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 <u>BIG</u> 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
- NIH website: https://grants.nih.gov/reproducibility/index.htm

RPG Application and Review

Element of Rigor	Section of Application	Criterion Score	Additional Review Consideration	Contribute to Overall Impact?
Scientific Premise	Research Strategy	Significance	NA	Yes
Scientific Rigor		Approach	NA	Yes
Consideration of Relevant Biological Variables Such as Sex		Approach	NA	Yes
Authentication of Key Biological and/or Chemical Resources	New Attachment	NA	Adequate or Inadequate	No

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

SCIENTIFIC PREMISE - WORK BY OTHERS

- Cite research by others that helped spark the idea for your proposed hypothesis/ research question
  - published literature
  - PA/RFA “Purpose” and “Background”

Read the instructions.

SCIENTIFIC PREMISE - WHAT RE: PRELIM DATA?

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

Stay within page limits.

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:

<u>Scientific Premise</u>

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

INNOVATION - WHAT NOT?

- Do not repeat assessment of strengths and weakness (should be in Significance section)

Read the instructions.

INNOVATION - WHERE?

- Paragraph 1: frame the status quo *diplomatically*
  - *"The current standard/status quo relating to _____ is _____."*

Russell & Morrison, pg 97

APPROACH
- WHAT?

Enough detail that experiments can be replicated

- WHAT NOT?

- Manufacturer instructions
- Standard scientific procedures
- Etc.

APPROACH - WHERE?

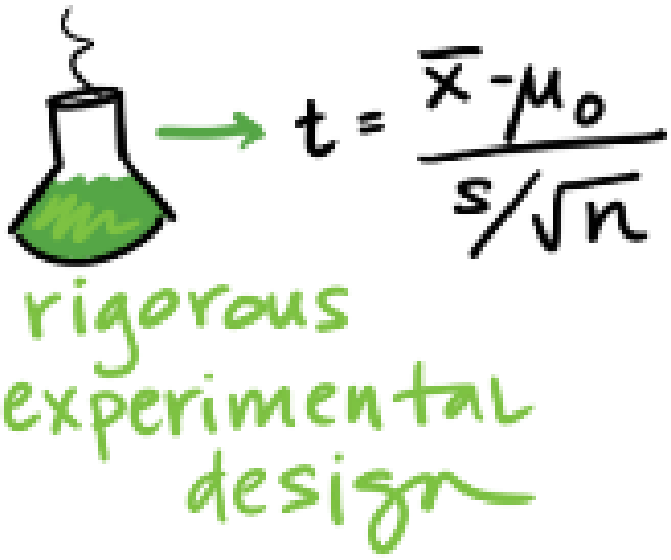
- Significance
  - Methodologic feasibility (cited work/prelim data)
  - Technical ability (prelim data)
- Potential Pitfalls/Alternate Strategies
  - Unvalidated biologic or chemical resources
  - Consideration of biological variables
  - Retrospective endpoint selection
  - Inadequate blinding

APPROACH - WHERE?

Research Strategy: Future Directions

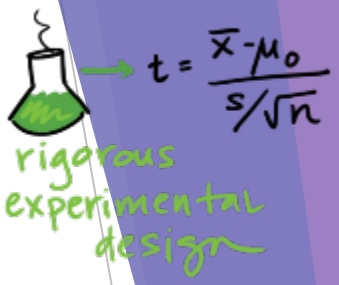
- Ability to translate and replicate results
- NIH requirements are designed to improve:
  - Transparency
  - Adequate reporting on the design, conduct, and analysis of experiments

2. SCIENTIFIC RIGOR



Read the instructions.

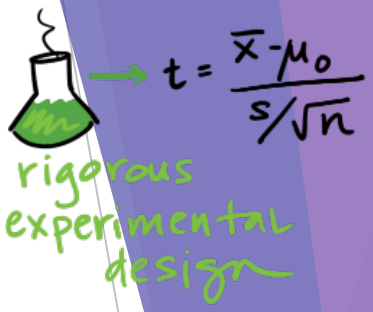
SCIENTIFIC RIGOR - WHAT?



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

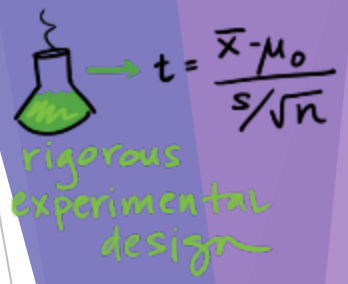
- Robust and unbiased results are:
  - Obtained with solid, well-controlled experiments and
  - Capable of being reproduced under well-controlled conditions, using reported experimental details.

SCIENTIFIC RIGOR - WHAT?



- 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)

SCIENTIFIC RIGOR - WHERE?



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

Stay within page limits.

