Pilot and feasibility studies for pragmatic cluster randomised trials

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Housekeeping

• All participants will be muted

• Enter **all questions** in the Zoom Q&A or **chat box** and send to All Panelists and Attendees

• Moderator will review questions from chat box and ask them at the end

• Want to continue the discussion? Look for the associated podcast released about 2 weeks after Grand Rounds.

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Outline

• What are pilot and feasibility studies?
• How to design a pilot or feasibility study
• Special considerations for pragmatic trials
• Special considerations for cluster randomised trials
• Closing remarks
What are pilot and feasibility studies?
Use of terms

• Large and growing number of studies in the literature described as feasibility or pilot studies

• Terms pilot and feasibility (and other terms e.g. exploratory, preliminary, small…) used inconsistently

• Development of a framework
Methods

• Delphi survey
• Open meeting at a trial methodology conference
• Review of existing definitions
• International consensus meeting with experts
• Review of empirical pilot and feasibility studies
Definitions

• Feasibility studies are studies that ask whether something can be done, whether we should proceed with it — and if so, how.

• Pilot studies ask the same question but have a specific design feature: in a pilot study, a future study or part of a future study is conducted on a smaller scale.
Conceptual framework
How to design a pilot or feasibility study
Form the objectives

- What are the areas of uncertainty about feasibility?
- Form objectives
- Methods, results, conclusions all to match the objectives
Example objectives

• To investigate whether the relevant population will agree to take part in a potential randomised study

• To test the feasibility of the randomisation procedure

• To test the data collection

• To confirm whether the proposed intervention is acceptable to all stakeholders

Note that the objective of a pilot or feasibility study should **NOT** be to assess effectiveness
Choosing the study design

• Design should be appropriate to answer the objectives
• Is the proposed intervention acceptable? > Qualitative approach?
• Can you collect the data? > Non-randomised intervention study?
• Can you recruit and randomise patients? > Randomised pilot study?
Sample size rationale

- Sample size should be appropriate to answer the primary feasibility objective

- E.g. Primary objective to estimate recruitment rate > Calculate number of participants to estimate rate to certain degree of accuracy

- Sometimes no calculation is needed and the sample size rationale may be based on logistics, resources, and/or time.

- Should never perform a formal sample size calculation to determine effectiveness as this is not the aim of a pilot
Advice from the literature

• Browne (1995) - a minimum of 30 patients to estimate a parameter
• Julious (2005) - 12 per group as a rule of thumb
• Stallard (2012) - approx. 3% of sample size planned for main study
• Sim and Lewis (2012) - 50+ per group based on upper CI of variance estimate
• Cocks and Torgerson (2013) - 9% of sample size of main planned study
• Teare et al (2014) - 35 /group to estimate SD or 60-100 /group for event rate
• Whitehead et al (2015) - rules of thumb depending on standardised effect size
Progression criteria

• Making a decision about whether to proceed with the next stage

- Below a certain figure > Don’t proceed
- Below a certain figure > Perhaps proceed with changes
- Below a certain figure > Do proceed
## Example traffic light progression criteria

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Green</th>
<th>Amber</th>
<th>Red</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant recruitment</td>
<td>Inclusion rate of one participant per general practitioner or</td>
<td>(n &lt; 6 after first month). If recruitment rate falls behind, screening</td>
<td>No recruitment after 2 months</td>
</tr>
<tr>
<td></td>
<td>physiotherapist every month (approximately n = 6-9/month)</td>
<td>logs and reasons for exclusion will be explored after the first month</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>to adjust eligibility criteria.</td>
<td></td>
</tr>
<tr>
<td>Completion of the outcome measures</td>
<td>Mean &lt; 120 min to complete all objective outcome measures, and that</td>
<td>Between 121 and 150 min. or only 50–66% of participants found the</td>
<td>&gt; 150 min or &lt; 50% of participants</td>
</tr>
<tr>
<td></td>
<td>at least 67% of participants found the duration acceptable.</td>
<td>duration acceptable.</td>
<td>found the duration acceptable</td>
</tr>
<tr>
<td>Participant retention</td>
<td>10 or more participants show up at 16-week follow up</td>
<td>Only 6–9 participants show up at 16-week follow up.</td>
<td>Below 6 participants show up at</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16-week follow up.</td>
</tr>
<tr>
<td>Adherence to exercise intervention</td>
<td>Minimum 75% of participants adhering to at least 75% of exercise</td>
<td>Only 50–75% of participants adhering to 50–75% of exercise sessions.</td>
<td>&lt; 50% of participants adhering to</td>
</tr>
<tr>
<td></td>
<td>sessions.</td>
<td></td>
<td>&lt; 50% of exercise sessions</td>
</tr>
<tr>
<td>Adverse events</td>
<td>No or minor adverse events with no participants discontinuing the</td>
<td>Minor or serious adverse events leading to 2 or less participants</td>
<td>Serious adverse events leading to</td>
</tr>
<tr>
<td></td>
<td>study</td>
<td>discontinuing the study</td>
<td>&gt; 2 participants discontinuing the</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>study</td>
</tr>
</tbody>
</table>

