Pilot and feasibility studies for pragmatic trials have unique considerations and areas of uncertainty

Claire L Chan*[1], Monica Taljaard*[2,3], Gillian A Lancaster,[4] Jamie C Brehaut[2,3], Sandra M Eldridge[1]

*Joint first authors

[1]Centre for Clinical Trials and Methodology, Queen Mary University of London, London, E1 2AB, UK

[2]Ottawa Hospital Research Institute, Clinical Epidemiology Program, Centre for Practice-Changing Research, The Ottawa Hospital, Ottawa, ON, K1H 8L6, Canada

[3]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada.

[4]Keele Clinical Trials Unit, School of Medicine, Keele University, Keele, Staffordshire, ST5 5BG, UK.

CLC**:** c.l.chan@qmul.ac.uk
MT: mtaljaard@ohri.ca
GAL: g.lancaster@keele.ac.uk
JCB: jbrehaut@ohri.ca
SEM: s.eldridge@qmul.ac.uk

Corresponding author:
Monica Taljaard
Clinical Epidemiology Program
Ottawa Hospital, Civic Campus
1053 Carling Avenue, Civic Box 693
Admin Services Building, ASB 2-004
Ottawa, ON K1Y 4E9
613-798-5555 x18618 phone

Word count: 3998 of MAX 3000 words

ABSTRACT (Word count: 196 OF Max 200 words)

Background and Objective: Feasibility studies are increasingly being used to support the development of, and investigate uncertainties around, future large-scale trials. The future trial can be designed with either a pragmatic or explanatory mindset. Whereas pragmatic trials aim to inform the choice between different care options and thus, are designed to resemble conditions outside of a clinical trial environment, explanatory trials examine the benefit of a treatment under more controlled conditions. There is existing guidance for designing feasibility studies, but none that explicitly considers the goals of pragmatic designs. We aimed to identify unique areas of uncertainty that are relevant to planning a pragmatic trial.

Results: We identified ten relevant domains, partly based on the PRECIS-2 framework, and describe potential questions of uncertainty within each: intervention development, research ethics, participant identification and eligibility, recruitment of individuals, setting, organisation, flexibility of delivery, flexibility of adherence, follow-up, and importance of primary outcome to patients and decision-makers. We present examples to illustrate how uncertainty in these domains might be addressed within a feasibility study.

Conclusion: Researchers planning a feasibility study in advance of a pragmatic trial should consider feasibility objectives specifically relevant to areas of uncertainty for pragmatic trials.

KEY WORDS: pilot study, feasibility study, pragmatic trial, areas of uncertainty, usual care, progression criteria

WHAT IS NEW?

Key findings:

- Objectives of a feasibility study in preparation for a trial with pragmatic intention ought to differ from those of a study in preparation for a trial with explanatory intention.

What this adds to what is known:

- Examining the pragmatic-explanatory continuum indicator summary (PRECIS-2) we identified eight domains particularly relevant to feasibility studies for trials with pragmatic intention and added two new domains.
- Areas of uncertainty specific to pragmatic goals can be defined within each domain and should be considered when formulating feasibility objectives for a feasibility study.

What is the implication, what should change now:

- When undertaking feasibility studies, trialists should think about whether their proposed future trial has a pragmatic intention or has pragmatic elements.
- Feasibility studies for a trial with pragmatic intention should be deliberately designed to address pragmatic feasibility objectives.

1. PILOT AND FEASIBILITY STUDIES FOR PRAGMATIC TRIALS

Pilot and feasibility studies are often an essential step prior to embarking on a full-scale randomised controlled trial. Using the definitions set out in a recent framework,[1] feasibility studies are studies that ask whether something can be done, whether we should proceed with it — and if so, how. Pilot studies are a subset of feasibility studies; they ask the same question but have a specific design feature (e.g., randomisation) which mirror something that is intended to happen in a future large trial. In other words, in a pilot study, a future study or part of it (e.g., an intervention arm only) is conducted on a smaller scale. Since feasibility studies are designed to support the development of a future study by investigating areas of uncertainty about that future study,[2] they should include clearly formulated feasibility objectives together with pre-specified progression criteria to guide the decision of whether to progress to the next stage or not.

