Practical What & Where of Rigor and Reproducibility in the NIH Application

SIU School of Medicine
Office of Grants & Contracts with Sophia Ran, PhD
Recent Training Sessions

NIH Regional Seminar
Rigor and Reproducibility: Back to Basics
Chicago, IL
Oct 27, 2016

Write Winning Grant Proposals
John D. Robertson, PhD
Grant Writers’ Seminars and Workshops
Oct 28, 2016
Why?

- NIH, researchers, educators, journals, reviewers, funding agencies, disease advocacy groups, pharmaceutical industry agree:  

The inability to translate and replicate results is a BIG problem.

(Landis, S.C., et al., 2012)
Why?

- Calls for researchers to include methodological rigor in study design in order to translate results
- Ultimate goal: translate basic science into clinical studies and human intervention
  - Erroneous scientific rationale leads to unsuccessful clinical trials, exposing study patients to harm
  - Wastes resources and energy (NIH and institution)

(Landis, S.C., et al., 2012)
New Policies

Applies to:

- Research
- Career Development
- Centers
- People-based
- Program Projects
- Small Business
- Resource-Related

Does Not Apply to:

- Administrative Supplements
- Conferences
- Construction
- Instrumentation
- Publication Support
Planned Policy

- Individual Fellowships
- Institutional Training
- Institutional Career Development Awards

In 2017, these will require formal training and instruction in rigorous experimental design and transparency to enhance reproducibility.

(see NOT-OD-16-034)
Four Areas of Clarification

1. Scientific Premise
2. Scientific Rigor
3. Relevant Biological Variables
4. Authentication of Key Biologics and/or Chemical Resources
Specific Points of Rigor & Reproducibility

- Randomization
- Blinding
- Sample Size Estimation
- Data Handling
Resources

- A CCR Statistician is available to help determine study power and statistical analysis plan: Email: statistics@siumed.edu
- Resources such as Clayton, Collins, and Landis articles on Reference slide
<table>
<thead>
<tr>
<th>Element of Rigor</th>
<th>Section of Application</th>
<th>Criterion Score</th>
<th>Additional Review Consideration</th>
<th>Contribute to Overall Impact?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific Premise</td>
<td></td>
<td>Significance</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Scientific Rigor</td>
<td>Research Strategy</td>
<td>Approach</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Consideration of Relevant Biological Variables Such as Sex</td>
<td></td>
<td>Approach</td>
<td>NA</td>
<td>Yes</td>
</tr>
<tr>
<td>Authentication of Key Biological and/or Chemical Resources</td>
<td>New Attachment</td>
<td>NA</td>
<td>Adequate or Inadequate</td>
<td>No</td>
</tr>
</tbody>
</table>
1. SCIENTIFIC PREMISE
SCIENTIFIC PREMISE
- WHAT?

- The project’s foundation of knowledge (work completed in the past)
- Critical analysis of the quality and strength of the research used to form the basis for the proposed hypothesis/research question
Cite research by others that helped spark the idea for your proposed hypothesis/ research question

- published literature
- PA/RFA “Purpose” and “Background”
Special considerations for preliminary data:

- Strong scientific rationale?
- Rigorous experimental design?
- Consideration of relevant biological variables?
- Authenticated biological and chemical resources?
SCIENTIFIC PREMISE
- WHERE?

▲ Specific Aims
▲ Research Strategy
  ▼ Significance
  ▼ Innovation
▲ Approach
  ▶ Research Design
  ▶ Potential Pitfalls & Alternate Approaches
▲ Future Directions

Russell & Morrison, pg 80
SCIENTIFIC PREMISE

SPECIFIC AIMS
SPECIFIC AIMS - WHAT?

- Few citations in Specific Aims section
- Essential references to justify project need
  - Most important, seminal, ‘linchpin’ references
  - Not review articles
SPECIFIC AIMS
- WHERE?

- Introductory paragraph to introduce need (gap)

- Long term goal paragraph with central hypothesis and scientific rationale

Example, Russell & Morrison 2016, pg 77
SCIENTIFIC PREMISE

RESEARCH STRATEGY

Significance
Innovation
Approach
SIGNIFICANCE
- WHAT?

Describe the scientific premise for the proposed project, including GENERAL consideration of the strengths and weaknesses of published research or preliminary data crucial to the support of your application.
SIGNIFICANCE
- WHAT?

- Scientific rigor of cited/prelim work
- Justify the need for the proposed research by assessing the foundation of knowledge supporting the proposal
- PA/RFA “Purpose” and “Background”
SIGNIFICANCE
- WHERE?

Significance:

Scientific Premise

Overall Scientific Premise
Scientific Premise for Aim #1
Scientific Premise for Aim #2
(add for addl aims if needed)

Sentence that frames the problem as relevant to FOA or I/C.

Russell & Morrison, pg 90
INNOVATION
- WHAT?

- Tactfully discuss the status quo and the Innovative aspects of your project that depart from it

- Establish the firm foundation supporting your claim to enable new funding agency goals that would be unattainable without the proposed work
Do not repeat assessment of strengths and weakness (should be in Significance section)
Paragraph 1: frame the status quo diplomatically

“The current standard/status quo relating to ________________ is _________________. “
Enough detail that experiments can be replicated

- WHAT NOT?

- Manufacturer instructions
- Standard scientific procedures
- Etc.
APPROACH - WHERE?