Analysis

• **No hypothesis tests** related to effectiveness estimates

• Lancaster et al 2004 recommend the analysis should be mainly descriptive and should focus on confidence intervals

• Methods should be specified for how each of the pilot or feasibility study objectives will be addressed, and this can be qualitative or quantitative

• Investigate missing data and understand why they are missing and what can be done to prevent missing data in the future study
CONSORT Extension for pilot trials

- The recently published CONSORT extension for pilot trials can be used for designing and planning a pilot trial, not just reporting.

- Checklist applies to randomised trials conducted in preparation for a future definitive trial of effectiveness or efficacy where the primary aim is feasibility of the future definitive trial.
Special considerations for pragmatic trials
Pragmatic clinical trials

• Aimed at choosing between routine care options
• Interested in the benefit of the treatment in ‘routine clinical practice’ or ‘as it would be implemented outside a trial setting’
Why are there special considerations for pilot and feasibility studies for pragmatic trials?

• Pilot and feasibility studies often focus on how to achieve high treatment fidelity, adherence and compliance

• Pragmatic trials are intended to inform effectiveness of interventions in conditions of potentially imperfect treatment fidelity, adherence and compliance

• While some areas of uncertainty may be common across explanatory and pragmatic trials, in general objectives of a pilot or feasibility study for a pragmatic trial ought to differ
Publication coming soon…

• Claire L Chan*, Monica Taljaard*, Gillian A Lancaster, Jamie C Brehaut, Sandra M Eldridge. Pilot and feasibility studies for pragmatic trials have unique considerations and areas of uncertainty.
Methods

• We adopted PRECIS-2 as a convenient initial framework for considering the nature of pilot and feasibility studies conducted in advance of pragmatic trials.

• The pragmatic-explanatory continuum indicator summary (PRECIS-2) can be used to assess the pragmatic/explanatory nature of trials.

Kirsty Loudon et al. BMJ 2015;350:bmj.h2147
Results

• We omitted the primary analysis domain of PRECIS-2 and selected eight of the original nine PRECIS-2 domains

• We also identified two additional domains relevant to feasibility or pilot studies for pragmatic trials
Ten domains of potential areas of uncertainty for pilot or feasibility studies

1. Intervention development
2. Research Ethics
3. Eligibility
4. Recruitment
5. Setting
6. Organisation
7. Flexibility of delivery
8. Flexibility of adherence
9. Follow-up
10. Primary outcome
Ten domains of potential areas of uncertainty for pilot or feasibility studies

1. Intervention development
2. Research Ethics
3. Eligibility
4. Recruitment
5. Setting
6. Organisation
7. Flexibility of delivery
8. Flexibility of adherence
9. Follow-up
10. Primary outcome
Domain 1: Intervention development

<table>
<thead>
<tr>
<th>Domain</th>
<th>Highly pragmatic approach</th>
<th>Highly explanatory approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention development</td>
<td>Develop an intervention that, if shown to be effective, would be ready and acceptable for implementation in usual care</td>
<td>Develop an intervention that exerts its effects through a postulated causal pathway with less consideration to its complexity and acceptability in clinical practice</td>
</tr>
</tbody>
</table>