There has been a rising interest in pragmatic trials over the past two decades.[3] The term "pragmatic" was first used to describe approaches to trial design by Schwartz and Lellouch in 1967: they contrasted the explanatory approach, aimed at elucidating a mechanism of action, with the pragmatic approach, aimed at choosing between routine care options.[4] Roland and Torgerson distinguished between the former as measuring efficacy, i.e., the benefit of the treatment under ideal conditions, and the latter as measuring effectiveness, i.e., the benefit of the treatment in routine clinical practice.[5] Treweek and Zwarenstein argue that more trials should have a pragmatic attitude to trial design, urging trialists to think about design choices that maximise applicability as much as they think about internal validity.[6]

There is existing guidance for designing pilot and feasibility studies,[7,8,9,10] but none that explicitly considers the goals of pragmatic trials. Because pragmatic trials emphasise external

validity, a pilot pragmatic trial may need to include considerations of both internal and external validity. For example, an emphasis on piloting procedures to achieve high adherence to the protocol may not be useful to inform the design of a trial that aims to test effectiveness of an intervention in conditions of potentially imperfect adherence. In this paper, we consider potential areas of uncertainty that might be examined as part of a feasibility study in advance of a pragmatic trial. While some areas of uncertainty may be common across explanatory and pragmatic trials, (e.g., the need to estimate parameters required for sample size calculation), here we focus on considerations specific to pragmatic trials. First, we describe the framework that was used to identify potential areas of uncertainty relevant to pragmatic trials. Next, we describe these areas of uncertainty, identify potential feasibility objectives within each, and present examples of feasibility studies for pragmatic trials (published or unpublished) addressing such areas of uncertainty.

2. IDENTIFICATION OF POTENTIAL DOMAINS OF UNCERTAINTY

We used the well-known pragmatic-explanatory continuum indicator summary (PRECIS-2) as a convenient initial framework to identify potential areas of uncertainty.[11] PRECIS-2 has been developed to assess the pragmatic or explanatory nature of trials, acknowledging that a trial may exist on a continuum between explanatory and pragmatic. It identifies nine domains in which a trialist can make explicit design choices according to its pragmatic or explanatory intention: eligibility, recruitment, setting, organisation, flexibility in delivery, flexibility in adherence, follow-up, primary outcome, and primary analysis. Based on discussions amongst the study team and a literature review, we selected eight of the nine domains as potentially relevant. We omitted the primary analysis domain of PRECIS-2 since this domain is concerned with the extent to which all data are included in the analysis of the primary outcome which is a decision to be made rather than something that needs “testing” in a

feasibility study. Moreover, analysis in feasibility studies tends to be based on descriptive statistics rather than formal statistical analyses of effectiveness. We also identified two additional domains relevant to feasibility studies for pragmatic trials: intervention development and research ethics. Pragmatic trials may be designed to inform a decision about whether to adopt a particular intervention in practice; thus, the feasibility study may be concerned not only with intervention implementation but also with refining components of the intervention and testing its acceptability in practice. Research ethics was added because pragmatic trials may raise unique ethical issues.[12]

3. DOMAINS OF UNCERTAINTY FOR PRAGMATIC TRIALS

Table 1 describes the identified domains and explains how a highly pragmatic approach is distinct from a highly explanatory approach within that domain. Table 2 identifies potential feasibility questions or areas of uncertainty within each of the domains, as well as relevant examples for illustration. Appendix 1 provides summary boxes for each example showing the specific feasibility objectives, the study designs used to address the objectives, and the key findings.

3.1. Domain 1: Intervention development

In the later stages of developing a complex intervention, it becomes important to establish whether it is feasible to implement it into routine clinical practice, whether it would be acceptable to stakeholders (e.g., patients and clinicians) and whether it is ready for uptake outside of the research setting after the main trial is completed.[13] The feasibility stage would be useful for identifying barriers to adoption, for example stakeholder-specific, resource, organisational, or cultural barriers. It would also be useful for identifying facilitators to effective adoption, and distinguishing elements that are required and the elements that are

optional or may be administered flexibly (see domains 7 and 8).[14] Identification of barriers and facilitators at an early stage allows for changes to be made before the main trial goes ahead. A variety of study designs may be used to assess barriers and facilitators and should ideally be guided by framework-based approaches such as the theoretical domains framework.[15]

The ADNAT study[16] (Appendix 1: Box 1) and ACE[17] (Appendix 1: Box 2) are examples of mixed-methods feasibility studies that assessed acceptability of the intervention to stakeholders. Investigators conducted surveys, focus groups and interviews to assess feasibility outcomes such as resources needed to set up and sustain implementation, training needs, perceived value, acceptability, and potential barriers to adoption.

3.2. Domain 2: Research ethics

For many pragmatic trials, research ethics considerations are no different from those in explanatory trials. However, some pragmatic trials may involve waived or altered forms of consent[18] which are thought to facilitate recruitment. If the ethical approach, including notification or informed consent, is novel, or if there is otherwise uncertainty about whether patients and ethics committees would find the planned approach acceptable, a feasibility study can help refine the ethics-relevant procedures for the planned trial. This can take the form of focus groups or interview studies and/or feedback from research ethics committees in an initial pilot trial. Challenges during the review process of the large trial could delay trial implementation and lead to unwanted heterogeneity in procedures across participating sites. The pilot trial offers an opportunity to identify the likely range of concerns that might be raised by research ethics committees across jurisdictions to be included in the large trial and communicate with site investigators and research ethics committees about potential solutions.

