *et al.* Results of a feasibility randomised clinical trial on pain education for low back pain in Nepal: The Pain Education in

Nepal-Low Back Pain (PEN-LBP) feasibility trial. *BMJ Open* 2019;**9**:e026874. doi:10.1136/bmjopen-2018-026874

142 Wiangkham T, Duda J, Sayeed Haque M, *et al.* A cluster randomised, double-blind pilot and feasibility trial of an active behavioural physiotherapy intervention for acute whiplash-associated disorder (WAD)II. *PLoS One* 2019;**14**:e0215803. doi:10.1371/journal.pone.0215803

143 Yeung J, Middleton L, Tryposkiadis K, *et al.* Randomised controlled trial to investigate the effectiveness of thoracic epidural and paravertebral blockade in reducing chronic post-thoracotomy pain (TOPIC): A pilot study to assess feasibility of a large multicentre trial. *BMJ Open* 2019;**9**:e023679. doi:10.1136/bmjopen-2018-023679

144 Sharma S, Jensen MP, Moseley GL, *et al.* Pain education for patients with non-specific low back pain in Nepal: Protocol of a feasibility randomised clinical trial (PEN-LBP Trial). *BMJ Open* 2018;**8**:e022423. doi:10.1136/bmjopen-2018-022423

145 Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC Med Res Methodol* 2013;**13**:104. doi:10.1186/1471-2288-13-104

146 Connelly LM. Pilot studies. *MedSurg Nurs* 2008;**17**:411–3.https://go.gale.com/ps/i.do?p=AONE&sw=w&issn=10920811&v=2.1&it=r&id=GALE%7CA192589717&sid=googleScholar&linkaccess=fulltext (accessed 21 Jul 2020).

147 Moore CG, Carter RE, Nietert PJ, *et al.* Recommendations for planning pilot studies in clinical and translational research. Clin. Transl. Sci. 2011;**4**:332–7. doi:10.1111/j.1752-8062.2011.00347.x

148 Viechtbauer W, Smits L, Kotz D, *et al.* A simple formula for the calculation of sample size in pilot studies. *J Clin Epidemiol* 2015;**68**:1375–9. doi:10.1016/j.jclinepi.2015.04.014

149 NIHR RDS. Justify sample size for a feasibility study. https://www.rds-london.nihr.ac.uk/resources/justify-sample-size-for-a-feasibility-study/ (accessed 21 Jul 2020).

150 Nielsen Norman Group. Quantitative Studies: How Many Users to Test? https://www.nngroup.com/articles/quantitative-studies-how-many-users/ (accessed 21 Jul 2020).

151 Rosala-Hallas A, Gamble C, Blazeby J, *et al.* A review of current practice in the design and assessment of internal pilots in UK NIHR clinical trials. *Trials* 2019;**20**:1–5. doi:10.1186/s13063-019-3669-9

152 Herbert E, Julious SA, Goodacre S. Progression criteria in trials with an internal pilot: an audit of publicly funded randomised controlled trials. *Trials* 2019;**20**:1–9. doi:10.1186/s13063-019-3578-y

153 Shiwa SR, Moseley AM, Maher CG, *et al.* Language of publication has a small influence on the quality of reports of controlled trials of physiotherapy interventions. *J Clin Epidemiol* 2013;**66**:78–84. doi:10.1016/J.JCLINEPI.2012.08.004

154 Maas E, Maher C, Moseley A, *et al.* Funding is related to the quality, conduct, and reporting of trial reports in musculoskeletal physical therapy: A survey of 210 published trials. *https://doi.org/101080/0959398520161222472* 2016;**32**:628–35. doi:10.1080/09593985.2016.1222472

155 Geha NN, Moseley AM, Elkins MR, *et al.* The Quality and Reporting of Randomized Trials in Cardiothoracic Physical Therapy Could Be Substantially Improved. *Respir Care* 2013;**58**:1899–906. doi:10.4187/RESPCARE.02379

