

## Clinical Trials Program at NINDS

Scott Janis, Ph.D.  
National Institute of Neurological  
Disorders and Stroke  
National Institutes of Health



## National Institute of Neurological Disorders and Stroke



The mission of NINDS is to reduce the burden of neurological disease through research on the healthy and diseased brain, spinal cord, and nerves of the body.



## Overview

- Training Awards (K grants)
- Research Awards (e.g., R01, R03, R21)
- Clinical Trials Program
  - Pilot Study Grants (PAR-03-174)
  - Planning Grants (PAR-03-051)
  - Grants for Efficacy Trials



## NINDS Funding Opportunities

### Mentored Research Career Development Awards:

- K01 [Research Scientist Development Award - Research and Training](#)
- K08 [Clinical Investigator Award](#)
- K23 [Mentored Patient-Oriented Research Career Development Award](#)

### Independent Scientist Career Development Awards:

- K02 [Research Scientist Development Award - Research](#)
- K24 [Mid-Career Investigator Award in Patient Oriented Research](#)

### Research Project Grants:

- R01 [Research Project Grant](#)
- R21 [Exploratory / Developmental Grant](#)



## Research Project Grants

### •R21 [Exploratory/Developmental Grant](#)

Supports pre-clinical feasibility studies; novel high risk/high payoff research. Up to two years of support. Non-renewable. **No Clinical Research Projects.**

### •R03 [NIH Small Research Grant Program](#)

Limited use: e.g., projects leading to a defined product, resource or "deliverable" that has inherent value to the neuroscience community; Research projects focused on secondary analysis of clinical data sets.

### •R01 [Research Project Grant](#)

A Research Project Grant supports a focused research program conducted by a principal investigator with or without collaborators, postdoctoral trainees, graduate students and/or technicians.



## NINDS Clinical Trial Program

Pilot study



Planning grant



Efficacy trial



## PILOT Study Program

**P**RELIMINARY  
**I**NVESTIGATIONS  
**L**EADING TO **O**PTIMAL  
**T**RIALS  
IN NEUROLOGY



## Pilot Study Grant – Overview

- Purpose: to provide specific data about an intervention necessary to design a subsequent efficacy trial.
- Mechanism: R01 through PAR -03-174.
- Limit: 3 years and generally < \$350K/yr.
- Review: NINDS-appointed review group (NSD-K).



## Pilot Study – Primary Objectives

- Studies of safety and tolerance, PK, or biological activity (e.g., markers of therapeutic activity).
- Studies to optimize the intervention strategy (e.g., optimal dose, duration).
- Studies to select the best of several possible interventions or dosages, based on tolerance or markers of activity.
- Studies to define the target population (e.g., identify inclusion and exclusion criteria).



## Pilot Study – Secondary Objectives

- Determine optimal outcome measure
- Evaluate surrogate outcomes, questionnaires or rating scales
- Develop and refine data collection procedures
- Develop and refine outcome assessment methods
- Evaluate feasibility of administration of study intervention
- Determine the best methods for identifying and recruiting study subjects



## Pilot Study – What do we mean by “Feasibility”?

- Examples of feasibility issues:
  - What is the optimal outcome measure to use?
  - Will data collection run smoothly?
  - Can clinicians correctly administer the intervention?
  - How should we recruit study subjects?
- Feasibility issues are appropriate as secondary aims of a pilot study.



## Pilot Study – How About Efficacy?

- Pilot studies are not intended to address efficacy.
- Pilot studies provide specific data needed to design a subsequent, adequately-powered efficacy trial.
- A control group and blinding are usually not necessary in a pilot study.