- Would the potential intervention, if shown to be effective, be acceptable to stakeholders and used in clinical practice?
## Domain 2: Research ethics

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</thead>
<tbody>
<tr>
<td>Research Ethics</td>
<td>Adopt waived or altered forms of consent to minimize additional burden over usual care procedures</td>
<td>Adopt traditional full informed consent procedures</td>
</tr>
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</table>

- Is the research ethics approval process feasible?
Domain 3: Eligibility

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<tr>
<td>Eligibility</td>
<td>Include participants in the trial that are similar to those who would receive the intervention if it were part of usual care</td>
<td>Include a subsample of the target population more likely to show a beneficial effect</td>
</tr>
</tbody>
</table>

- Does the proposed method of identifying participants correctly identify eligible participants?
## Domain 4: Recruitment (of individuals)

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>Recruit participants with no more effort than would be used in usual care to engage with patients</td>
<td>Recruit participants using more intensive recruitment strategies set up for research purposes</td>
</tr>
</tbody>
</table>

• Can we successfully recruit participants that resemble the population that would be likely to receive the intervention if rolled out beyond a trial?
### Domain 5: Setting (recruitment of sites)

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Setting</td>
<td>Include a range of sites and settings similar to where the results are intended to apply</td>
<td>Perform the trial in a setting with conditions intended to maximize the potential of demonstrating efficacy</td>
</tr>
</tbody>
</table>

- Can we successfully recruit a variety of sites that resemble settings where the intervention would be used if implemented outside the trial?

- Is it feasible to recruit participants in such settings?
### Domain 6: Organisation

<table>
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<tr>
<th>Domain</th>
<th>Highly pragmatic approach</th>
<th>Highly explanatory approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organisation</td>
<td>Use no more resources, provider expertise, or organizational structure than those available in usual practice</td>
<td>Employ specialized resources, such as trained professionals to deliver the intervention</td>
</tr>
</tbody>
</table>

- What feasibility challenges arise from implementing the trial using no more resources than those readily available?
## Domain 7: Flexibility of delivery

<table>
<thead>
<tr>
<th>Domain</th>
<th>Highly pragmatic approach</th>
<th>Highly explanatory approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexibility of delivery</td>
<td>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</td>
<td>Ensure providers comply with a highly standardized protocol for delivery of the intervention</td>
</tr>
</tbody>
</table>

- 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?
 Domain 8: Flexibility of adherence

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Flexibility of adherence</td>
<td>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 be in usual care</td>
<td>Put measures in place to ensure participants adhere to the intervention as much as possible</td>
</tr>
</tbody>
</table>

- Is some minimum level of adherence possible such that the intervention can plausibly achieve a difference that would affect decision making?
Domain 9: Follow-up

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<th>Highly explanatory approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>Data collection and follow-up guided by usual care practices</td>
<td>Follow participants intensively, through more frequent and longer visits</td>
</tr>
</tbody>
</table>

• 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?
### Domain 10: Primary outcome

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<th>Highly pragmatic approach</th>
<th>Highly explanatory approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>Select a primary outcome that is directly relevant to participants</td>
<td>Select a primary outcome on which the intervention is expected to have a direct effect</td>
</tr>
</tbody>
</table>

- What is an appropriate outcome(s) that would be important to patients and decision-makers?
Take home points

• When undertaking pilot and feasibility studies, trialists should think about whether their proposed future trial is pragmatic or has pragmatic elements

• Objectives of a pilot or feasibility study in preparation for a pragmatic trial ought to differ in focus from those of a study in preparation for an explanatory trial

• Pilot/feasibility studies should be deliberately designed to address the pragmatic feasibility objectives
Special considerations for cluster randomised trials
Cluster randomised trials (CRTs)

• Clusters are the unit of randomisation

• Logistical reasons, prevention of contamination, intervention at cluster level

• Useful for evaluating complex interventions

• Added complexity

• Important to ensure carrying out a CRT is feasible before conducting the main trial
Review of pilot CRTs

• Poor reporting of sample size rationale, and how the cluster design affects this