156 Neimann Rasmussen L, Montgomery P. The prevalence of and factors associated with inclusion of non-English language studies in Campbell systematic reviews: A survey and meta-epidemiological study. *Syst Rev* 2018;**7**:1–12. doi:10.1186/s13643-018-0786-6

157 Buscemi N, Hartling L, Vandermeer B, *et al.* Single data extraction generated more errors than double data extraction in systematic reviews. *J Clin Epidemiol* 2006;**59**:697–703. doi:10.1016/j.jclinepi.2005.11.010

158 Smith R. Peer review: A flawed process at the heart of science and journals. J. R. Soc. Med. 2006;**99**:178–82. doi:10.1258/jrsm.99.4.178

159 NIHR. Guidance on applying for feasibility studies. v2.0 Feb 2021. https://www.nihr.ac.uk/documents/nihr-research-for-patient-benefit-rfpb-programme-guidance-on-applying-for-feasibility-studies/20474 (accessed 4 Feb 2021).

160 Mellor K, Hejdenberg J, Morgan B, *et al.* Progression criteria in external randomised pilot trials: Protocol for a review of Research for Patient Benefit funding applications. *OSF* Published Online First: 29 June 2021.

doi:10.17605/OSF.IO/89AP7

161 Vandenbroucke JP, Von Elm E, Altman DG, *et al.* Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *Ann Intern Med* 2007;**147**. doi:10.7326/0003-4819-147-8-200710160-00010-W1

162 Von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Ann Intern Med* 2007;**147**:573–7. doi:10.7326/0003-4819-147-8-200710160-00010

163 NIHR. Research for Patient Benefit Programme - Guidance for Stage 1 applications. v4.0 Nov 2021. https://www.nihr.ac.uk/documents/research-for-patient-benefit-programme-guidance-for-stage-1-applications/20154 (accessed 16 Nov 2021).

164 NIHR. Research for Patient Benefit - Success rates. v1.1 Mar 2021. https://www.nihr.ac.uk/documents/research-for-patient-benefit-success-rates/21364 (accessed 16 Nov 2021).

165 Dimairo M, Boote J, Julious S, *et al.* Missing steps in a staircase: a qualitative study of the perspectives of key stakeholders on the use of adaptive designs in confirmatory trials. *Trials* 2015;**16**. doi:10.1186/S13063-015-0958-9

166 Nicholls SG, Carroll K, Weijer C, *et al.* Ethical Issues in the Design and Conduct of Pragmatic Cluster Randomized Trials in Hemodialysis Care: An Interview Study With Key Stakeholders. *Can J kidney Heal Dis* 2020;**7**:2054358120964119. doi:10.1177/2054358120964119

167 Nusbaum L, Douglas B, Damus K, *et al.* Communicating Risks and Benefits in Informed Consent for Research: A Qualitative Study. *Glob Qual Nurs Res* 2017;**4**. doi:10.1177/2333393617732017

168 Mellor K, Albury C, Hopewell S. Using progression criteria to determine feasibility of external randomised pilot trials: protocol for a qualitative study of stakeholder views. *OSF* Published Online First: 4 December 2020. doi:10.17605/OSF.IO/5N2KZ

169 Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): A 32-item checklist for interviews and focus groups. *Int J Qual Heal Care* 2007;**19**:349–57. doi:10.1093/intqhc/mzm042

170 Johnson RB, Onwuegbuzie AJ. Mixed Methods Research: A Research Paradigm Whose Time Has Come. *Educ Res* 2004;**33**:14–26. doi:10.3102/0013189X033007014

171 Creswell JW. *Research design: Qualitative, quantitative, and mixed methods approaches. 4th Edition*. 4th Editio. California: 2014. doi:10.1007/s13398-014-0173-7.2

172 Glaser BG, Strauss AL. *The discovery of grounded theory : strategies for qualitative research*. Aldine Pub

173 Corbin J, Strauss A. Grounded Theory Research: Procedures, Canons, and Evaluative Criteria. 1990.

174 Strauss A, Corbin J. *Basics of qualitative research: Grounded theory procedures and techniques.* Newbury Park: : SAGE Publications 1990.

