What you need to know about pilot studies: the what, why and how

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A tutorial on pilot studies: the what, why and how

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Objectives

• What a pilot study is and what it is not;
• The reasons for doing pilot studies;
• The challenges of pilot studies;
• Relationships between pilots and proof-of-concept studies and adaptive designs;
• How to evaluate the success of a pilot study (ie how to interpret the results of a pilot study);
• Common misconceptions about pilot studies;
• The ethics of pilot studies; and
• How to review a pilot study proposal or manuscript reporting results of a pilot.
Dictionary Definition

• Pilot (project)
  – Experimental
  – Exploratory
  – Test
  – Preliminary
  – Trial
  – Try out
Synonymous terms

• Feasibility study
• Vangard study
• Dress rehearsal
• Pre-study
Stats/Epi Dictionary Definitions

• **A small-scale test of the methods and procedures to be used on a larger scale** if the pilot study demonstrates that the methods and procedures can work
  

• **Small-scale investigation designed to test the feasibility of methods and procedures** for later use on a large scale or **to search for possible effects and associations** that may be worth following up in a subsequent larger study

Definitions of Pilot studies on the web

• A trial study carried out before a research design is finalised in order to assist in defining the research question or to test the feasibility, reliability and validity of the proposed study design:
  – www.cirem.org.uk/definitions.html

• A smaller version of a study is carried out before the actual investigation is done. Researchers use information gathered in pilot studies to refine or modify the research methodology for a study and to develop large-scale studies:
  – www.mh.state.oh.us/offices/oper/glossary.html

• A project that is done, to test the basic protocols and design to be used in a research study. It is at this stage that the variables are refined to produce results that are meaningful:

• A small study carried out before a large-scale study in order to try out a procedure or to test a principle:
African Proverb (Ashanti, Ghana)

You never test the depth of a river with both feet
Feasibility Studies and Cartoons

Yoga feasibility studies
Different types of “Pre”-studies

• Phase I/II trials
• Proof-of-concept studies
• Pilot studies
  – Qualitative
  – Quantitative
• Internal pilot studies
The Focus

• Pilot studies for phase III studies
  – comparing two or more drugs or intervention strategies to assess efficacy and safety
Fig 1 Key elements of the development and evaluation process
Reasons for Pilot/Feasibility Studies

- Recruitment and retention problems
- Ambiguous situations
- Time and resource problems
- Machinery problems
- Data management problems
- Assessment of safety, dose and response
Pilot vs Proof-of-concept study

• **Proof-of-concept (POC) study:**
  – to determine if a treatment (drug) is biologically active or inactive

• Usually based on surrogate makers as endpoints

• Usually Phase I/II studies
  – assessing safety, dose levels and response to new drugs

Proof of concept is not necessarily proof of feasibility
Adaptive Trial Designs and Piloting
(Chow C-S, Chang M. Adaptive design methods in clinical trials – a review. *Orphanet J Rare Dis.* 2008; 3: 11)

- **Adaptive trial design:** Modification or change made to
  - trial design or statistical procedures during the conduct of a clinical trial

**Diagram:**
- Active
- PLA (Placebo)

Interim results indicates additional patients required to preserve the power

Usually used in internal pilot studies
Designed to inform sample size calculation for the main study
An Example
Pilot Cluster-randomization Trial

Strategies to *Enhance Venous Thromboprophylaxis in* Hospitalized Medical Patients:
The SENTRY Pilot Trial

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Feasibility Objectives

• To determine adherence rates to the risk assessment model and standardized order form
  – ‘definitely feasible’ if the risk assessment form is completed for ≥70% of eligible patients.
  – ‘possibly feasible’ if the risk assessment form is completed for 50%-69% of eligible patients
  – ‘not feasible’ if the risk assessment form is completed for <50% of eligible patients

• To determine rates of appropriate prophylaxis achieved using the VTE risk assessment and standardized order form
  – ‘definitely feasible’ if there is a >25% relative increase in the proportion of at-risk patients receiving appropriate prophylaxis (defined in the section that follows) in the intervention hospitals versus the usual care hospitals. This represents an increase from the 61% baseline rate of appropriate prophylaxis identified in Phase I to 76.25%.
  – ‘possibly feasible’ if there is a 10-25% relative increase
  – ‘not feasible’ if there is a <10% relative increase

