Pilot Studies in Clinical Research

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Question: ~*Aims for Intervention*

External K? Pilot/mechanistic/proof of concept

Internal K? Pilot/mechanistic/proof of concept

Internal pilot funding? Pilot

R03/R21?

Pilot/mechanistic/proof of concept/

hypothesis generating/exploratory

R01? Short-term efficacy/futility

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 (page doesn't work anymore!)

Very good references:

El-Kotob, Giangregorio. Pilot and feasibility studies in exercise, physical activity and rehabilitation research. *Pilot Feasibility Stud* 2018, 4:137.

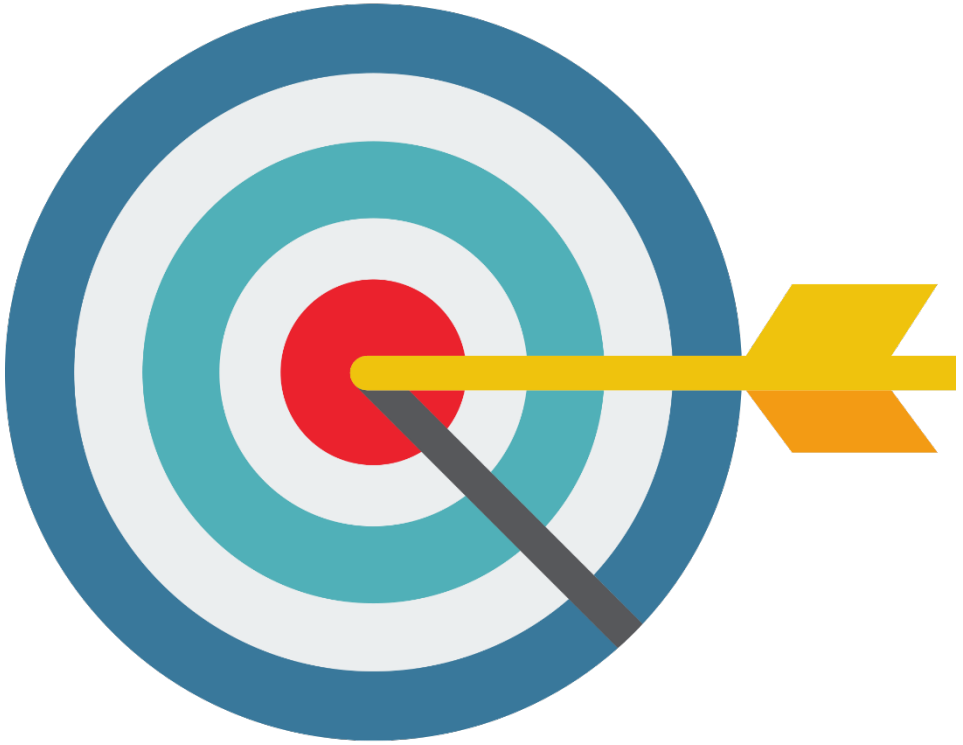
Leon, Davis, Kraemer. The role and interpretation of pilot studies in clinical research. *J Psychiatr Res* 2011

