Statistical Considerations in Pilot Studies

Matthew J. Gurka, PhD

Professor, Dept. of Health Outcomes & Policy

Associate Director, Institute for Child Health Policy

Goals for Today

1. Statistical analysis plan for pilot studies

2. The basics of a power analysis (for planning future studies; why pilot studies are so important)

3. Pilot studies – sample size considerations for feasibility

Pilot Study: DON’T DO THIS

- Analysis plan: Statistical procedures as appropriate

- Sample size: No sample size calculations are provided due to the pilot nature of this study.

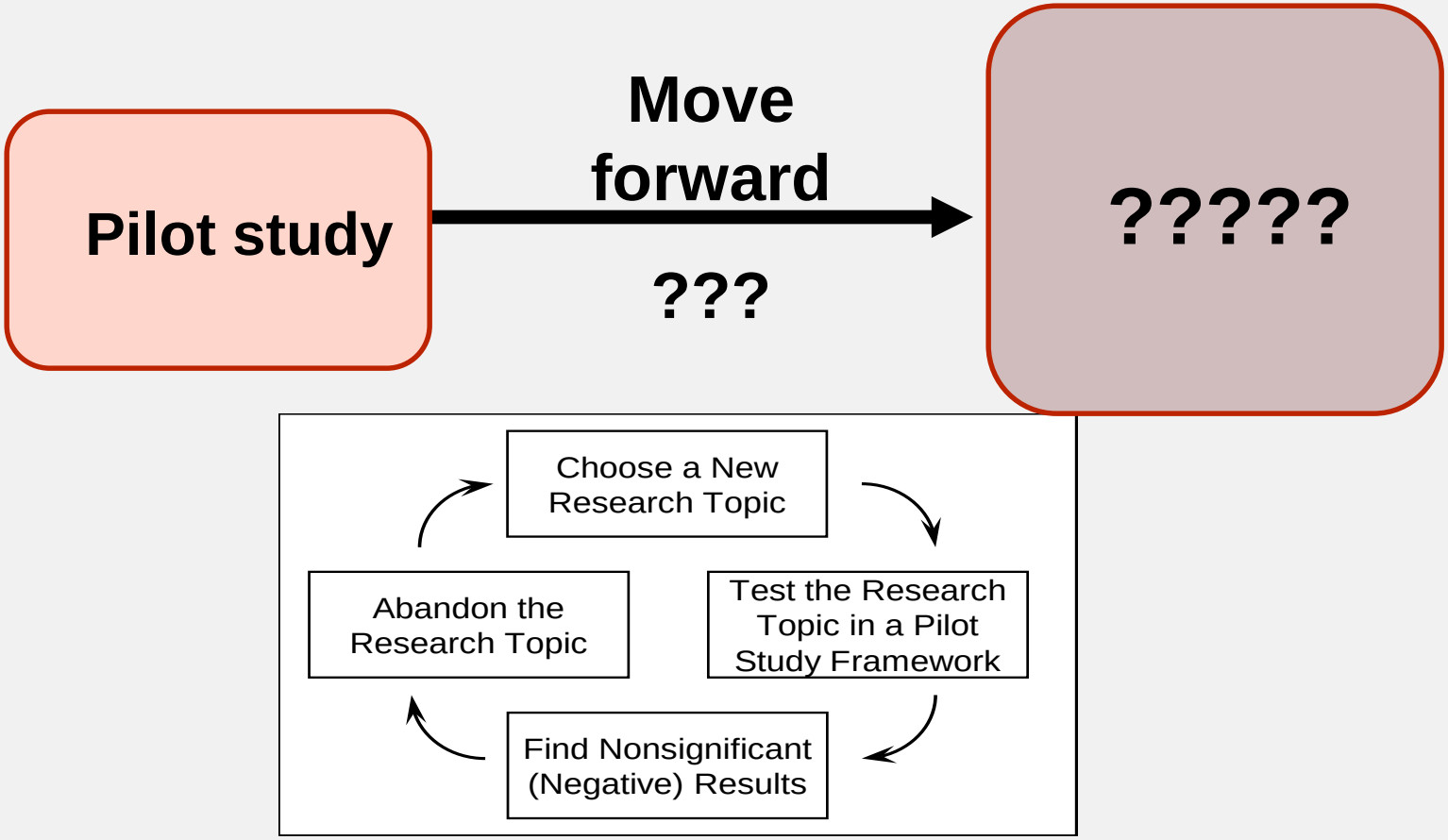
Pilot Studies: Is it Feasible?