doi:10.4135/9781452230153

175 Silverman D. *Interpreting qualitative data*. Sixth edition. Los Angeles: 2020.

176 Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;**3**:77–101. doi:10.1191/1478088706qp063oa

177 Braun V, Clarke V. Can I use TA? Should I use TA? Should I *not* use TA? Comparing reflexive thematic analysis and other pattern-based qualitative analytic approaches. *Couns Psychother Res* 2020;:capr.12360. doi:10.1002/capr.12360

178 Gale NK, Heath G, Cameron E, *et al.* Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol* 2013;**13**:117. doi:10.1186/1471-2288-13-117

179 Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qual. Res. Sport. Exerc. Heal. 2019;**11**:589–97. doi:10.1080/2159676X.2019.1628806

180 Sale JEM. The role of analytic direction in qualitative research. *BMC Med Res Methodol* 2022;**22**:66. doi:10.1186/S12874-022-01546-4

181 Denzin NK. *The research act : a theoretical introduction to sociological methods*. Print. Abingdon: : Aldine Pub 2017.

182 Silverman D. *Doing qualitative research*. Fifth edition. Los Angeles ; London: 2017.

183 Byrne D. A worked example of Braun and Clarke's approach to reflexive thematic analysis. *Qual Quant* 2021;**56**:1391–1412. doi:doi.org/10.1007/s11135-021-01182-y

184 Robinson RS. Purposive Sampling. In: Michalos AC, ed. *Encyclopedia of Quality of Life and Well-Being Research*. Dordrecht: : Springer Netherlands 2014. 5243–5. doi:10.1007/978-94-007-0753-5_2337

185 Palinkas LA, Horwitz SM, Green CA, *et al.* Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research. *Adm Policy Ment Heal Ment Heal Serv Res* 2015;**42**:533–44. doi:10.1007/s10488-013-0528-y

186 Valerio MA, Rodriguez N, Winkler P, *et al.* Comparing two sampling methods to engage hard-to-reach communities in research priority setting. *BMC Med Res Methodol 2016 161* 2016;**16**:1–11. doi:10.1186/S12874-016-0242-Z

187 QMUL. Pilot and feasibility studies: Giving your research the best chance of success. https://pilotandfeasibilitystudies.qmul.ac.uk/ (accessed 29 Apr 2021).

188 Chan CL. A website for pilot and feasibility studies : giving your research the best chance of success. *Pilot Feasibility Stud* 2019;**5**:4–6.

189 UKCRC | UK Clinical Research Collaboration. https://www.ukcrc.org/ (accessed 5 Jun 2020).

190 Network Hubs :: TMRP. https://www.methodologyhubs.mrc.ac.uk/about/tmrp/ (accessed 5 Jun 2020).

191 About the UKTMN - UKTMN. https://www.tmn.ac.uk/page/AboutUKTMN (accessed 18 Nov 2020).

192 Research Design Service | NIHR. https://www.nihr.ac.uk/explore-nihr/support/research-design-service.htm (accessed 5 Jun 2020).

193 Saunders B, Sim J, Kingstone T, *et al.* Saturation in qualitative research: exploring its conceptualization and operationalization. *Qual Quant* 2018;**52**:1893–907. doi:10.1007/s11135-017-0574-8

194 Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qual Health Res* 2016;**26**:1753–60. doi:10.1177/1049732315617444

195 Sebele-Mpofu FY. Saturation controversy in qualitative research: Complexities and underlying assumptions. A literature review. Cogent Soc. Sci. 2020;**6**. doi:10.1080/23311886.2020.1838706

196 Thorne S. The Great Saturation Debate: What the 'S Word' Means and Doesn't Mean in Qualitative Research Reporting. Can. J. Nurs. Res. 2020;**52**:3–5. doi:10.1177/0844562119898554