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

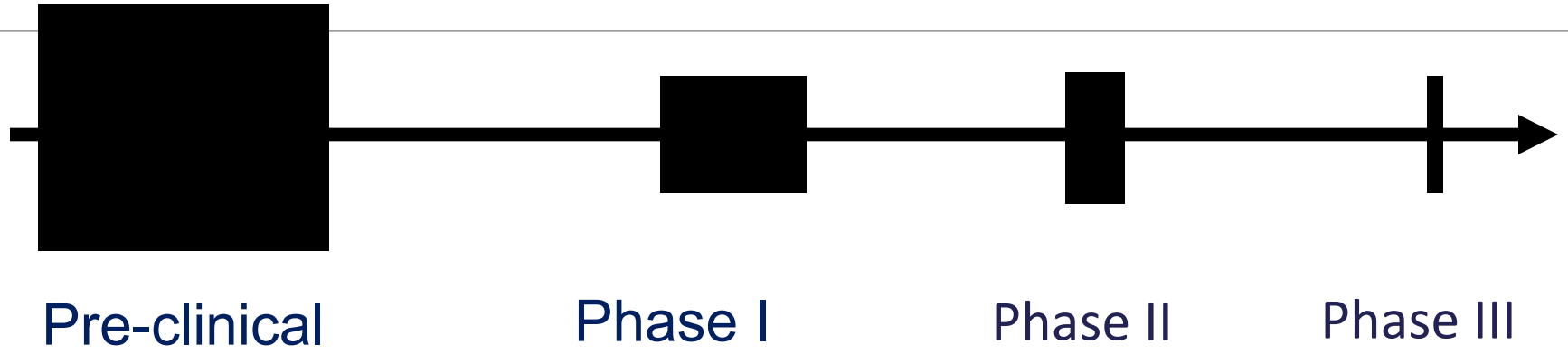
Thabane, Ma, Cheng, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol* 2010 Jan 6;10:1.

Dobkin BH. Progressive Staging of Pilot Studies to Improve Phase III Trials for Motor Interventions. *Neurorehabil Neural Repair.* Mar-Apr 2009;23(3):197-206.

The Full Study



Drug trials: Staging



For non-pharmacological interventions, the staging is not standardized.

Reasons for conducting pilot studies

1. Designing/assessing the feasibility of a (full-scale) research protocol
   - Inclusion/exclusion measurable, randomization willingness, adherence, logistics
2. Sampling frame & technique effective
   - Recruitment sources
3. Estimating rates and variability in outcomes for future sample size analysis
   - % response, SD of gait speed
4. Testing mechanistic efficacy/ 'proof of concept'
   - Delta physical activity at 4 weeks

Pilot studies are not for preliminary efficacy.

Freedland (2020) Pilot trials in health-related behavioral intervention research: Problems, solutions, and recommendations. *Health Psychology* 39(10): 851-862.

Design of Pilot Studies

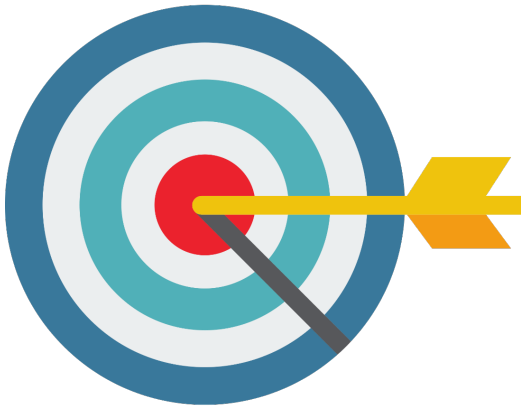
What is the larger study?