- Definition: “Preparatory studies designed to test the performance characteristics and capabilities of study designs, measures, procedures, recruitment criteria, and operational strategies that are under consideration for use in a subsequent, often larger, study.”

(Very Good) Reference:

Moore, Carter, Nietert, Stewart. Recommendations for planning pilot studies in clinical and translational sciences. *Clinical and Translational Sciences* 2011;4:332-337

Staging Research



(Figure) Moore, Carter, Nietert, Stewart. Recommendations for planning pilot studies in clinical and translational sciences. *Clinical and Translational Sciences* 2011;4:332-337

Pilot Studies

- Overarching Goal:

  Keep the Next Study in Mind

- Pilot study aims and methods should align with the goals of the subsequent study

- Aims of a pilot can range from evaluating feasibility of the protocol to investigating potential mechanisms of efficacy for a new intervention

Pilot Studies

- Pilot studies contribute to the development and design of future (larger) studies by:
  - Refining the research hypotheses
  - Identifying barriers to successful study completion
  - Evaluating acceptability of methods and instruments to participants
  - Estimating the time required for study participation
  - Providing estimates of missing data and dropout

Pilot Studies

- Pilot studies contribute to the development and design of future (larger) studies by:
  - Estimating rates and variability in outcomes
  - Testing mechanistic efficacy/ ‘proof of concept’

Design of Pilot Studies

- What is the larger study?
  - Population and design are often the same
    - Obtain relevant estimates
    - Demonstrate feasibility
      - Ex: Will participants be willing to be randomized?
- What is being tested in the pilot?
  - Study design
  - Measures
  - Procedures

Pilot Clinical Trials

- External Pilot trial separate from larger trial
- Internal Pilot trial
  - Interim analysis to assess sample size assumptions

(Lancaster, Dodd, Williamson 2004)

Analysis of Pilot Studies

- How are outcomes operationalized?
  - Feasibility
    - Recruitment
    - Implementation
    - Acceptability
  - Variability
  - Response rates

Pilot Studies Should Have:

- Good data management (REDCap not Excel)
  - Excellent time to develop/test data collection process for the larger study
- Analysis plan that directly aligns with aims
  - Descriptive
  - Confidence interval estimation
  - Hypothesis testing results: preliminary…interpret with caution; maybe increased α
- Future work? What are next steps?
  - Must be VERY clear

Power Analysis in General

- Only as good as the preliminary data that go into it
  - Why we need good preliminary data!
  - *Items in red on next few slides are what we should be obtaining from our pilot studies*

Components of a Power Analysis

- Sample size
- Size of the effect of interest
  - What is clinically meaningful to you?
- Variability
  - Any estimates of it?
- Significance level
  - Usually 0.05
- Power
  - Usually target 0.80 or 0.90

Power Analysis: Continuous Outcome

- Variance (SD) estimate
- Correlations if clustered/longitudinal
- Effect size
  - Not usually from what others (or you!) observed
  - What is a meaningful difference?
- Can you account for covariate adjustment in power analysis?
  - Yes, but not very well (pilots can help here too)

Power Analysis: Binary Outcome

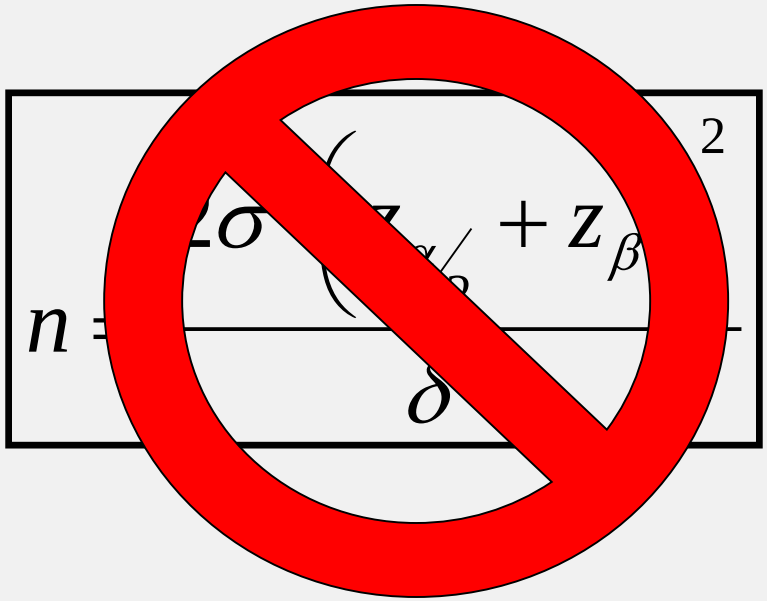
- Overall (or control) rate of the event
- Correlations if clustered/longitudinal
- Effect size
  - What is a meaningful difference?
- Can you account for covariate adjustment in power analysis?
  - Yes