## Pilot Study – Review Criteria - 1

- **SIGNIFICANCE**
  - importance of problem
  - rationale for the proposed study
  - significance of eventual definitive clinical trial
  - state of equipoise with respect to the proposed intervention
  - potential impact on health care, quality of life
  - role of pilot in design of definitive clinical trial



## Pilot Study – Review Criteria - 2

- **APPROACH**
  - plans for the sequence of clinical studies
  - scientific soundness of methodology
  - soundness of analysis plans
  - completeness and quality of the protocol
  - ethical issues
  - adequacy of safety monitoring plans
  - adequacy of data management procedures



## Pilot Study – Review Criteria - 3

- **INNOVATION**
  - aims of the study original
  - proposed study design, methods, and interventions may not necessarily be innovative
  - underlying aims should represent an advancement in the field



## Pilot Study – Review Criteria - 4

- **INVESTIGATOR**

- training and expertise in the clinical problem and the proposed intervention
- training and expertise in clinical trials
- ability to organize and manage the research group



## Pilot Study – Review Criteria - 5

- **ENVIRONMENT**

- appropriate agreements with participating industry sponsors, if any, are established



## Pilot Study – Summary

- Intended to provide specific data about the intervention.
- Feasibility issues are appropriate as secondary aims.
- Grant application must explain how the pilot study will advance the design of a subsequent efficacy trial.



## II. Planning Grants



## Planning Grant – Overview

- Purpose: to provide support for the organization of activities critical for the successful implementation of high-risk, complex, or large-scale clinical trials .
- Limit: 12 mos. and \$150,000 (total).
- Not renewable.
- Mechanism: R34 through PA -03-051.
- Review: NINDS-appointed review group.



## Planning Grant – Examples

- **Examples:**
  - Develop a detailed manual of operations and set of data collection forms
  - Organize a group of study investigators
  - Develop adequate plans for recruitment of patients
- **No data collection**



## Planning Grant – Application

- Primary review criteria
  - Rationale and significance of the future efficacy trial
    - *Results of preliminary studies, any pilot study*
    - *Appropriateness of intervention(s) and selection of endpoints*



## Planning Grant – Application

- Primary review criteria – cont.
  - Design of future efficacy trial
    - *Protocol for the future efficacy trial: adequate detail to evaluate randomization scheme, data management, analysis, recruitment and retention plans, etc.*
  - Outline of the projected direct cost of the efficacy trial
  - Planning period activities



### III. Grants for Efficacy Trials



### Efficacy Trial Grant – Overview

- Purpose: to compare the efficacy of a new treatment intervention in humans relative to a control.
- Mechanism: R01 or U01.
- Review: CSR study section or, if multi-center, NINDS-appointed review group.



### Background & Rationale

- Include the scientific rationale, preclinical data, and pilot trial data used to justify and design the efficacy trial.
- Clearly specify the (null and alternative) hypotheses (primary and secondary) to be tested.
- Clarify why the treatment effect to be looked for is both clinically relevant and realistic.



### Research Plan

- Briefly summarize the trial design.
- Clarify why the outcome variables were chosen and how they relate to the study hypotheses.
- Include a power analysis showing that the sample size is adequate.



## Research Plan Details

- Statistical design and analysis, including analysis techniques, handling of dropouts, confounding variables.
- Data management plan, including acquisition, flow, storage, quality control, and auditing.
- Treatment plan.
- Randomization and blinding.
- Adverse event handling and reporting.



## Research Plan Details

- Training/standardization of personnel/protocols across centers.
- Plans for Follow-up.
- Endpoint adjudication.
- Noncompliance and dropout.
- Plans for Ensuring Reliability, Standardization, and Validity of measurements
- Recruitment of women and minorities.
- Human subjects concerns.



## Appendices

- Protocol
- Manual of Operations
- Data Collection Forms



## Top Five Mistakes Applicants Make

5. Inadequately describing data management plans.
4. Having inadequate subject recruitment plans.
3. Hypothesizing an unrealistically large treatment effect. (The penicillin effect.)
2. Believing that submitting a lousy application will yield useful feedback from the review committee. (First impressions count!)
1. **Failing to consult with the NIH before writing the application.**



## Clinical Trial Resources at NINDS

[www.ninds.nih.gov/funding/clinical\\_trials/clinical\\_research.htm](http://www.ninds.nih.gov/funding/clinical_trials/clinical_research.htm)

- The NINDS clinical research website has:
  - Information on the pilot study and planning grant programs.
  - A template clinical trial protocol.
  - An outline of a Manual of Operations.
  - NINDS Terms of Award for Clinical Research.
  - NIH and NINDS policies and procedures.