197 O'Reilly M, Parker N. 'Unsatisfactory Saturation': A critical exploration of the notion of saturated sample sizes in qualitative research. *Qual Res* 2013;**13**:190–7. doi:10.1177/1468794112446106

198 Sim J, Saunders B, Waterfield J, *et al.* Can sample size in qualitative research be determined a priori? Int. J. Soc. Res. Methodol. 2018;**21**:619–34. doi:10.1080/13645579.2018.1454643

199 Caelli K, Ray L, Mill J. 'Clear as Mud': Toward Greater Clarity in Generic Qualitative Research: *http://dx.doi.org/101177/160940690300200201* 2016;**2**:1–13. doi:10.1177/160940690300200201

200 Morse JM. "Data were saturated . . . ". *Qual Health Res* 2015;**25**:587–8.

doi:10.1177/1049732315576699

201 Vasileiou K, Barnett J, Thorpe S, *et al*. Characterising and justifying sample size sufficiency in interview-based studies: systematic analysis of qualitative health research over a 15-year period. *BMC Med Res Methodol* 2018;**18**:148. doi:10.1186/s12874-018-0594-7

202 Guide to the UK General Data Protection Regulation (UK GDPR) | ICO. https://ico.org.uk/for-organisations/guide-to-data-protection/guide-to-the-general-data-protection-regulation-gdpr/?q=identify (accessed 28 Jan 2022).

203 Data Protection Act 2018. https://www.legislation.gov.uk/ukpga/2018/12/contents/enacted (accessed 28 Jan 2022).

204 Lincoln YS, Guba EG. *Naturalistic Inquiry*. Newbury Park, CA: : Sage Publications 1985. https://books.google.co.uk/books?hl=en&lr=&id=2oA9aWlNeooC&oi=fnd&pg=PA5&sig=GoKaBo0eIoPy4qeqRyuozZo1CqM&dq=naturalistic+inquiry&prev=http://scholar.google.com/scholar%3Fq%3Dnaturalistic%2Binquiry%26num%3D100%26hl%3Den%26lr%3D&redir_esc=y#v=onepage&q=naturalistic inquiry&f=false (accessed 13 Aug 2020).

205 Lub V. Validity in Qualitative Evaluation: Linking Purposes, Paradigms, and Perspectives. *Int J Qual Methods* 2015;**14**:160940691562140. doi:10.1177/1609406915621406

206 Cohen D, Crabtree B. Qualitative Research Guidelines Project. 2006.

207 Hanson CS, Ju A, Tong A. Appraisal of qualitative studies. In: *Handbook of Research Methods in Health Social Sciences*. Springer Singapore 2019. 1013–26. doi:10.1007/978-981-10-5251-4_119

208 Elliott R, Timulak L. Descriptive and interpretive approaches to qualitative research. In: *A handbook of research methods for clinical and health psychology*. New York, NY, US: : Oxford University Press 2005. 147–59. doi:10.1093/med:psych/9780198527565.001.0001

209 Bergen N, Labonté R. "Everything Is Perfect, and We Have No Problems": Detecting and Limiting Social Desirability Bias in Qualitative Research. *Qual Health Res* 2020;**30**:783–92. doi:10.1177/1049732319889354

210 Mellor K, Eddy S, Peckham N, *et al.* Progression from external pilot to definitive randomised controlled trial: a methodological review of progression criteria reporting. *BMJ Open* 2021;**11**:e048178. doi:10.1136/bmjopen-2020-048178

211 Mellor K, Dutton SJ, Hopewell S. Feasibility and progression of a cohort of external randomised pilot trials: A web-based survey study. *OSF* Published Online First: 2021. doi:10.17605/OSF.IO/D28HR

212 Sharma A, Minh Duc N, Luu Lam Thang T, *et al.* A Consensus-Based Checklist for Reporting of Survey Studies (CROSS). *J Gen Intern Med* Published Online First: 2021. doi:10.1007/S11606-021-06737-1