Identifying potential challenges in the research ethics review process is particularly important for common pragmatic trial designs such as stepped wedge and cluster cross-over trials in which the timing of the intervention delivery is varied according to a fixed schedule.[19,20]

The FLUID trial[21] (Appendix 1: Box 3) is a pilot cluster crossover trial in hospitalised patients comparing two commonly used resuscitation fluids. The intervention was conceptualized as a hospital policy to predominantly stock only one type of fluid for a period, and the trial was designed with a waiver of patient informed consent. The investigators recognised that different research ethics boards may have variable interpretation of the justification for waiver of consent which can result in delays to ethics approval and impede adherence to the scheduled timing of crossing over. The pilot trial aimed to measure the time to research ethics approval, with a successful time defined as taking no longer than 90 days from submission to approval.

3.3. Domain 3: Participant Identification and Eligibility

Pragmatic trials deliberately choose less restrictive eligibility criteria so that participants are similar to those who would receive the intervention if it were implemented outside a trial. While the eligibility criteria for a trial depend on the research question and objectives, a feasibility study might test whether the procedures or processes for implementing eligibility screening are adequate to select participants who resemble the target population. Investigators could compare their sample to patients in the target population to determine whether to loosen or tighten certain criteria. Overly restrictive eligibility criteria might also be detected during the pilot stage if recruitment is more challenging than anticipated (see domain 4).

In the STOP CRC study[22] (Appendix 1: Box 4), the investigators conducted a pilot study to determine whether they could use real-time electronic health record data to correctly identify eligible patients. They measured numbers of patients eligible and recruited and confirmed that their electronic health record embedded approach was able to identify eligible patients.

3.4. Domain 4: Recruitment of individuals

The most pragmatic approach to recruitment would be to simply include all eligible participants who present in settings where the intervention might eventually be used if shown to be successful. However, ethical design of randomised controlled trials usually requires participant consent, and outcomes may need to be collected from participants, which means that some form of recruitment is needed. Before embarking on a large-scale trial, investigators might want to ensure that their recruitment processes are adequate to ensure a sufficient number of participants resembling the target population can be recruited. It might be important to assess whether specific subgroups, such as vulnerable populations and populations traditionally excluded from clinical trials, can be successfully recruited, especially if the future planned trial aims to examine treatment effect heterogeneity across defined subgroups. The Trial Forge Include Ethnicity framework[23] provides a set of questions and accompanying worksheets to help trialists think more carefully about their target populations and how elements of their intervention and recruitment strategies can be designed to be more inclusive. Reflecting on these questions during the feasibility stage can help trialists implement changes to alleviate potential barriers to trial participation before embarking on the large trial. A theory-guided approach to designing pre-trial surveys for trialists seeking to optimise their trial recruitment strategies is also in development.[24]

The HOCKEY FIT study[25] (Appendix 1: Box 5) was a pilot trial that aimed to recruit using methods that were easy to implement and with no added costs. To assess the feasibility of recruitment of hard to reach individuals, they examined the length of time needed to recruit, the number of individuals who expressed interest but were ineligible, and the number who were randomised but withdrew before follow-up sessions. The DIAMOND study[26] (Appendix 1: Box 6) and the ongoing oTTer project[27] (Appendix 1: Box 7) were pilot trials which aimed to identify any potential recruitment difficulties and determine how representative the trial participants were compared to the wider population receiving the intervention. The DIAMOND study identified several factors that negatively affected recruitment and concluded that alternative settings need to be considered for the future trial.

3.5. Domain 5: Setting (recruitment of sites)

A pragmatic trial can promote applicability by demonstrating effectiveness of an intervention across a range of settings, professionals who might be involved, and populations served by the sites. Thus, investigators might want to test and refine their processes for including a variety of relevant sites before embarking on a large trial. This might involve testing whether all types of sites (e.g., academic and community hospitals) can be recruited to participate or testing whether an adequate number of individuals can be identified at different types of sites. The feasibility study might determine willingness of sites to participate, level of commitment from staff, and possible challenges that might affect recruitment. Given their limited sample size, it may be difficult to demonstrate ability to recruit a "representative" sample of sites in a pilot trial, but a feasibility study may include a survey of available sites or providers to assess interest. If the future trial design is a cluster randomised trial, it may be useful to demonstrate within the feasibility study that sites would be willing to be randomised to a control arm which does not receive the novel intervention or, in the case of a wait-list control design,

receives it at the end. Such results could inform the decision of whether to adopt a stepped wedge cluster randomised design (in which all sites gradually receive the intervention during the trial itself) or parallel arm design (in which potentially only half of the sites receive the intervention). As stepped wedge designs are vulnerable to increased risks of bias compared to parallel arm designs, a good rationale is required before adopting a stepped wedge.[28] A survey conducted as part of a feasibility study might provide convincing evidence that recruitment difficulties are likely unless all sites can be offered the intervention during the trial.