Power Analysis: Attrition

- Don’t forget to account for dropout rate!
  - Final power analysis → 100 subjects
    - 100 subjects with complete data!
  - Need to estimate dropout rate too
    - Ex: 20% dropout → 100/0.80 = 125 subjects enrolled

Sample Size for Pilot Studies

- Investigator must still justify sample size



Pilot Studies: Sample Size

- Most outcomes are dichotomous
  - "Feasibility" measures
    - Recruitment
    - Implementation
    - Retention
    - Acceptability
  - Adverse events
  - Response rates in controls
- Continuous outcomes: variability (and means)

→***Base sample size on precision***

- A lot of "Rules of Thumb"

Pilot Studies: Sample Size
Rules of Thumb

- Rule of 12 (continuous outcome): Sufficiently precise estimates of mean and variance
  - Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharm Stat*. 2005;4(4):287-291
- Rule of 10 (binary outcome): 10 participants with the outcome for each predictor (logistic regression) – *for reliable estimates* (NOT sufficient statistical power)
  - vanBelle G. *Statistical Rules of Thumb, 2nd edition* (2008)

Example

A feasibility study assessing a lifestyle intervention targeting obesity among adolescents with asthma

(1) To assess the feasibility of a family-based lifestyle intervention

(2) To obtain preliminary estimates to plan a larger trial

Example: Sample Size Justification

- We are primarily interested in precise estimates of feasibility and acceptability, as well as outcome variability that will aid in the planning of a larger, sufficiently powered efficacy trial. A sample size of 32 per group will allow us to be relatively precise in our conclusions regarding feasibility outcomes. For example, if we observe a 15% attrition rate out of the 32 enrolled in the intervention group, the 95% CI for that rate would be (2.6%, 27.4%).

Example: Sample Size Justification

- A sample size of 32 per group will give us precise estimates of the variability in change in BMI z-score. Allowing for a conservative 20% dropout, we will have roughly 25 total in the intervention group, which meets the threshold for a sufficiently precise estimate of the variance of BMI change in this population to use in future studies (Julious 2005).