213 Hakoum MB, Noureldine H, Habib JR, *et al.* Authors of clinical trials seldom reported details when declaring their individual and institutional financial conflicts of interest: a cross-sectional survey. *J Clin Epidemiol* 2020;**127**:49–58. doi:10.1016/J.JCLINEPI.2020.05.026

214 Bellucci C, Hughes K, Toomey E, *et al.* A survey of knowledge, perceptions and use of core outcome sets among clinical trialists. *Trials* 2021;**22**. doi:10.1186/S13063-021-05891-5

215 Matvienko-Sikar K, Avery K, Blazeby JM, *et al.* Use of core outcome sets was low in clinical trials published in major medical journals. *J Clin Epidemiol* 2022;**142**:19–28. doi:10.1016/J.JCLINEPI.2021.10.012/ATTACHMENT/A8BC04E3-8F8C-4689-8231-4C01CA9F58F2/MMC7.DOCX

216 Wyatt JC. When to Use Web-based Surveys. *J Am Med Inform Assoc* 2000;**7**:426. doi:10.1136/JAMIA.2000.0070426

217 Ahuvia A. Traditional, Interpretive, and Reception based Content Analyses: Improving the Ability of Content Analysis to Address Issues of Pragmatic and Theoretical Concern. *Source Soc Indic Res* 2001;**54**:139–72.https://www.jstor.org/stable/27526933 (accessed 16 Mar 2022).

218 Bengtsson M. How to plan and perform a qualitative study using content analysis. *NursingPlus Open* 2016;**2**:8–14. doi:10.1016/J.NPLS.2016.01.001

219 Hsieh H-F, Shannon SE. Three Approaches to Qualitative Content Analysis. Published Online First: 2005. doi:10.1177/1049732305276687

220 Online surveys. https://www.onlinesurveys.ac.uk/ (accessed 21 Feb 2022).

221 O'Cathain A, Thomas KJ. 'Any other comments?' Open questions on questionnaires - A bane or a bonus to research? *BMC Med Res Methodol* 2004;**4**:1–7. doi:10.1186/1471-2288-4-25/FIGURES/1

222 Mellor K. Survey pdfs. OSF. 2021.https://osf.io/7jnvx/ (accessed 21 Feb 2022).

223 Central University Research Ethics Committee (CUREC) Best Practice Guidance 06. Internet-mediated research. 2021;**7.1**.https://researchsupport.admin.ox.ac.uk/files/bpg06internet-basedresearchpdf (accessed 21 Feb 2022).

224 Östlund U, Kidd L, Wengström Y, *et al.* Combining qualitative and quantitative research within mixed method research designs: A methodological review. *Int J Nurs Stud* 2011;**48**:369. doi:10.1016/J.IJNURSTU.2010.10.005

225 Bradley S. Methodological triangulation in healthcare research. *Nurse Res* 1995;**3**:81–9. doi:10.7748/NR.3.2.81.S8

226 Aschbrenner KA, Kruse G, Gallo JJ, *et al.* Applying mixed methods to pilot feasibility studies to inform intervention trials. *Pilot Feasibility Stud 2022 81* 2022;**8**:1–13. doi:10.1186/S40814-022-01178-X

227 Donald G. A brief summary of pilot and feasibility studies: Exploring terminology, aims, and methods. *Eur J Integr Med* 2018;**24**:65–70. doi:10.1016/j.eujim.2018.10.017

228 Yardley L, Ainsworth B, Arden-Close E, *et al.* The person-based approach to enhancing the acceptability and feasibility of interventions. *Pilot Feasibility Stud* 2015;**1**. doi:10.1186/s40814-015-0033-z

229 Hynes L, Murphy AW, Hart N, *et al.* The MultimorbiditY COllaborative Medication Review And DEcision Making (MyComrade) study: a protocol for a cross-border pilot cluster randomised controlled trial. *Pilot Feasibility Stud*

2022;**8**:1–16. doi:10.1186/S40814-022-01018-Y/TABLES/3

230 Swain J, King B. Using Informal Conversations in Qualitative Research: *https://doi.org/101177/16094069221085056* 2022;**21**:1–10. doi:10.1177/16094069221085056