The SHIFT cluster randomised trial[29] (Appendix 1: Box 8) included embedded feasibility work in the form of semi-structured interviews during the main trial to investigate the feasibility of recruiting and retaining representative general practices in the trial. The feasibility work identified several factors that were important in recruiting and retaining practices.

3.6. Domain 6: Organisation

A more pragmatic trial design would aim to use no more resources, provider expertise, or organisational structure than those readily available in usual practice. Explanatory trials often take place in research centres, whereas pragmatic trials often involve a broader range of centres, some of which may lack research expertise. Thus, it is important to investigate organisational challenges in advance of a pragmatic trial. A feasibility study may also be useful to determine what additional resources or training is needed for staff to participate in a trial (e.g. research ethics training, methods of handling and reporting adverse events).

The QUEST study[30] (Appendix 1: Box 9) included a pilot trial in which investigators recruited from three different sites to test feasibility and ensure they had experience with trying to set up the trial in sites with different characteristics. The Dodds study[31] (Appendix 1: Box 10) was a pilot study that encountered a major issue necessitating a change in the organisation required to deliver the large trial.

3.7. Domain 7: Flexibility of Intervention delivery

Pragmatic trials might allow the delivery to vary according to the needs of the different sites by not preventing or restricting access to other available treatments, and not closely monitoring adherence to the protocol. However, it is important to define the intervention clearly, with attention to the elements that are required and the elements that are optional or may be administered flexibly. If staff need training, then the training would be considered part of the intervention in a pragmatic trial. A feasibility study may assess whether the core part of the intervention can be delivered as intended and determine the degree of flexibility required to allow delivery without additional support, or to avoid disruption to usual care. The feasibility study may also aim to determine the extent to which being part of a trial may result in staff delivering the intervention differently than the way they would deliver it as part of usual care: if delivery in the trial deviates from how it would be done in usual care, the large trial may need to put additional procedures in place to ensure less research intrusion into care delivery.

In the STOP CRC pilot study[32] (Appendix 1: Box 4), existing clinic staff could choose which intervention components they would deliver. The feasibility study estimated the extent to which staff delivered different components of the intervention sufficiently well.

3.8.Domain 8: Flexibility of adherence

Fidelity violations are not necessarily a threat to the validity of a pragmatic trial in the same way that they are in an explanatory trial; we do not want to enforce adherence more than would be the case in usual care, but there still needs to be a certain level of adherence for the intervention to be evaluated and plausibly achieve a difference that would affect decision-making. Certain core components of the intervention may require higher degrees of implementation fidelity, as discussed in domains 1 and 7. A feasibility study may aim to determine whether this minimum level of adherence is possible in the large trial. The required minimum level of adherence needs to be set according to the specific question and context. The estimated level of adherence from the feasibility study can also usefully inform sample size calculation for the future trial as lower levels of adherence may lead to an attenuation of the detectable difference.

In the FLUID trial[21] (Appendix 1: Box 3) physicians could deviate from the allocated intervention for individual patients in their care. Investigators measured hospital adherence to the allocated study fluid, with a target of > 80% for the trial to be worthwhile. The TIME trial[33] (Appendix 1: Box 11) is an example of a pragmatic trial in which recruitment was terminated because of insufficient separation in dialysis session duration (the intervention) between the trial arms. This was because providers could deviate from the protocol. A pilot trial could have been useful to identify whether a minimum level of adherence was possible, before launching into the main trial.

3.9. Domain 9: Follow-up

In explanatory trials, participants are often followed up intensively, through more frequent and longer visits. In principle, the most pragmatic approach to follow-up would be to not

obtain follow-up data directly from participants but to use, for example, electronic medical records instead. However, a defining feature of pragmatic trials is that the results should be useful to decision-makers. Outcome selection (choosing the right outcome) is therefore even more important than outcome source. Where an appropriate outcome to inform decision-making is not available routinely, pragmatic trials need to collect data directly from participants but in a way that does not interfere too much with routine clinical practice. A feasibility study can test the planned procedures for either routinely collected data or participant data collection in a non-intrusive manner. McCord et al. discuss the potential barriers and challenges that routinely collected data present for randomised trials.[34] During a feasibility study, a check of routinely collected data could be made for completeness and validity. Alternatively, participants could be asked to complete questionnaires and completeness of responses and length of time needed to complete the questionnaires can be assessed. Feasibility of less intrusive data collection methods such as text messaging can also be tested.