• To explore the attitudes of health care providers towards the intervention
Other Examples

• Assessing the feasibility of implementing an intensive insulin algorithm to achieve 2 different target glucose ranges

• Assessing the feasibility of a large-scale trial
  – COMPETE (Computerization of Medical Practices for the Enhancement of Therapeutic Effectiveness) trial
    • http://www.compete-study.com/index.htm
  – C-CHAP (Community Cardiovascular Health Awareness Program) trial
    • http://www.chapprogram.ca/resources.html
Sample Sizes for Pilot Studies

- Size calculations may not be required for some pilot or exploratory studies

- A pilot study may be used to generate information to be used for sample size calculations

- Consider using feasibility objectives for sample size justification
Example: SENTRY Pilot RCT

Using CI approach to establish “definite feasibility”

- **Primary Feasibility Objective:** To determine adherence rates to the risk assessment model and standardized order form
  - Using a 95% CI with a margin of error (ME) of 0.05, with a lower bound of this CI of 0.70;
    \[
    p \pm 1.96 \sqrt{\frac{p(1-p)}{n}}
    \]
  - Need at least 289 patients in each group
Sample size and Pilot studies

- The sample for a pilot needs to be representative of the target population
  - It should be sufficient to address the key feasibility objectives
  - It should also be based on the same inclusion/exclusion criteria

- *PoC study*: Require sample size estimation based on surrogate markers

- The sample used in the pilot may be carried to the main study
  - Caution is needed to ensure that the key features of the main study are preserved in the pilot (e.g., blinding in RCTs)
  - Increases the efficiency of a study
Criteria for Success

• It is always important to state the criteria for success or feasibility

• Outcome can be
  - Stop - main study not feasible;
  - Continue, but modify protocol - feasible with modifications
  - Continue without modifications - feasible as is
  - Continue without modifications, but monitor closely - feasible with close monitoring

• The criteria should be based on key primary feasibility aims

• Example: PROTECT Pilot Trial
    • 98.5% of patients had to receive study drug within 12 hours of randomization;
    • 91.7% of patients had to receive every scheduled dose of the study drug in a blinded manner;
    • 90% or more of patients had to have lower limb compression ultrasounds performed at the specified times; and
    • > 90% of necessary dose adjustments had to have been made appropriately in response to pre-defined laboratory criteria.
Challenges with Pilot Studies

• Most are not well designed
  – No clear feasibility objectives
  – No clear rationale for piloting
  – No clear analytic plans
  – No clear criteria for success of feasibility

• Most are not reported/published

• It can be dangerous to use pilot studies to estimate treatment effects
  – Estimates may be unrealistic/biased

• If not used cautiously, results of pilot studies can potentially mislead sample size/power calculations
  – Arch Gen Psychiatry 2006;63:484-489.
Common Misconceptions

• A small study that can be completed quickly
  – A small study done by a student/intern

• A small study that does not require any funding
  – I don’t have any funding to do a big study!
  – My boss told me to do it!

• A small study that has limited funding
  – I have funding for only 10 patients!
  – I have limited SEED funding!
Common Misconceptions

• A small single centre study
  – I don’t have the resources for a large multi-centre study!

• A small study that is similar in size as someone else’s published study
  – So-and-so did a similar study with 6 patients and got statistical significance - ours uses 12 patients (double the size)!

• We did a similar pilot before (got it published!)
  – Pilot studies should always be viewed in the context of the main study
Publishing Results of Pilot Studies

- Can I publish the results of a pilot study?
  - Yes, every attempt should be made to publish them

- Why is it important to publish the results of pilot studies?
  - To provide information about feasibility to the research community
  - To save resources (avoid duplication of efforts)
  - We have ethical and scientific obligation to do so
What's happening in practice?

  - Searched EMBASE and MEDLINE for “pilot” or “feasibility” in title, 2000-2009 (limits: human, RCT, English, parallel groups)

The number of studies with the term “pilot” or “feasibility” in the title seems to be increasing with time.
Earlier studies showed major challenges with editorial policies

  - Surveyed 7 journals: BMJ, Lancet, JAMA, NEJM, BJC, BJOG, BJS
  - Searched “pilot” or “feasibility” in title or abstract in 2000--2001
  - 90 unique studies
    - 4/90 specifically stated that the pilot was in preparation for a bigger RCT
  - Contacted the editors of the 7 journals screened
    - 4/7 indicated no publication policy
    - 1/7 indicated the journal did not publish pilot studies

  - Repeated Lancaster et al study for publications in 2007-8
  - 54 unique studies
  - Contacted the editors of the journals screened
    - 4/7 indicated no publication policy...