- Population
- Design

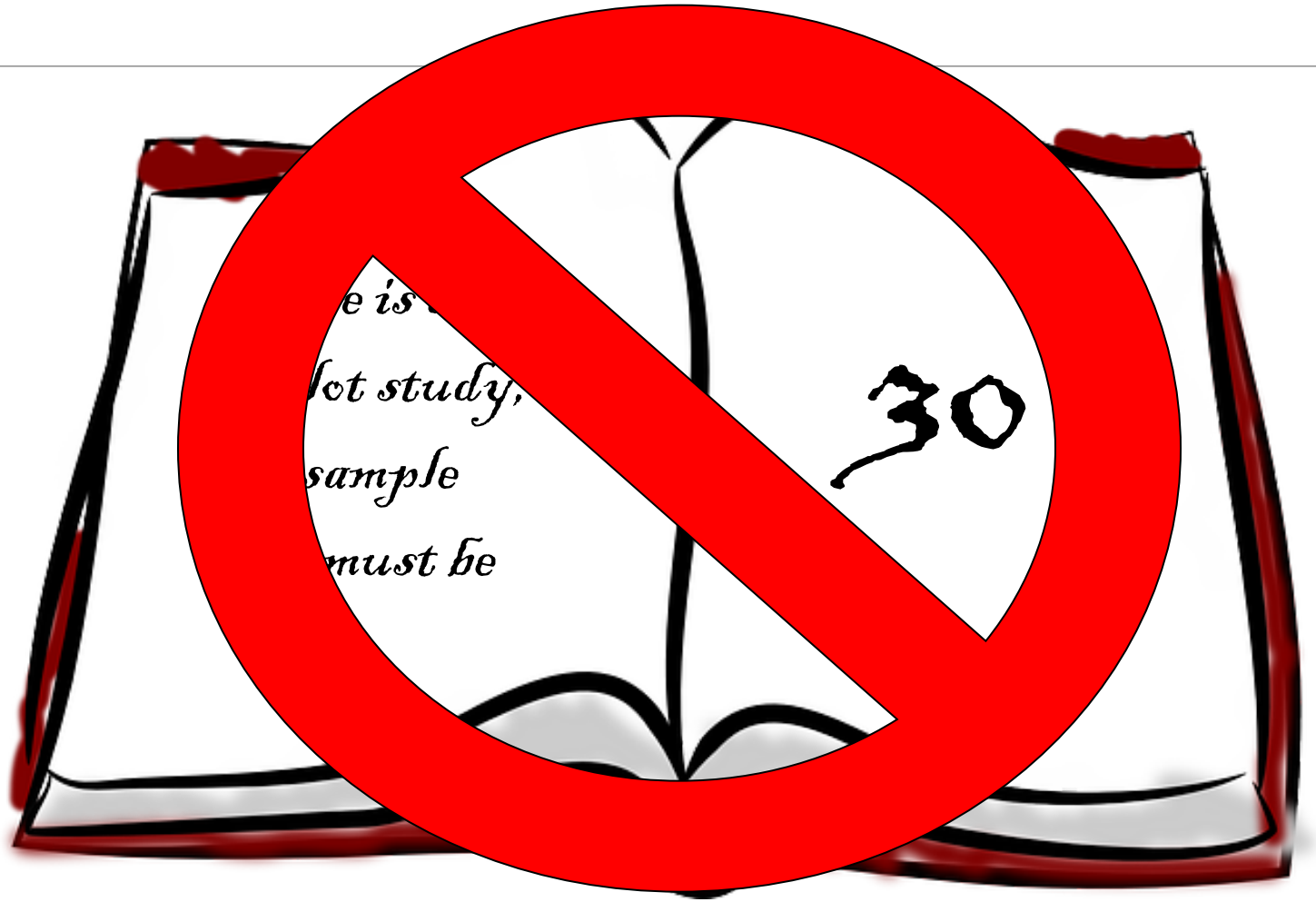
What is being tested in the pilot?

- Study design
- Measures
- Procedures

NO LIMITS with study design

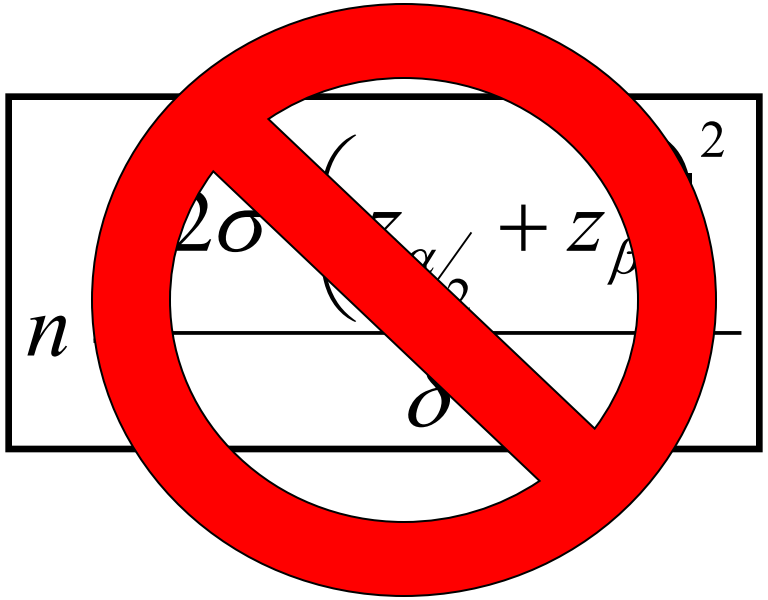


Statistics Handbook



Sample Size for Pilot Studies

Investigator must still justify sample size



“Pilot” study: *DON’T DO THIS*

Analysis plan: Statistical procedures as appropriate

Sample size: No sample size analysis is provided due to the pilot nature of this study.