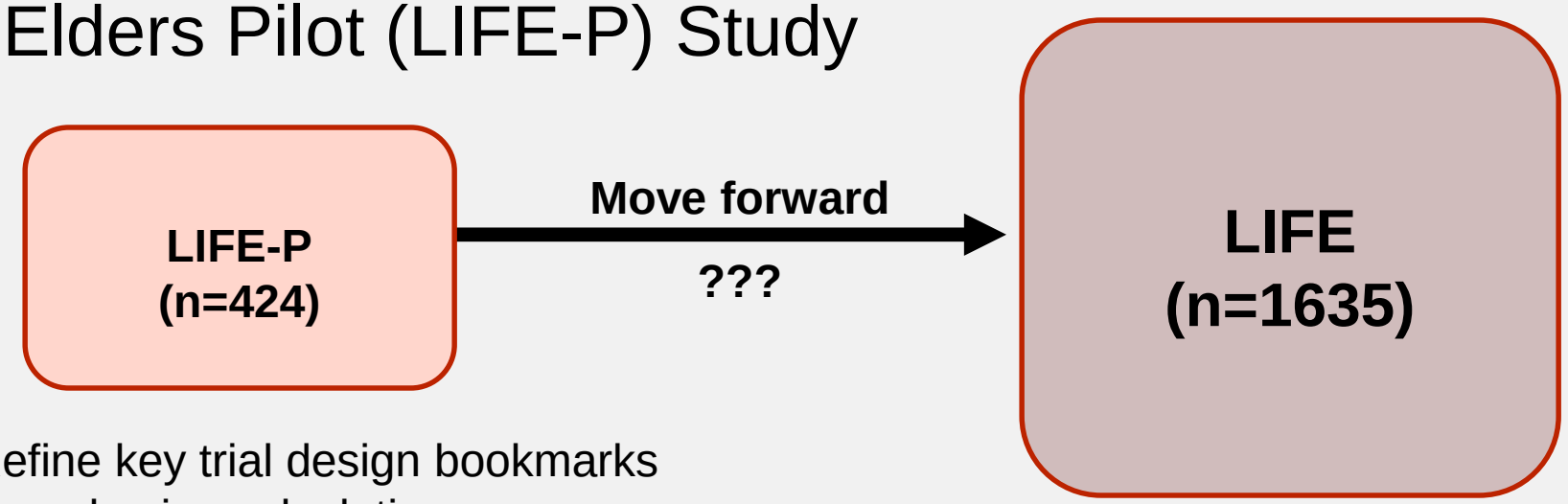
Published Pilot

- Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) Study
  - Persons at risk for disability (age 70-89)
  - Randomized to
    - Moderate intensity physical activity intervention
      - Aerobic, strength, balance, flexibility
      - Adoption, transition, maintenance (25 – 52 wks)
    - Successful aging health education

Rejeski, Fielding, Blair, et al *Contemporary Clinical Trials* 2005;26;141-154

Published Pilot

- Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) Study



- Refine key trial design bookmarks
- Sample size calculations
- Methods for recruitment
- Participant retention
- Adherence to and safety of the interventions
- Organizational infrastructure
- Internal validity of PA: SPPB and 400-meter walk speed at 6 mo and 12 mo ➔ powered for this

1°Major mobility disability—inability to walk 400 m

LIFE-P

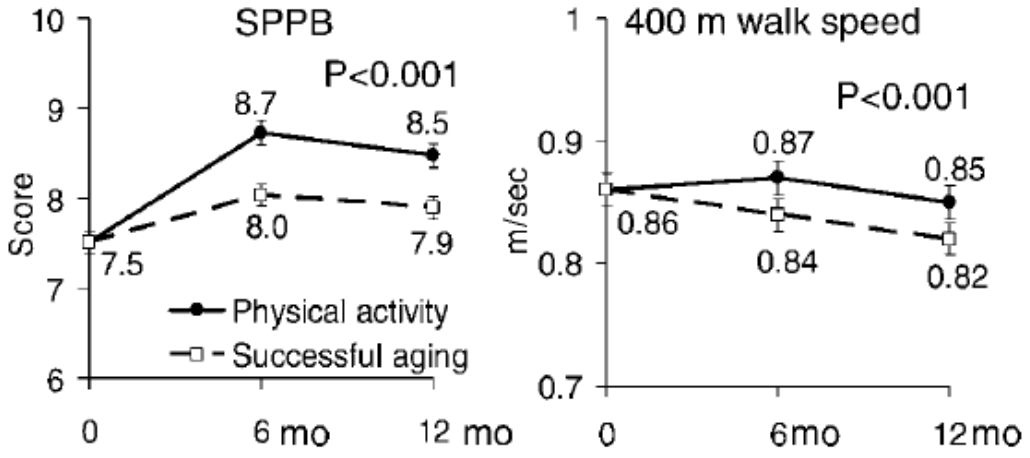


Figure 2. Short Physical Performance Battery (SPPB) score and 400 m walk speed according to randomized groups at baseline and during follow-up. Means estimated from repeated measures analysis of covariance adjusted for gender, field center and baseline values.

Conclusion:
- SPPB modifiable
- PA safe
- Adherence good

Next steps:
Does improvement in performance translate to benefits on clinically relevant outcomes?

The LIFE Study Investigators. *Journal of Gerontology: MEDICAL SCIENCES* 2006, 6: 1157-1165

Conclusions

- A well-developed analysis plan for pilot studies is essential
- No matter where you are in the research life cycle, you must consider sample size
  - Formal power analysis for larger studies
  - Feasibility and precision for pilot studies
- Consult a knowledgeable biostatistician early

Conclusions

- Finally, use a little space in your proposal to educate/remind reviewers of the intention of pilot studies

- References help!
  - Moore, Carter, Nietert, Stewart. Recommendations for planning pilot studies in clinical and translational sciences. *Clinical and Translational Sciences* 2011;4:332-337.
  - Leon, Davis, Kraemer. The role and interpretation of pilot studies in clinical research. *Journal of Psychiatric Research* 2011; 45: 626-629.