231 Netz Y, Lidor R, Ziv G. Small samples and increased variability-discussing the need for restricted types of randomization in exercise interventions in old age. *Eur Rev Aging Phys Act* 2019;**16**:1–8. doi:10.1186/S11556-019-0224-3/TABLES/4

232 Gillies K, Brehaut J, Coffey T, *et al.* How can behavioural science help us design better trials? *Trials* 2021;**22**:1–7. doi:10.1186/S13063-021-05853-X/FIGURES/1

233 Möhler R, Köpke S, Meyer G. Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare: Revised guideline (CReDECI 2). *Trials* 2015;**16**:1–9. doi:10.1186/s13063-015-0709-y

234 Guyatt G, Oxman AD, Akl EA, *et al.* GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;**64**:383–94. doi:10.1016/j.jclinepi.2010.04.026

235 Campbell SM, Braspenning J, Hutchinson A, *et al.* Research methods used in developing and applying quality indicators in primary care. *BMJ* 2003;**326**:816–9. doi:10.1136/BMJ.326.7393.816

236 Lengnick-Hall R, Gerke DR, Proctor EK, *et al.* Six practical recommendations for improved implementation outcomes reporting. *Implement Sci* 2022;**17**:1–8. doi:10.1186/S13012-021-01183-3/PEER-REVIEW

237 Fordyce CB, Malone K, Forrest A, *et al.* Improving and sustaining the site

investigator community: Recommendations from the Clinical Trials Transformation Initiative. *Contemp Clin Trials Commun* 2019;**16**:100462. doi:10.1016/J.CONCTC.2019.100462

238 Davies L, Beard D, Cook JA, *et al.* The challenge of equipoise in trials with a surgical and non-surgical comparison: a qualitative synthesis using meta-ethnography. *Trials* 2021;**22**. doi:10.1186/S13063-021-05403-5

239 Wartolowska K, Collins GS, Hopewell S, *et al.* Feasibility of surgical randomised controlled trials with a placebo arm: a systematic review. *BMJ Open* 2016;**6**. doi:10.1136/BMJOPEN-2015-010194

240 Kearney A, Daykin A, Shaw ARG, *et al.* Identifying research priorities for effective retention strategies in clinical trials. *Trials* 2017;**18**:1–12. doi:10.1186/S13063-017-2132-Z/TABLES/4

241 Sekhon M, Cartwright M, Lawes-Wickwar S, *et al.* Does prospective acceptability of an intervention influence refusal to participate in a randomised controlled trial? An interview study. *Contemp Clin Trials Commun* 2021;**21**:100698. doi:10.1016/J.CONCTC.2021.100698

242 Baldeh T, MacDonald T, Kosa SD, *et al.* More pilot trials could plan to use qualitative data: a meta-epidemiological study. *Pilot Feasibility Stud* 2020;**6**:164. doi:10.1186/s40814-020-00712-z

243 Haeussler C, Assmus A. Bridging the gap between invention and innovation: Increasing success rates in publicly and industry-funded clinical trials. *Res Policy* 2021;**50**:104155. doi:10.1016/J.RESPOL.2020.104155

244 Beets MW, Pfledderer C, von Klinggraeff L, *et al.* Fund behavioral science like the frameworks we endorse: the case for increased funding of preliminary studies by the National Institutes of Health. *Pilot Feasibility Stud 2022 81* 2022;**8**:1–14. doi:10.1186/S40814-022-01179-W

245 Laterre PF, François B. Strengths and limitations of industry vs. academic randomized controlled trials. *Clin Microbiol Infect* 2015;**21**:906–9. doi:10.1016/J.CMI.2015.07.004

246 Clinical Trial Feasibility - Contract Pharma. https://www.contractpharma.com/issues/2019-04-01/view_features/clinical-trial-feasibility/ (accessed 27 Apr 2022).

