Clinical Research Grants Workshop: the NAN Program and Beyond!

NAN Annual Meeting, New York City
Friday, October 24
8:30 AM - 11:30 AM

The NAN Clinical Research Grants (CRG) Program

- Provides funding for clinical neuropsychology research unlikely to be funded via other mechanisms
- Currently provides ~$30K/year
- Strong track record of accomplishment by prior awardees
- Competitive, peer-review mechanism
  - Next submission deadline: 5/1/2009!

NAN CRG Workshop Participants and Awardees

- Robert M. Bilder, PhD; UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA. (Organizer & Chair)
- Mark S. Aloia, PhD; National Jewish Medical and Research Center, Denver CO.
- Robert H. Paul, PhD; Department of Psychology, University of Missouri, St. Louis, MO.
- Geoffrey Tremont, PhD; Neuropsychology Program, Department of Psychiatry, Rhode Island Hospital, Providence, RI.
- Jeannette Wasserstein, PhD; CNSupport and Mt. Sinai School of Medicine, New York, NY.
- Anita M. Hubley, PhD; Dept. of ECPS, University of British Columbia, Vancouver, BC, Canada (2007 Awardee)
- Risa Nakase Thompson Richardson, PhD; Methodist Rehabilitation Center, Department of Neuropsychology, Jackson, MS (2007 Awardee)

NAN CRG Awardees: 2007-2008

- A Comparison of Five Process Scoring Systems Adapted for Use with both the Rey-Osterrieth and Modified Taylor Complex Figures
  - Anita M Hubley, PhD; University of British Columbia
- The Value of Effort Testing and Predictive Utility of Effort Indices on the CVLT-2 In Predicting Outcomes In a Consecutive Series of Acute TBI Rehabilitation Admissions
  - Risa Nakase Thompson Richardson, PhD; Methodist Rehabilitation Center, Jackson MS

Rob Paul

Assistant Professor, Department of Psychology,
University of Missouri-St. Louis
Email: paulro@umsl.edu

- Mechanisms for funding NP research
- NIH Grants
  - R-series
  - K-series
  - Other training awards
- Beyond the NIH

Why seek funding?

The obvious reasons:

- Research is expensive
  - Subject payments
  - NP tests and forms, copy costs, equipment
  - Biomarkers, neuroimaging, etc
  - Money for conferences, networking

- The less obvious reasons
  - Indirect costs to your employer
    - Marketability, job security, etc

NIH Grants

- NIH Research Project Grant Program (R01)
  - Used to support a discrete, circumscribed research project
  - NIH's most commonly used grant program
  - No specific dollar limit
  - Advance permission required for $500K or more (direct costs) in any year
  - Generally awarded for 3 -5 years
  - More info at /grants/guide/pa-files/PA-07-070.html

Paraphrased from NIH.gov

NIH Grants

- NIH Small Grant Program (R03):
  - Limited funding for a short period of time to support: pilot or feasibility studies, collection of preliminary data, secondary analysis of existing data, small, self-contained research projects, development of new research technology, etc.
  - Limited to two years of funding
  - Direct costs generally up to $50,000 per year
  - Not renewable
  - Utilized by more than half of the NIH institutes
  - More info at /grants/guide/pa-files/PA-06-180.html
- Paraphrased from NIH.gov

Misconceptions surrounding the RO1/RO3

- Only experienced PIs can obtain an RO1
  - New applicants are provided some latitude but the science must be sound.
- It is easier to get an RO3 vs. RO1
  - True if you lack pilot data, but the quality of the science must be solid for both.
- Preliminary Studies (section) is only important for an RO1
  - This section is always important, as it describes your familiarity with research.
- Always ask for 5 years of funding with an RO1
  - Let the science guide the duration and justify the need.

NIH Grants

- Exploratory/Developmental Research Grant Award (R21)
  - Encourages new, exploratory and developmental research projects by providing support for the early stages of project development. Sometimes used for pilot and feasibility studies.
  - Limited to up to two years of funding
  - Combined budget for direct costs for the two year project period usually may not exceed $275,000.
  - No preliminary data are generally required (though helpful)
  - Most ICs utilize
  - See /grants/guide/pa-files/PA-06-181.html
  - Paraphrased from NIH.gov

NIH Grants

- NIH Clinical Trial Planning Grant (R34) Program
  - Designed to permit early peer review of the rationale for the proposed clinical trial and support development of essential elements of a clinical trial
  - Usually project period of one year, sometimes up to 3
  - Usually, a budget of up to $100,000 direct costs, sometimes up to $450,000
  - Used only by select institutes
  - Paraphrased from NIH.gov