The FEMuR study[35] (Appendix 1: Box 12) aimed to test methods for obtaining routinely collected data on health service use, evaluate data quality, and compare the routinely collected data with patient-completed data. The PREDOVE study[36] (Appendix 1: Box 13) assessed the feasibility and acceptability of administering various repeat questionnaires to the sample of women; questionnaire completion rates were found to be low and a decision was made to obtain outcomes from routinely collected sources instead.

3.10. Domain 10: Primary outcome

In a pragmatic trial, the chosen outcome should directly inform decision-making and be measured as it would be measured in usual care. More than one candidate primary outcome

may be of interest since clinical decisions are often made based on a variety of considerations including effectiveness, side-effects, and costs. Different stakeholders may have different perspectives about the outcome on which to base their decision. Furthermore, clinical and patient-reported outcomes may have different sample size requirements. Feasibility studies can be used to engage with stakeholders to inform the final choice of primary outcome(s) and to generate estimates that are useful to inform the final sample size. Stakeholder opinion on the choice of primary outcome will need to be balanced with the requirement that the outcome can be both accurately and feasibly collected (see domain 9).

The aim of the PROBE Project[37] (Appendix 1: Box 14) was to develop a questionnaire with outcomes that were important to patients living with haemophilia, and then perform a feasibility study of implementing the questionnaire. Patient representatives provided extensive input in the identification and measurement of key patient-reported outcomes.

4. DISCUSSION

We identified ten domains relevant to pragmatic trials that researchers can consider in designing feasibility studies. As a first step, we recommend that trialists think about whether their future trial aims to answer a pragmatic or explanatory question. Unless a trial with pragmatic intention is deliberately designed to support applicability to usual care, it may not succeed in its goal of informing a clinical decision. Completing a PRECIS-2 wheel or table after a pilot trial can be useful in identifying domains in which pragmatic elements can be further improved in the future trial. We note that the example studies discussed here were selected specifically because they had feasibility objectives reflecting pragmatic goals in a future planned study. These studies may not necessarily be pragmatic in all possible respects; however, few trials are pragmatic in all domains. Even when a trial is not explicitly labelled

as pragmatic, it may well have pragmatic elements and so the issues raised here for feasibility studies should be a consideration for many or most trialists.

We added the domain of research ethics as a potential area of uncertainty, recognising that the ethics of pragmatic trials is an area in need of further development.[38] There are currently no explicit guidelines for the ethical conduct of pragmatic trials and different research ethics committees may vary in their assessments about the appropriateness of the planned ethical approach. Informed consent has implications for both internal and external validity of the trial and may be seen to be at odds with the pragmatic ideal. Although some believe that low risk pragmatic trials should be permitted with waivers of consent,[39] others believe that alterations such as integrated consent are more appropriate.[40] Empirical reviews indicate that the majority of pragmatic trials do obtain participant informed consent although there is limited evidence about the use of alterations of consent.[41,42] Differential identification and recruitment of participants is a particular challenge in cluster randomised trials in which participants may need to be recruited after randomisation, and blinding is difficult or impossible.[43] Rather than adopt a waiver of informed consent, investigators may choose to implement alterations to streamline recruitment and engage with patients, ethicists, research ethics committees and other relevant stakeholders to refine procedures during the feasibility stages of their research.

Some of our proposed domains have similarities with the criteria proposed by the Readiness Assessment for Pragmatic Trials (RAPT) model which can be used to assess when a health systems intervention is ready for implementation in an embedded pragmatic trial.[44] The RAPT model identifies nine domains in which a non-pharmacological intervention of interest can be scored from low to high readiness. Interventions with high degrees of readiness are

those that have previously been demonstrated to be efficacious and have well-documented protocols, have risks known to be minimal, can be implemented within existing health system resources, rely only on outcomes that are already routinely captured, are cost-effective, are acceptable to providers and staff, align with stakeholder priorities, and are likely to inform clinical care or policy. While some of the criteria in the RAPT model are associated with more pragmatic trials, they are not required features of pragmatic trials. Our focus here is on domains of potential uncertainty relevant to any planned trial with pragmatic intention or with one or more pragmatic elements.

This conceptual paper has provided domains of uncertainty relevant to pragmatic trials and examples of questions that researchers might ask. By considering specific areas of uncertainty due to the pragmatic elements in a future trial, as we have done here, researchers should be able to design feasibility studies that better inform their future trial. Finally, we believe that pre-registration of a pilot trial with clearly specified primary and secondary feasibility objectives and progression criteria can lower the risk of studies inappropriately moving on to a larger trial.

AUTHOR CONTRIBUTIONS:

CLC: Methodology, Writing-Original Draft. MT: Conceptualization, Methodology, Writing – Original Draft. GAL: Methodology, Writing – Review & Editing. JCB: Methodology, Writing – Review & Editing. SML: Methodology, Supervision, Writing – Review & Editing.

ACKNOWLEDGEMENTS:

We are grateful to Jeremy Grimshaw who contributed to the conception of the idea for this project and contributed to preliminary group discussions amongst the authors.