Sample size: Our other studies have used n=20 and that allowed us to detect the differences we expect to see.

Pilot Studies: Sample Size

Most outcomes are dichotomous

- “Feasibility” measures
- Adverse events
- Base N on precision or hypothesis testing

Means and standard deviation

- n=12 or n>30 per parameter

Mechanistic hypotheses

In addition to ……..$$, risk, and other things

Pilot Studies Must Have

1) Good data management (

not Excel)

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

3) Future work? What are next steps?
   - Must be VERY clear

Sample Size for The *NEXT* Comparative Study

"This pilot study will provide the effect size for planning the sample size of the larger efficacy trial."

Kraemer HC, Mintz J, Noda A, Tinklenberg J, Yesavge JA. Caution regarding the use of pilot studies to guide power calculations for study proposals. *Archives of General Psychiatry.* 2006;63:484–489.

Why not take effect size from pilot?

Example:

- Intervention vs Control
  - Gait speed at 6 months
  - δ=0.5 ➔ true effect size, ½ SD
- Pilot N=20 to look for “preliminary efficacy”

What does this mean?

Example:

- Pilot N=20 to look for “preliminary efficacy”
  - See effect size of <0.5➔ 50%
  - See effect size of >0.5➔ 50%
  - See effect size 0.6!
    - 80% Power for larger study then N=72
    - Power is 67% for the δ=0.5
    - N should be 102!

Example: Pilot

Title: A feasibility study assessing baseline exercise level and quality of life in patients with bone cancer

(1) **to assess the feasibility of collecting** baseline exercise and QOL levels of newly diagnosed bone cancer patients

(2) **to assess the feasibility of monitoring** the activity of a patient with bone cancer over the course of a week.

Example: Sample Size Justification

Approach n=25 eligible subjects & obtain baseline exercise and QOL data.

If n=20 of 25 (i.e. 80%) of eligible patients who are approached agreed to participate

- 80% (with a 95% confidence interval ranging from 59% to 93%)
- evidence that at least a majority of patients would be willing to participate in such surveys.

Example: Sample Size Justification

Approach n=10 subjects to wear pedometer for 1 week.

If 8 of the 10 subjects be fully compliant

- 80% (95% confidence interval 44% to 97%)
- providing some evidence that this is feasible in this patient population.

Feasibility, Safety and Phase II

Study in PARkinson disease of eXercise (SPARX)

- De novo PD (age 40-80)
- Multicenter
- Randomized to
  - High intensity (80-85% HRMax)
  - Moderate intensity (60-65% HRMax)
  - Usual Care

Moore CG, Schenkman M, Kohrt WM, Delitto A, Hall DA, Corcos D. Study in Parkinson disease of exercise (SPARX): translating high-intensity exercise from animals to humans. *Contemp Clin Trials*. 2013;36(1):90-98. NINDS R01 NS074343

SPARX (Phase 2) (n=126)