NIH Grants

- NIH Pathway to Independence (PI) Award (K99/R00)
  Also see, New Investigators Program web page
- Provides up to five years of support consisting of two phases
- Phase I provides 1-2 years of mentored support for highly promising, postdoctoral research scientists
- Phase II - up to 3 years of independent support contingent on securing an independent research position
- Award recipients will be expected to compete successfully for independent R01 support
- Eligible Principal Investigators include postdoctoral candidates who have terminal clinical or research doctorates who have no more than 5 years of postdoctoral research training
- PI does not have to be a U.S. citizen
- Paraphrased from NIH.gov

NIH Grants

- NIH Academic Research Enhancement Award (AREA)
  - Support small research projects by students and faculty in health professional schools and other academic components that have not been major recipients of NIH research grant funds
  - Eligibility limited (see /grants/funding/area.htm)
  - Direct cost limited to $150,000 over entire project period
  - Project period limited to up to 3 years
  - Most NIH ICs utilize
  - More info at /grants/guide/pa-files/PA-06-042.html
  - Paraphrased from NIH.gov

Mentored NIH Training Grants

- Mentored training grants are available from NIH at the predoctoral, postdoctoral, and career levels.
  - Referred to as F and K series.
    - Institutional training grants (T series) also exist
- All assume applicant needs training
  - Common NP mistake is to propose NP training, stats training, research training.
  - Training needs to be novel and necessary for career goals.

Mentored NIH Training Grants – K series

- Mentored Clinical Scientist Research Career Development Award (K08)
- Supported by NIA, NIAAA, NIAID, NIAMS, NIBIB, NCI, NICHD, NIDCD, NIDCR, NIDDK, NIDA, NIEHS, NEI, NIGMS, NHLBI, NIMH, NINDS, NCCAM, and ODS.
- The K08 provides support and "protected time" to individuals with a clinical doctoral degree for an intensive, supervised research career development experience in the fields of biomedical and behavioral research, including translational research.
  - Paraphrased from NIH.gov

Mentored NIH Training Grants

- Mentored Research Scientist Development Award (K01)
- Supported by NIA, NIAAA, NIAID, NIAMS, NIBIB, NCI, NICHD, NIDCD, NIDDK, NIDA, NIEHS, NIMH, NINDS, NINR, NHGRI, NCCAM, NCRR, and ODS.
- Provide support and "protected time" (3-5 years) for an intensive, supervised career development experience in the biomedical, behavioral, or clinical sciences leading to research independence.
- Awards are not renewable, nor are they transferable from one principal investigator to another.
- Number of institutes provide separate funding for KO1s to promote diversity.
  - Paraphrased from NIH.gov

Mentored NIH Training Grants

- Mentored Patient-Oriented Research Career Development Award (K23)
- Supported by NIA, NIAAA, NIAID, NIAMS, NIBIB, NCI, NICHD, NIDCD, NIDCR, NIDDK, NIDA, NIEHS, NIGMS, NINR, NEI, NHLBI, NIMH, NINDS, NCCAM, and ODS.
- Purpose is to support the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research.
- Clinically trained professionals interested in further career development in biomedical research that is not patient-oriented should refer to the Mentored Clinical Scientist Career Development Award (K08).
  - Paraphrased from NIH.gov

Mentored NIH Training Grants

- Paul B. Beeson Career Development Awards in Aging (K08 & K23)
- This program is supported by NIA.
- This program provides 3-5 years of support to clinically-trained faculty members in strong research environments to enable them to gain skills and experience in aging research, under the guidance of a mentor or mentors, and to establish an independent program of research in this field.
  - Paraphrased from NIH.gov

NonMentored NIH Training Awards

- Independent Scientist Award (K02)
- Supported by NIA, NIAAA, NIAID, NIAMS, NICHD, NIDCD, NIDCR, NIDA, NIEHS, NHLBI, NIMH, NINDS, and ODS.
- The K02 provides support for newly independent scientists who can demonstrate the need for a period of intensive research focus as a means of enhancing their research careers.
- The K02 is intended to foster the development of outstanding scientists and to enable them to expand their potential to make significant contributions to their field of research.
  - Paraphrased from NIH.gov

