Planning Pilot Studies in Clinical and Translational Science

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The origin of this talk
CTSA pilot group: Will you serve as a statistical reviewer for this application/protocol?

Biostatistician: Yes, happy to.

Study: ‘Effectiveness of TREATMENT in older postmenopausal women’

The origin of this talk
Aim: To determine the feasibility of testing TREATMENT in older postmenopausal women.

Design:
• Randomized Controlled Trial
• Double-blind, placebo-controlled
• N=20
• Baseline, 16 weeks
• 12 outcomes

The origin of this talk
• Analysis 1: mixed models for repeated measures
• Analysis 2: Statistical procedures as appropriate
• Sample size: No sample size analysis is provided due to the pilot nature of this study.

Summary
Despite the small number of subjects, this pilot study will provide valuable preliminary data to support further evaluation of the TREATMENT in humans. This study represents the first attempt to test the hypothesis humans. The data will be critical for obtaining NIH funding for a larger study which will compare the effects of TREATMENT to other interventions.
Why should you know more about designing good pilot and exploratory studies?

- High prevalence in health sciences research
- Pilot study funding opportunities
- Future research proposals

More reasons....

- RFA-HL-12-019: Pilot studies to develop and test novel low-cost methods for the conduct of clinical trials (R01)
- PAR-10-005: NHLBI Clinical Trial Pilot Studies (R34)
- PAR-10-282: Pilot and Feasibility Clinical Research Grants in Arthritis and Musculoskeletal and Skin Diseases (R21)

Pilot studies

- Definition: Preparatory investigation

  “...the aspects of your full study that are novel, untested, complex, or innovative.”

  www.cmh.edu/stats/plan/pilot.asp

Drug trials: Staging

- Pre-clinical
- Phase I
- Phase II
- Phase III

Example: oncology

1. Developing protocol
2. Complication rates
3. Potential efficacy

Move forward

Phase III

Staging Research

Pilot study

Move forward

????

Choose a New Research Topic

Find Nonsignificant (Negative) Results

Test the Research Topics in a Pilot Study Framework

Abandon the Research Topic
Research Areas of Pilot Studies

- **R34:**
  - Perform studies to determine appropriate population, intervention, or outcome
  - Test the feasibility of an outcome or intervention in the field

- **R21:**
  - Developing biomarkers and novel imaging
  - Exploring alternative designs of clinical trials
  - Conducting “first-in-human” trials

Reasons for conducting pilot studies

1. Designing/assessing a research protocol
   - Compliance
   - Adherence
   - Inclusion/exclusion criteria
   - Testing equipment and materials
   - Training staff

2. Assessing the feasibility of a (full-scale) study
   - Logistics
   - Recruitment
   - Resources needed

Reasons for conducting pilot studies

5. Establish if sampling frame & technique are effective

6. Estimating rates and variability in outcomes

7. Testing mechanistic efficacy/‘proof of concept’

Design of Pilot Studies

- What is the larger study?
  - Population
  - Design

- What is being tested in the pilot?
  - Study design
  - Measures
  - Procedures

- **NO LIMITS** with study design

External Pilot Clinical Trials

- Pilot trial separate from larger trial
- If external pilot studies for RCTs
  - Well conducted
  - Clear aims
  - Formal framework
  - Leads to
    - publishable work
    - higher quality RCTs

Internal Pilot Clinical Trials

- Main study planned on “best available data.”

“A dash of epidemiology added to some case histories, clinical impressions, statistical hunches, budgetary nudges, and unwarranted optimism.”

(Wittes and Brittain, 1990)
Internal Pilot Clinical Trials

**Original N**

- Internal pilot
- Prespecified

\[ n_p = \pi N \]

“update” \( \rightarrow N \) or \( N^* > N \)

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Sample Size for Pilot Studies

- Investigator must still justify sample size

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Pilot Studies: Sample Size

- Most outcomes are dichotomous
  - Must operationalize “feasibility” measures
  - Adverse events
  - Base N on precision or hypothesis testing

- Means and standard deviation
  - ROT \( n=12 \)
  - ROT \( n>30 \) per parameter
  - 80% upper limit

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Pilot Studies: Sample Size

- Mechanistic hypotheses

- In addition to
  - Participant availability
  - Research burden per participant
  - Research risk
  - Budget restrictions
  - Stage of research

