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

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Key Paper

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

Feasibility and piloting
- Testing procedures
- Estimating recruitment and retention
- Determining sample size

Development
- Identifying the evidence base
- Identifying or developing theory
- Modelling process and outcomes

Evaluation
- Assessing effectiveness
- Understanding change process
- Assessing cost effectiveness

Implementation
- Dissemination
- Surveillance and monitoring
- Long term follow-up
Reasons for Pilot 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 of Adaptive Trial Designs]

**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
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 (eg blinding in RCTs)
  – Increases the efficiency of a study
    • Stat Med 1990:9(1-2);65-71; discussion 71-2.
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 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

• 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 ...[state primary objective of the main study] . A feasibility or pilot study is a study that... [state a general definition of a feasibility study]. The specific feasibility objectives of this study are ...[state the specific feasibility objectives of the pilot study]. We will determine that it is feasible to carry on the main study if ...[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 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