Faculty Transition Grants

- Career Transition Awards provide support to an individual postdoctoral fellow in transition to a faculty position:
-
- NCI: The NCI Transition Career Development Award (K22)
- NCI: NCI Transition Career Development Award to Promote Diversity (K22)
- NCCAM: Complementary and Alternative Medicine Career Transition Award (K22)
- NHLBI: NHLBI Career Transition Award (K22)
- NIAAA: NIAAA Career Transition Award (K22)
- NIAID: NIAID Research Scholar Development Award (K22)
- NICHD: NICHD Career Transition Award (K22)
- NIDDK: NIDDK Career Transition Award (K22) in Patient-Oriented Research

Postdoctoral NIH Training Grants

- Ruth L. Kirschstein National Research Service Awards (NRSA) for Individual Senior Fellows (F33)
- Supported by NCI, NEI, NHLBI, NHGRI, NIA, NIAAA, NIAID, NIAMS, NICHD, NIDCD, NIDCR, NIEHS, NIGMS, NINDS, NINR, NCCAM, and ODS.
- The objective is to provide senior fellowship support to experienced scientists who wish to make major changes in the direction of their research careers or who wish to broaden their scientific background by acquiring new research capabilities as independent research investigators.
- Paraphrased from NIH.gov

Postdoctoral NIH Training Grants

- Ruth L. Kirschstein National Research Service Awards (NRSA) for Individual Postdoctoral Fellows (F32)
- Supported by NIA, NIAAA, NIAID, NIAMS, NIBIB, NCI, NICHD, NIDCD, NIDCR, NIDDK, NIDA, NIEHS, NEI, NIGMS, NHLBI, NHGRI, NIMH, NINDS, NINR, NCRR, and ODS.
- The objective of this program is to provide support to promising postdoctoral applicants who have the potential to become productive and successful independent research investigators in scientific health-related fields relevant to the missions of the participating NIH Institutes and Centers.
- Training plan of the award similar to a K award.
  - Paraphrased from NIH.gov

Common Errors in Training Grants

- Candidate
  - Limited research productivity in the past (less then 3 publications generally raises concern).
  - Large gaps in history where productivity was low without explanation for this hiatus.
  - Failure to describe the gap in the candidate's training background that requires additional mentored training.

Common Errors in Training Grants

- Training Plan
  - Lacks detail
  - Redundant with previous training
  - Not tied directly to career goals
  - Dependent on off-site mentors (bad fit to environment)
  - Too many mentors; mentors lack clear roles
  - Unrelated to proposed science
  - Too many goals (e.g., learning fMRI, DTI, SPECT)

Common Errors in Training Grants

- Science
  - Too complex or too broad in scope (really an RO1)
  - Not related to training goals/expertise of the mentor
  - Too much overlap with mentor's research/failure to define independence from mentor
  - No preliminary data
  - Aims lack hypotheses
  - Analytic plan not tied to the aims
  - No power analysis (or analysis based on wrong data)

Foundation Grants

- Opportunity for funding to support large and small projects.
- Can be ideal for junior investigators to obtain pilot data to support NIH grants.
- Competition still high. Review groups similar to NIH.
- Often less indirect costs to home institution, but still an effective way to promote your research and get going!!!

Foundation Grants

- Alzheimer's Association http://www.alz.org/professionals_and_researchers_researchprograms.asp
- Epilepsy Foundation http://www.epilepsyfoundation.org/research/grants.cfm
- Bill and Melinda Gates Foundation http://www.gatesfoundation.org/ForGrantSeekers/
- National Stroke Association (fellowship) http://www.stroke.org/site/PageServer?pagename=Fellow
- Parkinson's Disease Foundation http://www.pdf.org/Research/internationalresearch.cfm

Things to Remember when Writing Grants

Mark S. Aloia, PhD
Associate Professor of Medicine
National Jewish Health

Top 10 Things for Developing a Program of Research

1. Research something that is feasible.
2. Research something you like as long as long as it satisfies #1.
3. A program of research beings as a correlation.
4. You decide whether to move toward mechanism or treatment.

Top 10 Things for Developing a Program of Research

5. Focus on simple experiments.
6. Collaborate with experts.
7. Become an expert on one thing.
8. Publish your findings.
9. Rely on yourself for the promotion of your work.
10. Treat your program of research like a new business.

Grant Sections

- Specific Aims – 1 (1 page)
  - Outlines everything and includes hypotheses
- Background and Significance – 4 (5-6 pages)
  - Provides literature justification
- Preliminary Studies – 3 (5-6 pages)
  - Demonstrates team's abilities and pilot data
- Methods – 2 (12-13 pages)
  - Entire design, details, and justification for science.