247 NIHR. Glossary. https://www.nihr.ac.uk/glossary?letter=P&postcategory=-1 (accessed 19 Jun 2022).

248 Jefferson T, Alderson P, Wager E, *et al.* Effects of editorial peer review: A systematic review. J. Am. Med. Assoc. 2002;**287**:2784–6. doi:10.1001/jama.287.21.2784

249 Van Lent M, IntHout J, Out HJ. Peer review comments on drug trials submitted to medical journals differ depending on sponsorship, results and acceptance: A retrospective cohort study. BMJ Open. 2015;**5**. doi:10.1136/bmjopen-2015-007961

250 Patel J. Why training and specialization is needed for peer review: A case study of peer review for randomized controlled trials. *BMC Med* 2014;**12**:1–7. doi:10.1186/s12916-014-0128-z

251 Moher D, Schulz KF, Simera I, *et al.* Guidance for Developers of Health Research Reporting Guidelines. *PLOS Med* 2010;**7**:e1000217. doi:10.1371/JOURNAL.PMED.1000217

252 Reporting guidelines | The EQUATOR Network. https://www.equator-network.org/reporting-guidelines/ (accessed 15 Jun 2022).

253 Shanthanna H, Kaushal A, Mbuagbaw L, *et al.* A cross-sectional study of the reporting quality of pilot or feasibility trials in high-impact anesthesia journals. *Can J Anesth* 2018;**65**:1180–95. doi:10.1007/s12630-018-1194-z

254 Simera I, Moher D, Hoey J, *et al.* The EQUATOR Network and reporting guidelines: Helping to achieve high standards in reporting health research studies. *Maturitas* 2009;**63**:4–6. doi:10.1016/J.MATURITAS.2009.03.011

255 GOV.UK. Saving and Improving Lives: The Future of UK Clinical Research Delivery. 2021.

256 Charlesworth G, Burnell K, Hoe J, *et al.* Acceptance checklist for clinical effectiveness pilot trials: a systematic approach. *BMC Med Res Methodol* 2013;**13**:78. doi:10.1186/1471-2288-13-78

257 Sim J. Distinctive aspects of consent in pilot and feasibility studies. *J Eval Clin Pract* 2021;**27**:657–64. doi:10.1111/jep.13556

258 Khan MIUU, Mbuagbaw L, Holek M, *et al.* Transparency of informed consent in pilot and feasibility studies is inadequate: a single-center quality assurance study. *Pilot Feasibility Stud 2021 71* 2021;**7**:1–10.https://doi.org/10.1186/s40814-021-00828-w (accessed 19 Apr 2021).

259 Elliott J, Lodemore M, Minogue V, *et al.* Public co-applicants in research - Guidance on roles and responsibilities. Southampton: 2019. https://www.invo.org.uk/posttypepublication/public-co-applicants-in-research-guidance-on-roles-and-responsibilities/

260 Coulman KD, Nicholson A, Shaw A, *et al.* Understanding and optimising patient and public involvement in trial oversight: An ethnographic study of eight clinical trials. *Trials* 2020;**21**:1–15. doi:10.1186/s13063-020-04495-9

261 McConnell T, Best P, Davidson G, *et al.* Coproduction for feasibility and pilot randomised controlled trials: learning outcomes for community partners, service users and the research team. *Res Involv Engagem* 2018;**4**:1–11. doi:10.1186/s40900-018-0116-0

262 Goulao B, Poisson C, Gillies K. Patient and public involvement in numerical aspects of trials: a mixed methods theory-informed survey of trialists' current practices, barriers and facilitators. *BMJ Open* 2021;**11**:e046977. doi:10.1136/BMJOPEN-2020-046977

263 Goulao B, Bruhn H, Campbell M, *et al.* Patient and public involvement in numerical aspects of trials (PoINT): exploring patient and public partners experiences and identifying stakeholder priorities. *Trials* 2021;**22**:1–12. doi:10.1186/S13063-021-05451-X/FIGURES/2