

OAIC Symposium on Pilot Study Development

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Pilot Study: Definition

- A preliminary investigation intended to collect data to prepare for a larger, more definitive study.
- Generally small in size, scope, duration and budget.
- A Dictionary of Epidemiology (John M. Last, 3rd Edition): A small-scale test of the methods and procedures to be used on a larger scale if the pilot study demonstrates their feasibility (i.e., that these methods and procedures can work).

Objectives for Symposium

- To outline the training, knowledge and skills necessary for designing and performing high quality pilot studies.
- To provide an overview of crucial statistical and design issues necessary to develop a successful pilot study.
- To provide examples of OAIC funded pilot studies that illustrate skills needed to design and implement a successful pilot.

Rationale for Pilot Studies

- High quality pilot data are essential for developing focused research questions and rationale for developing definitive studies.
- Pilot data strengthens grant applications for external funding.
- A pilot study allows you to know what things go wrong so you can fix them before you start the larger, definitive study.

Pilot Study Session Program

- The Optimal Pilot Study: An Overview
 - Jeremy Walston, MD (JHU OAIC)
 - Andy Goldberg, MD (UMD OAIC)
- Real Life Pilot Experience
 - Steve Prior, PhD, UMD
 - Devon Dobrosielski, PhD, JHU
- Summary Discussion
 - John Sorkin, PhD, UMD
 - Karen Bandeen-Roche, PhD, JHU

Some Objectives of Pilot Studies

- Integrity of study protocol
- Testing of data collection forms or questionnaires
- Randomization procedure
- Recruitment and consent
- Acceptability of intervention
- Selection of most appropriate outcome measure
- Sample size calculation

Lancaster GA et al., J Eval Clin Pract 2004; 10; 307-12.

Additional Objectives

- Protocol testing and refinement
- Test and identify appropriate logistics
 - Participant burden
 - Approaches to recruitment
 - Baseline testing and methods (standardized and reproducible)
 - Intervention
 - Structure of follow-up

Types of Pilot Studies Intervention Evaluation

- Test feasibility of intervention
 - Susini et al. Radiofrequency ablation for minimally invasive treatment of breast carcinoma. A pilot study in elderly inoperable patients. *Gynecologic Oncology* 2007;104:304-310.
- Phase I and II drug trials
 - Creticos et al. Immunotherapy with a ragweed-toll-like receptor 9 agonist vaccine for allergic rhinitis. *N Engl J Med* 2006;355:1445-55.
- Test new technology
 - Collacott et al. Bipolar permanent magnets for the treatment of chronic low back pain. A pilot study. *JAMA* 2000;283:1322-1325
- Test a procedure
 - Toma et al. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. *Lancet* 2002;361:931-33.

Types of Pilot Studies Idea Generation

- Develop hypotheses
 - Currie et al. Age and functional correlations of markers of coagulation and inflammation in the elderly: functional implications of elevated crosslinked fibrin degradation products (D-dimers). *J Am Geriatr Soc* 1994;42:738-42.
- Explore initial hypotheses
 - Samani et al. Telomere shortening in atherosclerosis. *Lancet* 2001;472-473
- Explore associations
 - Hueber et al. A comparative analysis of bone and cartilage metabolism in two strains of guinea-pig with varying degrees of naturally occurring osteoarthritis. *Osteoarthritis and Cartilage* 2002;10:758-767

Types of Pilot Studies Clinical Trial Preparation

- Test feasibility of recruitment
 - Katula et al. Lifestyle interventions and independence for elderly pilot study: recruitment and baseline characteristics. *J Am Geriatric Soc* 2007; 55:674-683.
- Estimate sample size for full scale trial
 - Rejeski et al. The lifestyle interventions and independence for elders (LIFE) pilot study: design and methods. *Contemporary Clin Trials*. 2005;141-154.

Types of Pilot Studies Method Development

- Develop instruments or measures
 - Mohile et al. A pilot study of the Vulnerable Elders Survey-13 compared with comprehensive geriatric assessment for identifying disability in older patients with prostate cancer who received androgen ablation. *Cancer* 2007;109:802-10.
- Establish forms, procedures, data systems, working relationships
 - Taylor et al. Pilot study of the incidence and prognosis of degenerative Parkinson disorders in Aberdeen, United Kingdom: Methods and Preliminary Results. *Movement Disorders* 2006;21:976-982
- Test methodologies
 - Cavanaugh et al. Using step activity monitoring to characterize ambulatory activity in community-dwelling older adults. *J Am Geriatric Soc* 2007;55:120-124

A Really Good Reason to Do a Pilot Study Revisited...

- A pilot study allows you to know what things go wrong so you can fix them before you start the larger study.
 - Strengthens hypothesis and aims
 - Provides sample size estimates
 - Informs experimental design, methodological issues
 - Provides insight into limitations, potential pitfalls

Not Objectives of a Pilot Study

- Conduct definitive hypothesis testing
- Refine/finalize the specific aims for the definitive study
- Generate a definitive answer to the research question
- Therefore, always choose depth over breadth and be certain your research question is well-defined and unlikely to change in a meaningful way.