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- 41 pilot trials published in Circulation since 2004
- For most, editors requested the term ‘pilot’ be added to the title to acknowledge small size and lack of generalizibility
Most pilot studies do not show statistically significant results

“no evidence of effect” is not “evidence of no effect”


The focus in reporting the results of a pilot should be on **feasibility**, **NOT** statistical significance

See CONSORT checklist for reporting
Other Important Issues

• **Can I combine data from a pilot with data from the main study?**
  – Yes, provided the sampling frame is the same and so is the methodology

• **Can I combine the results of a pilot with the results of another study or in a meta-analysis?**
  – Yes, same conditions as above
  – Also depends on whether the main study is reported

• **Can a pilot ever exist on its own?**
  – Yes, if the results show that it is not feasible to go to the main study or there is no funding for the main study

• **Can I apply for funding for a pilot study?**
  – Yes, like any grant it is important to justify the need for piloting
  – The pilot has to be placed in the context of the main study
Other Important Issues

• Can I randomize patients in a pilot study?
  – Yes; to assess how a randomization might work in main study or whether it might be acceptable to patients
  – In general, it is always best for a pilot to maintain the same design as the main study

• Can I use the pilot to estimate the sample size for the main trial?
  – Yes, but be cautious
  – Consider supplementing with qualitative discussions
  – Use SS table to capture prevailing uncertainty

• Can I use the results of pilot study to treat my patients?
  – Not a good idea!
  – Pilot studies are primarily for assessing feasibility

• What can I do with a failed or bad pilot study?
  – No study is a complete failure, it can always be used as bad example!
The Ethics of Pilot Studies: Are pilot studies ethical?

• **Conducting underpowered trials is unethical**
  – According to Halpern et al: Underpowered trials are ethical in only 2 situations:
    • small trials of interventions for rare diseases
    • early-phase trials in the development of drugs or devices

• **Pilot studies of phase III trials (dealing with common diseases) are not addressed**
  – Is it ethical to conduct a study whose feasibility can not be guaranteed?
  – What obligation do we have to patients to disclose the feasibility nature of pilot studies?

• **Is it ethical to run phase III studies without piloting?**
  – No, it’s unethical to run phase III studies without looking into feasibility
The overall purpose of this pilot study is to assess the feasibility of conducting a large study to \[\text{state primary objective of the main study}\]. A feasibility or pilot study is a study that... \[\text{state a general definition of a feasibility study}\]. The specific feasibility objectives of this study are \[\text{state the specific feasibility objectives of the pilot study}\]. We will determine that it is feasible to carry on the main study if \[\text{state the criteria for success of feasibility}\]."
Key Messages

• Provide a good opportunity to assess feasibility of large full-scale phase III studies
  – It can enhance the success probability of the main study

• Pilot studies should be well designed
  – Clear feasibility objectives
  – Clear rationale for piloting - needs to be linked to main study
  – Clear analytic plans
  – Clear criteria for determining success of feasibility

• Pilot studies should be used cautiously for determining
  – Treatment effects
  – Power/sample size calculations

• They should be scrutinized the same way as full scale studies/RCTs
  – Require registration
  – They should also be published/reported in peer-review journals
CONSORT Extension for Pilot Studies—work in progress

✓ A **pilot** study:
  - a version of the main study that is run in miniature to test whether the components of the main study can all work together.

✓ A **feasibility** study
  - Is a piece of research done before a main study in order to answer the question “Can this study be done?”
    - willingness of participants to be randomised;
    - willingness of clinicians to recruit participants;
    - number of eligible patients;
    - follow-up rates, response rates to questionnaires, adherence/compliance rates, ICCs in cluster trials, etc;
    - time needed to collect and analyse data.
Some key references providing detailed coverage of pilot studies

- Arain M et al. What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Medical Research Methodology* 2010, 10:67