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Analysis of Pilot studies

- How are outcomes operationalized?
  - Feasibility
    - Recruitment?
    - Implementation?
    - Acceptability?
  - Variability
  - ‘Assay 1 better than Assay 2’

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Pilot studies must have

- Good data management

- Analysis plan that directly aligns with aims
  - Descriptive
  - Confidence interval estimation
  - Hypothesis testing results:
    preliminary...interpret with caution; maybe \( \alpha \)

- Future work? What are next steps?
  - Must be VERY clear
Core Sample Size Considerations for Comparative Studies

- Testable Hypothesis
- Statistical Method
- Minimum Clinically Significant Difference
- Estimate of Variation & Control data
- Statistical Errors ($\alpha$, $\beta$)

Warning: Next Steps using Pilot Data

- Control group data
- Standard deviations
- Effect sizes ($\delta$)

Warning: Next Steps using Pilot Data

Two likely results

1. Study will be aborted even when $\delta$ exists
2. If not aborted, sample size will be too small.

Example: K01

Phase II. Perform a Feasibility Study of the ‘Moore’ Intervention

Specific Aim. Conduct a randomized study at schools ($N=8$; $n=4$ intervention, $n=4$ control; 20 mentor-mentee pairs per school) to assess the feasibility of our intervention to provide data to inform a large multisite, randomized controlled trial with regard to the following outcomes:

Example: K01

A. Process outcomes:
   1. Determine our ability to recruit mentee-mentor pairs.
   2. Determine our ability to deliver the intervention (training, implementation, data collection) in busy school settings.
   3. Determine our ability to measure study outcomes.
PI #2 (K01)

B. Study outcomes:
1. Determine the variability and intraclass correlations that will form the basis for the larger effectiveness trial for the intervention.

Published Pilot #1

Local recruitment experience in a study comparing the effectiveness of LGID with LCHEA.......in women with PCOS

Objective: “Feasibility of a clinical trial comparing a LGD with a LCHEA......in women with PCOS.”

Contemporary Clinical Trials 2009; 30(5): 451-6

Published Pilot #1

Main outcomes:
• Eligibility and recruitment rates
• Compliance with allocated diet 6 mths
• Compliance with clinical assessments

Published Pilot #1

Analysis:
• No formal power calculation
• Aim for n=20 per arm
• Estimate standard deviations

Published Pilot #1

Results for 12 months:
1433 new and 2598 follow up patients, 153 OBGYN clinics
441 (11%) potentially eligible women
19 (0.4%) met the trial entry criteria.
11 consented
8 (73%) completed the study

Published Pilot #1

Conclusions:
• Multicenter trials would be needed
• Compliance was good
• Very important pilot
  – Mentioned 6 times!
Published Pilot #2
Glucose Regulation in Acute Stroke Patients (GRASP) Trial: A randomized pilot trial

Goal: “...to assess the feasibility and safety of 2 insulin infusion protocol targets in patients with acute ischemic stroke.”

Usual Care: 70 to 300 mg/dL
Loose Control: 70 to 200 mg/dL
Tight Control: 70 to 100 mg/dL

Published Pilot #2: Feasibility

Feasibility: In target at 24 hours
Loose Control: 92%
Tight Control: 44%

Published Pilot #2

Conclusions:
“Insulin infusion for patients with acute ischemic stroke is feasible and safe using insulin infusion protocol in the GRASP trial. Exploratory efficacy analysis supports further comparative study.”


EXPLORATORY efficacy analysis
Published Exploratory #1

The effects of inhaled and oral corticosteroids on serum inflammatory biomarkers in COPD: an exploratory study.

N=41 patients
RCT 3 arms
No power calculation

Therapeutic Advances in Respiratory Disease (Online, 5/22/09)

Published Exploratory #1

Conclusion:
- Some cytokines were repressed
- Larger clinical trial is needed to confirm

Therapeutic Advances in Respiratory Disease (Online, 5/22/09)

Summary
- Small studies are important for research in health sciences
- Clear aims and next steps are important
- Sample size justification is necessary but not conventional
- Hypothesis testing: depends on type of small study
- Manuscripts: Transparency is critical

References