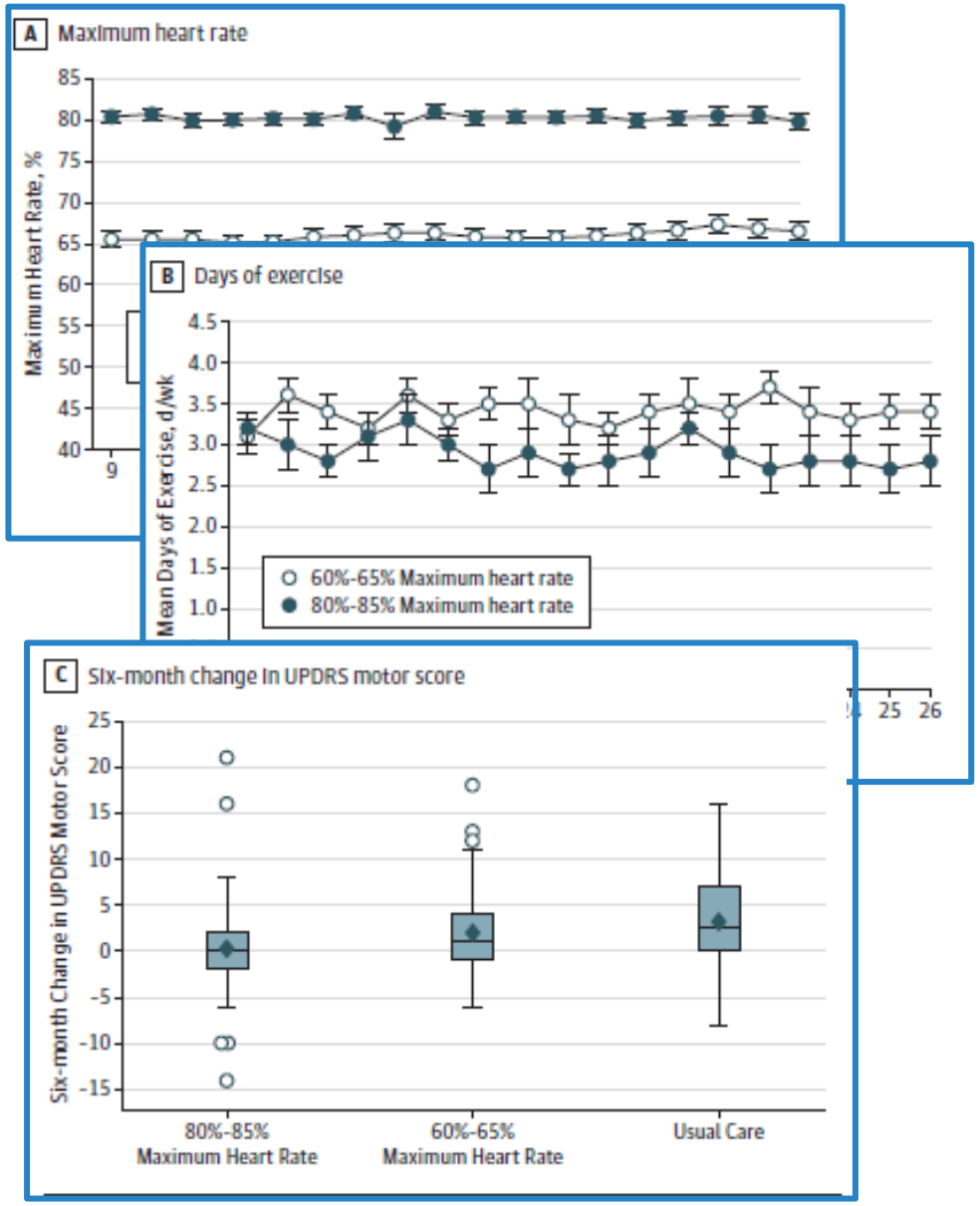
Move forward

7 different scenarios

SPARX3 (n=???)

- **Feasibility** of
  - Intensity
  - Frequency
- **Futility** for motor symptoms at 6 months
  - 3.5 futility threshold
- **Safety**

1° Disease progression, 12 months or initiation of dopaminergic medication



Conclusion:

- Feasible
- Safe
- High intensity warrants further investigation

Next steps:

Does high intensity exercise lessen disease progression?

SPARX3

Study in Parkinson's Disease of Exercise
Phase 3 Clinical Trial

Schenkman, Moore, Kohrt, Hall, Delitto, Comella, Josbeno, Christiansen, Berman, Kluger, Melanson, Jain, Robichaud, Poon, Corcos (2017) *JAMA Neurology* published online December 11, 2017.
NINDS R01 NS074343

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