• Poor reporting of progression criteria

• Studies performing hypothesis testing for effectiveness/efficacy
Sample size rationale

• Less than half of the pilot trials gave a rationale for the sample size

• Those that did gave rationales based on logistics, resources, time, a balance of practicalities and need for reasonable precision, a general statement it was considered sufficient to address the objectives of the pilot, formal and non-formal calculation to enable estimation of parameters in the future trial, and a formal calculation based on the primary feasibility outcome
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‘The decision to include eight apartment-sharing communities was based on practical feasibility that seemed appropriate according to funding and the personal resources available’

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‘two clusters per randomised treatment and the number of participants per cluster was based on the...df needed within each cluster to have reasonable precision to estimate a variance’

Progression criteria

• Less than 20% reported criteria to judge whether or how to proceed with the future definitive trial

• Those that did gave numbers that must be exceeded such as recruitment, retention, attendance and data collection percentages, and one gave categories of ‘definitely feasible’, ‘possibly feasible’ and ‘not feasible’

‘...definitely feasible, possibly feasible, or not feasible if the difference in the proportion of at risk patients receiving appropriate prophylaxis in the intervention hospitals versus the usual care hospitals was >25%, 10–25%, and <10% respectively’

Hypothesis testing

- Half the pilot trials incorrectly performed formal hypothesis testing for effectiveness
- Investigators wanting to assess effectiveness and use statistical tests to do so should be performing a properly powered main trial
- One may look at potential effectiveness as a secondary outcome, with a caveat about the lack of power
- Any interpretation of potential effect should be done by looking at the limits of the CI and one should also pay attention to features of the pilot which might have biased the result
Closing remarks
About

Aims and scope

_Pilot and Feasibility Studies_ encompasses all aspects of the design, conduct and reporting of pilot and feasibility studies in biomedicine. The journal publishes research articles that are intended to directly influence future clinical trials or large scale observational studies, as well as protocols, commentaries and methodology articles. The journal also ensures that the results of all well-conducted, peer-reviewed, pilot and feasibility studies are published, regardless of outcome or significance of findings.

Pilot and feasibility studies are increasingly conducted prior to a full randomized controlled trial. However, these studies often lack clear objectives, many remain unpublished, and there is confusion over the meanings of the words “pilot” and “feasibility”. _Pilot and Feasibility Studies_ provides a forum for discussion around this key aspect of the scientific process, and seeks to ensure that these studies are published, so as to complete the publication thread for clinical
This website is designed to support those conducting pilot and feasibility studies using randomised and non-randomised designs and those carrying out methodological research on these types of studies.
New website – cluster randomised trials

www.clusterrandomisedtrials.qmul.ac.uk

This website is designed to support those conducting cluster randomised trials and stepped wedge designs and those carrying out methodological research on these designs.
Thank you for listening
Questions?
References


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


Example pilot and feasibility studies for pragmatic trials
Example 1 – ADNAT

• **Objective:**
Determine feasibility of integrating the ADNAT App into UK paediatric diabetes care, and determine how staff perceive use of ADNAT

• **Design:**
Cohort mixed methods feasibility study

• **Findings:**
ADNAT was acceptable to staff, but lead clinician support would be essential. A CRT design with sequential but random rollout of ADNAT over multiple time periods would be more appropriate
Example 2 – FLUID

• Objectives:
  1) To determine whether having a waiver of consent results in delays to research ethics board approval at different sites
  2) To determine whether a minimum adherence of 80% to the study protocol is achievable

• Design:
Cluster crossover randomised pilot trial

• Findings:
Ongoing
Example 3 – Dodds

• **Objective:**
To identify potential issues in a research trial with low-income, publicly insured, minority adolescents using multiple technologies that, without proper execution, could reduce the effectiveness of the intervention and the accuracy of the method by which the intervention was measured

• **Design:**
Randomised pilot study
Example 4 – PreDOVE

• Objective:
  Assess the feasibility and acceptability of administering baseline questionnaires, administering repeat questionnaires over a 6-month period, and the acceptability of further, long term follow up

• Design:
  Cluster randomised pilot trial