FUNDING:

This work was supported by the Canadian Institutes of Health Research through the Project Grant competition (competitive, peer-reviewed), award number PJT-153045; and by the National Institute of Aging (NIA) of the National Institutes of Health under Award Number U54AG063546, which funds NIA Imbedded Pragmatic Alzheimer's Disease and AD-Related Dementias Clinical Trials Collaboratory (NIA IMPACT Collaboratory). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Claire Chan was partially funded by Sandra Eldridge's National Institute for Health Research (NIHR) Senior Investigator Award. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The funder played no role in the study.

COMPETING INTERESTS:

The authors declare that they have no competing interests.

Table 1: Main features of explanatory versus pragmatic trials within ten domains of potential areas of uncertainty for pilot or feasibility studies

Domain	Highly pragmatic approach	Highly explanatory approach
Intervention development	Develop an intervention that, if shown to be effective, would be ready and acceptable for implementation in usual care	Develop an intervention that exerts its effects through a postulated causal pathway with less consideration to its complexity and acceptability in clinical practice
Research Ethics	Adopt waived or altered forms of consent to minimise additional burden over usual care procedures	Adopt traditional full informed consent procedures
Eligibility	Include participants in the trial that are similar to those who would receive the intervention if it were part of usual care	Include a subsample of the target population more likely to show a beneficial effect
Recruitment	Recruit participants with no more effort than would be used in usual care to engage with patients	Recruit participants using more intensive recruitment strategies set up for research purposes
Setting	Include a range of centres and settings similar to where the results are intended to apply	Perform the trial in a setting with conditions intended to maximise the potential of demonstrating efficacy
Organisation	Use no more resources, provider expertise, or organisational structure than those available in usual practice	Employ specialised resources, such as trained professionals to deliver the intervention
Flexibility of delivery	Deliver the intervention with the same flexibility that is anticipated in usual care, often leaving the details of how to implement the intervention up to the providers	Ensure providers comply with a highly standardised protocol for delivery of the intervention
Flexibility of adherence	Allow participants to engage with the intervention with the same variability that is anticipated in usual care, monitoring and encouraging adherence no more than would take place in usual care	Put measures in place to ensure participants adhere to the intervention as much as possible
Follow-up	Data collection and follow-up guided by usual care practices	Follow participants intensively, through more frequent and longer visits
Primary outcome	Select a primary outcome that is directly relevant to participants	Select a primary outcome on which the intervention is expected to have a direct effect

Table 2: Example of areas of uncertainty for pragmatic trials that might be addressed in pilot or feasibility studies

Design element	Feasibility questions for a pragmatic approach	Examples
Intervention development	Would the potential intervention, if shown to be effective, be acceptable to stakeholders and used in clinical practice?	ADNAT (Box 1)* Project ACE (Box 2)
Research ethics	Is the ethical approach acceptable to stakeholders and is the research ethics approval process feasible?	FLUID (Box 3)
Participant identification and eligibility	Does the proposed method of identifying participants correctly identify eligible participants?	STOP CRC (Box 4)
Recruitment of individuals	Can we successfully recruit participants that resemble the population that would be likely to receive the intervention if rolled out beyond a trial?	HOCKEY FIT (Box 5) DIAMOND (Box 6) oTTer (Box 7)
Setting (recruitment of sites)	Can we successfully recruit a variety of centres that resemble settings where the intervention would be used if implemented outside the trial? Is it feasible to recruit participants in such settings?	SHIFT (Box 8)
Organisation	What feasibility challenges arise from implementing the trial using no more resources than those readily available?	QUEST (Box 9) Dodds (Box 10)
Flexibility of delivery	Are staff willing and able to deliver the intervention without additional training or support? Does being part of the trial result in staff delivering the intervention differently than the way they would deliver it as part of usual care?	STOP CRC (Box 4)
Flexibility of adherence	Is some minimum level of adherence possible such that the intervention can plausibly achieve a difference that would affect decision making?	FLUID (Box 3) TIME (Box 11)
Follow-up	Is it possible to obtain data for outcome assessment, without participant follow-up? Is it possible to collect data without imposing additional burden on participants?	FEMuR (Box 12) PREDOVE (Box 13)
Primary outcome	What is an appropriate outcome(s) that would be important to patients and decision-makers?	PROBE (Box 14)

*Boxes are detailed in the appendix.

APPENDIX 1: Example studies

REFERENCES

[1] Eldridge, S.M., et al., Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. *PLoS One*, 2016. **11**(3): p. e0150205

[2] Eldridge, S.M., et al., CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ*, 2016. **355**

[3] Patsopoulos, N.A., A pragmatic view on pragmatic trials. *Dialogues Clin Neurosci*, 2011. **13**(2): p. 217-24.