Specific Aims

- Purpose of the study
- Brief introduction – outline form
- Brief mention of team and/or preliminary studies.
- Overall goal of the study
- Aims with hypotheses and glimpse into design – will be cut and pasted throughout.

Aims

- Make it concise
- Highlight sentences that can be read alone to understand the study.
- Make aims more general and hypotheses more specific.
- No more than 4 aims – less is more!
- Not too much detail, but don't leave anything out.
- This is where you get your confidence!

Background and Significance

- Sets the stage for the study.
- Follows your outline.
- Provides justification for this as the next logical step.
- Here is where you test your sequence of studies.
- We usually want to do the study that is three ahead of where we are.

Background and Significance

- Outline key points that set the stage for the study.
- Use these as headings for this section.
- Not a dissertation!
- Don't overwrite this section.
- Again, highlight sentences.
- Summary at end, repeat aims and hypotheses.

Preliminary Studies

- Justification for your research team and environment.
- Outline your team and their expertise – including you.
- Outline what techniques, abilities, and data are needed to set the stage for the proposed study.
- Demonstrate these.

Preliminary Studies

- These are not all pilot data and NOT all your data.
- You are part of a team.
- Preliminary data demonstrate ability – feasibility, not proof of concept.
- Pilot data present proof of concept.
- Both are needed.

Methods

- Largest part of the grant.
- Starts with an overview.
- Experimental design considerations section.
- Participants (not subjects).
- Procedures
- Assessments
- Statistical and power analyses – for each hypothesis.

Experimental Design Considerations

- Top four decisions you made about the research design and your reasoning for making those choices.
- Threats to internal and external validity.
- Choice of groups.
- Demonstrate your thought process. They fund you as well as the study.

Threats to Internal Validity

- These are the potential things that could interfere with the relation between the IV and the DV.
- Example: How does the administration of glucose affect memory?
  - IV = Glucose of saccharin; DV = Memory
  - Non-IVs that can affect memory – Age, education, history, intelligence.

Threats to External Validity

- These are things that can make your well-controlled study difficult to apply to the natural setting.
- The study must have some real representation in life.
- Good studies struggle between the balance of internal and external threats.

Common Internal Threats

- History
- Maturation
- Testing
- Instrumentation
- Statistical Regression
- Selection Bias
- Attrition

Common External Threats

- Sample Characteristics
- Stimulus Characteristics and Settings
- Reactivity to Experimental Arrangements
- Multiple Treatment Interference
- Novelty Effects
- Reactivity of Assessment
- Test Sensitization
- Timing of Measurement

Solutions

- Nothing is perfect.
- Restrict the range of threats.
- Exclude some
- Match on others
- Don't assume you will control statistically.

- EXPLAIN YOU RATIONALE!

Stats and Power

- Each aim must have testable hypotheses.
- Explorations are not recommended, especially if they involve adding burden or new participants.
- Each hypothesis must have its own analyses.
- Each analysis must have its own power analysis.

Top Ten Do. . .

1. Call the program officer(s)
2. Get copies of successful and unsuccessful grants.
3. Find a mentor/working group
4. Organize your team to reflect the needs of the study.
5. Consider all mechanisms (even industry).

Top Ten Do. . .

6. Read the RFA/PA.
7. Get reviewers ahead of time (even for pay).
8. Include experimental design considerations (and read Kazdin!).
9. Keep aims to a single page – and order them in terms of certainty.
10. Enlist consultants!

Top Ten Don't. . .

1. Avoid criticism.
2. Rush your grant.
3. Be too ambitious.
4. Assume anything from the reviewers.
5. Avoid writing.
6. Be afraid to change something near the end.

Top Ten Don't. . .

7. Go it alone.
8. Underestimate the burden of administrivia.
9. Cover anything up.
10. Give up!

Bob Bilder

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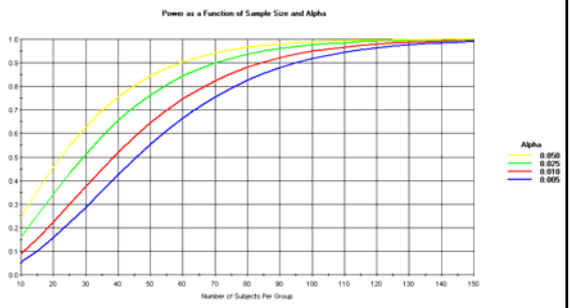
- Some final notes about data reduction specific to NP research protocols
  - The problem of test multiplicity
  - The importance of a reasonable power analysis
  - Justifying test selection using operational definitions of constructs and criteria for selection
- Let's design a study!