Can I Publish the Results of My Pilot Study?

- **JHU OAIC:**
 - **Angawal Y**, Zuniga MG, Davalos-Bichara M, Schubert MC, Walston JD, Hughes J, Carey JP. *Decline in Semicircular Canal and Otolith Function with Age*. Otol Neurotol 2012; Jul;33(5): 832-9.
 - **Kalyani RR**, Tian J, Xue ZL, Walston J, Cappola AR, Fried LP, Brancati FL, Blaum CS. *Hypertension and Incidence of Frailty and Lower Extremity Mobility Limitations in Older Women*. J Am Geriatr Soc. 2012 Sep 60(9): 1701-7.

Can I Publish the Results of My Pilot Study?

Yes!

- Number of pilot studies published in 2000-2001 in top journals
 - BMJ = 11
 - Lancet = 17
 - JAMA = 7
 - NEJM = 3
- Randomized pilot studies appear in meta-analyses as primary studies in some Cochrane systematic reviews

Lancaster GA et al., J Eval Clin Pract 2004; 10: 307-12.

Challenges in Designing and Writing a Pilot Study Protocol

Can I Publish the Results of My Pilot Study?

- **UMD OAIC:**
 - **Miller RR**, Shardell MD, Hicks GE, Cappola AR, Hawkes WG, Yu-Yahiro JA, Magaziner J. *Association between Interleukin-6 and lower extremity function after hip fracture – the role of muscle mass and strength*. J Am Geriatr Soc 2008;56(6):1050-1056.
 - **Michael K**, Goldberg AP, Treuth MS, Beans J, Normandt P, Macko RF. *Progressive adaptive physical activity in stroke improves balance, gait, and fitness: preliminary results*. Top Stroke Rehabil. 2009 Mar-Apr;16(2):133-9.

Too Ambitious

- Goal is to generate estimates of key outcomes of interest.
 - Don't bundle too much into an early stage project
 - Don't try to answer too many questions
- Differentiate feasibility with a few primary outcomes from mechanistic with predetermined hypothesis-driven outcomes.
- Collect sufficient, meaningful preliminary data to permit informed sample size calculations.
 - Means and SDs for quantitative variables (or proportions for categorical data) in intervention and control groups.
 - Estimate magnitude of effect that is likely to be observed in a definitive trial.

Slide 16

J6 we will need examples of successful pilots that have helped to launch careers from both of our OAICs.
JHU, 9/11/2012

Slide 17

J3 Andy, I would suggest that you start here.
JHU, 9/11/2012

Proposal Length

- Short - most pilot proposals 3-6 pages
 - Requires concise writing
 - Good resource: Gopen, G. D.; Swan, J. A. The Science of Scientific Writing. *American Scientist* 1990, 78 (6), 550-8.
 - Writing with the Reader in Mind: Expectation and Context
 - Subject-Verb separation, making for complex sentences is a common problem
 - "Maturation of B cells, which includes rearrangement and expression of immunoglobulin genes as well as selection for cells with functional immunoglobulins and against self-reactive B cells, takes place in the bone marrow."

Should Pilot Data Be Included in a Pilot Study Application?

- Yes, if it makes the case for the importance and sound conduct of the pilot and for the particular funding mechanism – e.g., R03, R21

Specific Aims

- Not definitive hypothesis testing or objective
 - Still requires well defined, purposeful objective(s)
 - Embedded in a larger good idea or leading to a good, innovative idea/project
 - Necessarily limited in number and scope - Keep these focused and feasible

Sample Selection

- By definition, working with small samples
 - Use as rigorous a strategy as possible but recognize the risk of less representative samples.
 - Try to make sure that your pilot subjects cover the entire range of subjects in your full study.
 - Do not slap on the label of pilot study when your sample size is too small.

Significance

- Emphasize the importance of area of inquiry and potential product in small space.
 - Scholarship has to be sharp and to the point, the key articles by the key people.
 - Rationale for the pilot clearly defined.
 - Theoretical model may or may not be necessary.

Approach

- Feasibility
 - Beware of the tendency to propose or do too much.
- Recruitment and retention
 - Propose a realistic recruitment and retention plan.
 - Reviewers know that recruitment difficulties extend to pilot studies.

Sample Size

- How Many Subjects for My Pilot Study?
 - Depends on the objective of the study.
 - Some pilots don't require formal sample size calculations.
 - Enough observations to provide useful information.
 - 95% Confidence interval approach if you know target for success (e.g. 70% of patients are able to complete the form).