► Significance

- Methodologic feasibility (cited work/prelim data)
- Technical ability (prelim data)

► Potential Pitfalls/Alternate Strategies

- Unvalidated biologic or chemical resources
- Consideration of biological variables
- Retrospective endpoint selection
- Inadequate blinding
Research Strategy: Future Directions

- Ability to translate and replicate results
- NIH requirements are designed to improve:
  - Transparency
  - Adequate reporting on the design, conduct, and analysis of experiments
2. SCIENTIFIC RIGOR

$$t = \frac{x - \mu_0}{s/\sqrt{n}}$$

rigorous experimental design

Read the instructions.
Describe the experimental design and methods proposed and how they will achieve robust and unbiased results.

Robust and unbiased results are:

- Obtained with solid, well-controlled experiments and
- Capable of being reproduced under well-controlled conditions, using reported experimental details.
Methods to reduce bias (examples)
- Use independent, blinded assessors
- Select primary endpoint prospectively
- Randomize to treatment groups
- Define inclusion/exclusion criteria in advance
- Predetermine handling outliers
- Conduct interim data analysis (statistics@siumed.edu)
Research Strategy: Approach

► Succinctly state what is planned
  ➢ Include information on sample numbers, blinding, statistical power and analyses
  ➢ Describe experimental animal numbers here (power); VAS no longer requires justification of animal numbers.

► Be transparent about your plans for analysis
3. RELEVANT BIOLOGICAL VARIABLES

consideration of sex and other biological variables
RELEVANT BIOLOGICAL VARIABLES - WHAT?

- Biological variables: sex, age, weight, underlying health conditions, types of strains, vendor source, suppliers, housing conditions (room temp., light/dark cycles)

- Types of studies: tissues, primary cells, samples from vertebrate animals and humans
  - If cells, tissues, or other samples are being implanted into a host, sex of both sample & host should be considered
RELEVANT BIOLOGICAL VARIABLES
- WHERE?

- Research Strategy (design, analyses), Vertebrate Animals, Human Subjects
- Propose to study one sex ONLY with strong justification from scientific literature, preliminary data, or other relevant considerations
  - Single-sex studies: pregnancy, ovarian & prostate cancer
  - Clinical Studies: Inclusion of Women and Minorities and Inclusion of Children
RELEVANT BIOLOGICAL VARIABLE DATA

- Data should be disaggregated, whether study was statistically powered to detect sex differences or not.
- Reporting descriptive statistics for males and females provides usual information for further study and understanding of differences in biology.
- Studies that control for sex in multivariate analyses should also report sex-specific results.
FAQ: Will I have to double my sample numbers?

- Statistical analysis will determine the sample size needed for statistically significant data
- May not need to double, but may need to use more
Reviewer Guidance to Evaluate Sex as a Biological Variable (SABV)

Main points
- NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies.
- Strong justification from the scientific literature, preliminary data, or other relevant considerations must be provided for applications proposing to study only one sex.
- This decision tree is meant to be used as a guide, but does not encompass the entire policy. See NOT-OD-15-102 for more information.

Does the study involve vertebrate animals or humans?¹

- NO
  - No further consideration of SABV required; not considered a weakness

- YES
  - Is the study intended to test for sex differences?²
    - NO
      - Acknowledge as a weakness in the critique and discussion and score accordingly
    - YES
      - Is the design/analysis adequately rigorous to test for sex differences?
        - YES
          - Acknowledge as a strength in the critique and discussion and score accordingly
        - NO
          - Acknowledge as a weakness in the critique and discussion and score accordingly

Notes
1 See FAQs on Inclusion, primary cells and tissues, and established cell lines.
2 See FAQs on considering sex as a biological variable and use of males and females in basic research.
3 See FAQ on justification of single sex studies.
4 Based on the research question and availability of relevant data, statistically powered comparisons between the sexes may not be required. Analyzing and publishing sex-based data, even in the absence of powered sex differences analyses, would permit the consideration of the influence of sex in the interpretation of study results and the appropriate generalization of research findings.
4. AUTHENTICATION OF BIOLOGICS AND CHEMICALS

authentication of key resources
AUTHENTICATION OF BIOLOGICS AND CHEMICALS - WHAT?

- Quality of resources is critical to the ability to reproduce results
- Key biological and/or chemical resources should be regularly authenticated to ensure identity and validity
AUTHENTICATION OF BIOLOGICS AND CHEMICALS - WHAT?

If applicable to the proposed science, briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies. No more than one page is suggested.

- Key biological and/or chemical resources include, but are not limited to, cell lines, specialty chemicals, antibodies, and other biologics.
- Standard laboratory reagents that are not expected to vary do not need to be included in the plan. Examples are buffers and other common biologicals or chemicals.
- Reviewers will assess the information provided in this Section. Any reviewer questions associated with key biological and/or chemical resource authentication will need to be addressed prior to award.
## AUTHENTICATION PLAN - WHERE?

### Introduction
1. Introduction to Application (Resubmission and Revision)

### Research Plan Section
2. Specific Aims
3. *Research Strategy
4. Progress Report Publication List

### Human Subjects Section
5. Protection of Human Subjects
6. Data Safety Monitoring Plan
7. Inclusion of Women and Minorities
8. Inclusion of Children

### Other Research Plan Section
9. Vertebrate Animals
10. Select Agent Research
11. Multiple PD/PI Leadership Plan
12. Consortium/Contractual Arrangements
13. Letters of Support
14. Resource Sharing Plan(s)
15. Authentication of Key Biological and/or Chemical Resources

### Appendix
16. Appendix
Contact Info

grants@siumed.edu
statistics@siumed.edu
References