NP Assessment for Research: Bonferroni of the Vanities

- Clinical NP accustomed to digesting hundreds of variables on the fly to diagnose/treat complex cases
- Research reviewers will not be impressed by the size of your variable list
- Many good projects fail (on review) because data reduction strategies are absent, vague, or inappropriate

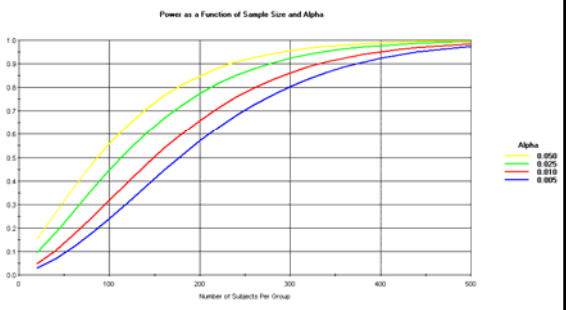
Power for Effect Size *d* = .6

(n of vars: 1, 2, 5, and 10)



Power for Effect Size *d* = .3

(n of vars: 1, 2, 5, and 10)



Data Reduction Strategies for NP Research

- Develop objective criteria for test selection and prioritize these for your specific study aims
  - Validity in measuring construct of interest
  - Reliability (internal consistency, test-retest)
  - Validity with respect to other external measures
  - Generalizability, comparability to prior literature or clinical practice
  - Burden: time, effort, ease of administration
  - In longitudinal designs: benefits/risks of alternate forms; estimate both test retest correlations and bias (prior exposure effects)

NP Construct Definition

- Be clear about what you say you are measuring and operationalize this construct
- Adequate construct assessment typically demands 3 independent indicators for the construct (but pragmatics may limit to two)
- Independence highly suspect when variables come from the same test (e.g., immediate and delayed recall from a memory test)
- With multiple indicators per construct, you can then form "composite" scores of higher reliability and validity

Constructing NP Composites

- "Rational" or "*a priori*" strategies
  - Decide in advance what variables load on what constructs, pre-specify data reduction strategy
- "Empirical" strategies
  - Factor analytic strategies: principal components or principal factor analysis
- Hybrid strategies
  - A priori plan tuned by empirical psychometric performance

Rational NP Composite Score Construction (1)

- Pick your constructs; assign your variables
- Inspect your data religiously (see Tabachnik & Fidell)
  - SPSS "Explore" a good start
  - Check both univariate and multivariate normality and homogeneity of variance
  - Transform raw data before applying standardization (converting to mean = 0 and SD = 1)
  - Always consider standardization with respect to what? (baseline, healthy…)
  - Reliance on pre-existing or published "norms" is often considered a fatal flaw

Rational NP Composite Score Construction (2)

- Examine scale properties of new, normalized, standardized variables when combined (i.e., SPSS "Scale", get coefficient alpha, inspect correlations)
- Factor analysis may also be used to generate similar insights into covariance structure
- After averaging z-scores, you need to re-standardize to interpret as standard scores, or at next stage of combination, because composites will have SD < 1

Using IRT to Refine Metrics

- For new instrument development, consider Item Response Theory (IRT) models
- Advantages – many: including more efficient assessment, computerized adaptive assessment, and ability to build in dynamic inclusion of new items while maintaining consistency w/ prior forms
- Challenges – usually need big samples (~500) to use effectively

Let's design a study!

- A new drug "Nanabuxeron" theoretically blocks the deposition of tau proteins in the brain
- Pre-clinical studies show efficacy in aging mouse, rat models; improved performance on rodent tests of memory and attention
- Phase I studies show the drug is safe and tolerated well in humans
- What do you now propose?

Study Design for Nanabuxeron

- Sample selection
  - Inclusion/exclusion criteria?
  - Sample size(s)?
- Study design
  - N of arms, parallel or cross-over(?), duration
  - N of assessments; multiple baselines(?); timing of assessments
  - Endpoint definition and test selection
- Power analysis

Thanks!

- We hope to have more information online, please visit www.nanonline.org under "Research & Publications"
- Check www.nanonline.org for updates on the NAN Clinical Research Grants program
- Comments or questions please: rbilder@mednet.ucla.edu
- Good luck!