[4] Schwartz, D. and J. Lellouch, Explanatory and pragmatic attitudes in therapeutical trials. *J Chronic Dis*, 1967. **20**(8): p. 637-48.

[5] Roland, M. and D.J. Torgerson, Understanding controlled trials: What are pragmatic trials? *BMJ*, 1998. **316**(7127): p. 285

[6] Treweek, S. and M. Zwarenstein, Making trials matter: pragmatic and explanatory trials and the problem of applicability. *Trials*, 2009. **10**(1): p. 37.

[7] Thabane, L., et al., A tutorial on pilot studies: the what, why and how. *BMC Medical Research Methodology*, 2010. **10**: p. 1.

[8] Arnold, D.M., et al., The design and interpretation of pilot trials in clinical research in critical care. *Critical care medicine*, 2009. **37**(1): p. S69-S74

[9] Arain, M., et al., What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Medical Research Methodology*, 2010. **10**(1): p. 67

[10] Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract*. 2004 May;10(2):307-12. doi: 10.1111/j..2002.384.doc.x. PMID: 15189396.

[11] Loudon, K., et al., The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ : British Medical Journal*, 2015. **350**

[12] Nicholls, S.G., Carroll, K., Zwarenstein, M. *et al.* The ethical challenges raised in the design and conduct of pragmatic trials: an interview study with key stakeholders. *Trials* **20,** 765 (2019). https://doi.org/10.1186/s13063-019-3899-x

[13] Hung A., B.C., Bekelman J., Fitz-Randolph M., Daniel Mullins C., Patient and Stakeholder Engagement in Designing Pragmatic Clinical Trials. In: Birnbaum H., Greenberg P. (eds) Decision Making in a World of Comparative Effectiveness Research. 2017, Singapore: Adis

[14] Keith, R.E., Crosson, J.C., O'Malley, A.S. *et al.* Using the Consolidated Framework for Implementation Research (CFIR) to produce actionable findings: a rapid-cycle evaluation approach to improving implementation. *Implementation Sci* **12,** 15 (2017).

[15] Atkins, L., Francis, J., Islam, R. *et al.* A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. *Implementation Sci* **12,** 77 (2017). https://doi.org/10.1186/s13012-017-0605-9

[16] Cooper, H., et al., A mixed methods study to evaluate the feasibility of using the Adolescent Diabetes Needs Assessment Tool App in paediatric diabetes care in preparation for a longitudinal cohort study. *Pilot and Feasibility Studies*, 2017. **4**(1): p. 13.

[17] Fiallo-Scharer, R., et al., Design and baseline data from a PCORI-funded randomized controlled trial of family-centered tailoring of diabetes self-management resources. *Contemp Clin Trials*, 2017. 58: p. 58-65

[18] McKinney Jr, R.E., et al., Use of altered informed consent in pragmatic clinical research. *Clinical Trials*, 2015. **12**(5): p. 494-502.

[19] Hemming K, Haines T P, Chilton P J, Girling A J, Lilford R J. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting *BMJ* 2015; 350 :h391 doi:10.1136/bmj.h391

[20] Hemming K, Taljaard M, Weijer C, Forbes AB. Use of multiple period, cluster randomised, crossover trial designs for comparative effectiveness research. BMJ 2020; 371:m3800

[21] McIntyre, L., et al., FLUID trial: a protocol for a hospital-wide open-label cluster crossover pragmatic comparative effectiveness randomised pilot trial. *BMJ Open*, 2018. **8**(8): p. e022780

[22] Coronado, G.D., et al., Strategies and opportunities to STOP colon cancer in priority populations: pragmatic pilot study design and outcomes. *BMC Cancer*, 2014. **14**(1): p. 55

[23] Treweek, S., Banister, K., Bower, P. *et al.* Developing the INCLUDE Ethnicity Framework—a tool to help trialists design trials that better reflect the communities they serve. *Trials* **22,** 337 (2021). https://doi.org/10.1186/s13063-021-05276-8

[24] Brehaut JC, Carroll K, Presseau J, Richards DP, Gordon J, Bénard A, Hudek N, Graham ID, Fergusson DA, Marlin S. A patient-focused, theory-guided approach to survey design identified barriers to and drivers of clinical trial participation. *J Clin Epidemiol*. 2021 Apr;132:106-115. doi: 10.1016/j.jclinepi.2020.12.013. Epub 2020 Dec 15. PMID: 33338563.