Thabane et al. BMC Medical Research Methodology 2010, 10:1

Review

- How will the review be done?
 - Ranges from NIH where same review criteria used as for R01 to small Foundation where one reviewer uses a 5 point Likert scale
 - Know the review process and criteria
- Who are the reviewers?
 - Find out who will be reviewing your application, if possible

Statistical Analysis

- Be clear about how the data will be interpreted and utilized.
- Analyses mainly descriptive.
- Confidence interval estimation appropriate in some situations.
- If hypothesis testing is done, treat as preliminary and interpret with caution.
- Outcome data useful to calculate sample sizes for larger study.

Potential for Extramural Support

- Does the project have a high likelihood of leading to future extramural, larger grant support?
- Be explicit about how/where pilot results will fit with larger grant- place the pilot study in the context of the full-blown study.
- Deciding on K23, R21 or R01 application

Budget



- Usually for specific expertise (data management, statistics, consultant), supplies, part of study assistant effort.
- Usually not for investigator salaries, full time study coordinators, equipment, travel.
- Pilots help understand resource requirements in full study.

Challenges in Conducting a Pilot Study

- Short time frame
- IRB approval - A pilot takes as long as a large study
- Subject recruitment and retention
 - Don't be deceived by small number of subjects needed
- Personnel problems
 - Research assistant gets sick, co-investigator or statistician moves
- Supply chain problems
 - Animals, reagents, databases hard to get
- Data inconclusive, uninformative

Challenges in Conducting a Pilot Study

- Short time frame
- Changes in laboratory or clinical practice
 - Affects recruitment, measures, interventions
- Equipment breakdown
 - Flow cytometer, multiplex assay system not working?
- "I never thought about that!"

Sources of Funding for Pilot Studies

- NIA early stage research mechanisms
- R03s – small grants (50k a year, two years)
 - <http://www.nia.nih.gov/GrantsAndTraining/FundingOpportunities/r03.htm>
 - includes Human Biospecimen Resources on Aging Research <http://grants.nih.gov/grants/guide/pa-files/PA-06-443.htm>
- R21s – exploratory/developmental grants (\$275k over two years)
 - Exploratory/Developmental Research Grant Award
 - <http://grants.nih.gov/grants/funding/r21.htm>
- NIA Center Programs –pilot studies cores
 - Older Americans Independence Centers
 - Demography Centers
 - Resource Centers on Minority Aging Research

Acknowledgment: Dr. Robin Barr – Pilot Studies Workshop, 2008 AGS Annual Meeting

Research Working Groups Help Pilots Succeed

- Multidisciplinary team of investigators from OAIC Cores.
- Developed to provide resources, monitor progress & accomplishments, problem solve, accelerate progress, access/cultivate collaborations, etc.
- Meet frequently during early phase of pilot to assure the project's rapid development, submission of regulatory materials & study implementation in a timely fashion.

Sources of Funding for Pilot Studies

- K24 (Mid-Career award in Patient-Oriented research)
 - \$50,000 a year that can be used to provide pilot funding
- K07 (Academic Leadership Award)
 - A portion of the \$100,000 a year may be used for pilot funding
- NIH Clinical and Translational Science Awards (CTSA) often have local small grant or pilot study mechanisms
- Secondary Data Analysis
 - NIA supports the National Archive of Computerized Data on Aging: <http://www.icpsr.umich.edu/NACDA/>
 - NIA's Behavioral and Social Research program lists many sources on its website: <http://www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/Resources.htm>
 - NIH dbGAP, a database of genome-wide association studies: <http://www.ncbi.nlm.nih.gov/gap>

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Final Pilot Study Wisdom

- Is it really a pilot? Over-ambitious vs. underwhelming.
- Right place, wrong time- does it match the RFA, review criteria, and eligibility? Seek advice!
- Write with purpose – make it compelling, feasible.
 - Statistics/power analysis: even a pilot study needs them.
 - "Gotta have some to get some"
- Can you really do all that with just a few bucks?
- Provide a theoretical model and timeline.

Sources of Funding for Pilot Studies

- AHRQ Small Research Grant Program (R03)
 - Priority areas include translating research into practice, patient safety and quality, patient centered care, payment and organization
 - <http://grants.nih.gov/grants/guide/pa-files/PA-06-448.html>
- AFAR Research Grants
 - up to \$75,000 for a one- to two-year award to junior faculty, broad range of biomedical, clinical topics <http://www.afar.org/grants.html>
- Robert Wood Johnson Foundation
 - multiple grants in \$50,000-100,000/year on wide range of health topics, some applicable to geriatrics <http://www.rwjf.org/grants/>
- VA Research - VA Research Foundation small grants

Sources of Funding for Pilot Studies

- Specialty Associations
 - American Heart Association Affiliate grant Programs
<http://www.americanheart.org/presenter.jhtml?identifier=9713>
 - American Diabetes Association
http://professional.diabetes.org/Diabetes_Research.aspx?cid=60655&rvp=18
- State, Local Community or Institutional Small Grants

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