[25] Petrella, R.J., et al., Hockey Fans in Training: A Pilot Pragmatic Randomized Controlled Trial. *Medicine & Science in Sports & Exercise*, 2017. **49**(12): p. 2506-2516

[26] Hamilton, F.L., et al., DIAMOND (DIgital Alcohol Management ON Demand): a mixed methods feasibility RCT and embedded process evaluation of a digital health intervention to reduce hazardous and harmful alcohol use. *Pilot and Feasibility Studies*, 2017. 3(1): p. 34

[27] Bowyer-Crane, C., et al., 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. *Pilot and Feasibility Studies*, 2019. **5**(1): p. 119

[28] Karla Hemming, Monica Taljaard, Reflection on modern methods: when is a stepped-wedge cluster randomized trial a good study design choice?, *International Journal of Epidemiology*, Volume 49, Issue 3, June 2020, Pages 1043–1052

[29] Dormandy, E., et al., Maximising recruitment and retention of general practices in clinical trials: a case study. *Br J Gen Pract*, 2008. **58**(556): p. 759-766

[30] Killaspy, H., et al., Feasibility Randomised trial comparing two forms of mental health supported accommodation (supported housing and floating outreach); a component of the QuEST (Quality and Effectiveness of Supported Tenancies) study. *Frontiers in psychiatry*, 2019. **10**.

[31] Dodds, C.M. and M.T. Britto, Learnings from a pragmatic pilot trial of text messaging for high risk adolescents with asthma. *Ann Allergy Asthma Immunol*, 2018

[32] Coronado, G.D., et al., Strategies and opportunities to STOP colon cancer in priority populations: pragmatic pilot study design and outcomes. *BMC Cancer*, 2014. **14**(1): p. 55

[33] Dember LM, Lacson E, Brunelli SM, Hsu JY, Cheung AK, Daugirdas JT, Greene T, Kovesdy CP, Miskulin DC, Thadhani RI, Winkelmayer WC, Ellenberg SS, Cifelli D, Madigan R, Young A, Angeletti M, Wingard RL, Kahn C, Nissenson AR, Maddux FW, Abbott KC, Landis JR. JASN May 2019, 30 (5) 890-903; **DOI:** 10.1681/ASN.2018090945

[34] Mc Cord, K.A., et al., Routinely collected data for randomized trials: promises, barriers, and implications. *Trials*, 2018. **19**(1): p. 29.

[35] Williams, N.H., et al., Hip fracture in the elderly multidisciplinary rehabilitation (FEMuR) feasibility study: testing the use of routinely collected data for future health economic evaluations. *Pilot and Feasibility Studies*, 2018. **4**(1): p. 76

[36] Feder, G., et al. Prevention of domestic violence (PreDoVe). 2005 [cited 2019 22 Jan]; Available from: http://webspace.qmul.ac.uk/spriebe/publications/pub%20by%20year/2005/2005%20-%20Preventon%20of%20domestic%20violence%20(PreDoVe)%20-%20Report%20to%20the%20Nuffield%20Foundation.pdf

[37] Skinner, M., et al., The Patient Reported Outcomes, Burdens and Experiences (PROBE) Project: development and evaluation of a questionnaire assessing patient reported outcomes in people with haemophilia. *Pilot and Feasibility Studies*, 2018. **4**(1): p. 58.

[38] Taljaard, M., Weijer, C., Grimshaw, J.M. *et al.* Developing a framework for the ethical design and conduct of pragmatic trials in healthcare: a mixed methods research protocol. *Trials* **19,** 525 (2018). https://doi.org/10.1186/s13063-018-2895-x

[39] Dal-Ré R, Avendaño-Solà C, Bloechl-Daum B, de Boer A, Eriksson S, Fuhr U et al. Low risk pragmatic trials do not always require participants' informed consent. BMJ 2019; 364 :l1092

[40] Kim SY, Miller FG. Informed consent for pragmatic trials--the integrated consent model. *N Engl J Med*. 2014 Feb 20;370(8):769-72. doi: 10.1056/NEJMhle1312508. PMID: 24552326.

[41] Lin LY, Jochym N, Merz JF. Refusal rates and waivers of informed consent in pragmatic and comparative effectiveness RCTs: A systematic review. *Contemp Clin Trials*. 2021 Mar 15;104:106361. doi: 10.1016/j.cct.2021.106361. Epub ahead of print. PMID: 33737197.

[42] Zhang JZ, Nicholls SG, Carroll K, Nix HP, Goldstein CE, Hey SP, Brehaut JC, McLean PC, Weijer C, Fergusson DA, Taljaard M. Informed consent in pragmatic trials: Results from a survey of trials published 2014-2019". Under review.

[43] Eldridge S, Kerry S, Torgerson DJ. Bias in identifying and recruiting participants in cluster randomised trials: what can be done? BMJ. 2009 Oct 9;339:b4006. doi: 10.1136/bmj.b4006. PMID: 19819928.

[44] Baier, R.R., Jutkowitz, E., Mitchell, S.L. *et al.* Readiness assessment for pragmatic trials (RAPT): a model to assess the readiness of an intervention for testing in a pragmatic trial. *BMC Med Res Methodol* **19,** 156 (2019).