3. RELEVANT 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

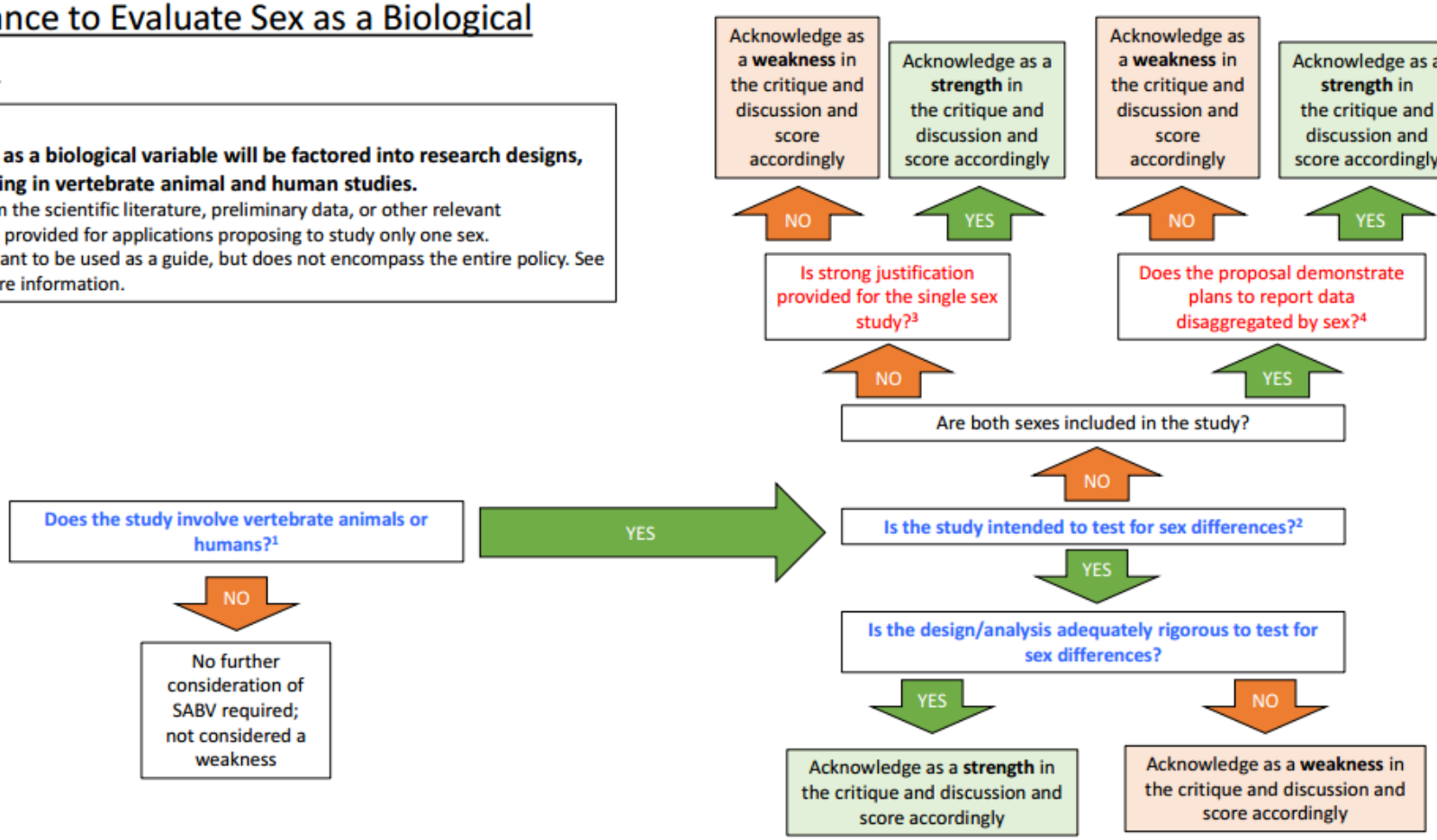
FAQ: Will I have to double my sample numbers?

- 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.



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 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?

View Burden Statement

PHS 398 Research Plan

OMB Number: 0925-0001
Expiration Date: 10/31/2018

Introduction				
1. Introduction to Application (Resubmission and Revision)		Add Attachment	Delete Attachment	View Attachment
Research Plan Section				
2. Specific Aims		Add Attachment	Delete Attachment	View Attachment
3. *Research Strategy		Add Attachment	Delete Attachment	View Attachment
4. Progress Report Publication List		Add Attachment	Delete Attachment	View Attachment
Human Subjects Section				
5. Protection of Human Subjects		Add Attachment	Delete Attachment	View Attachment
6. Data Safety Monitoring Plan		Add Attachment	Delete Attachment	View Attachment
7. Inclusion of Women and Minorities		Add Attachment	Delete Attachment	View Attachment
8. Inclusion of Children		Add Attachment	Delete Attachment	View Attachment
Other Research Plan Section				
9. Vertebrate Animals		Add Attachment	Delete Attachment	View Attachment
10. Select Agent Research		Add Attachment	Delete Attachment	View Attachment
11. Multiple PD/PI Leadership Plan		Add Attachment	Delete Attachment	View Attachment
12. Consortium/Contractual Arrangements		Add Attachment	Delete Attachment	View Attachment
13. Letters of Support		Add Attachment	Delete Attachment	View Attachment
14. Resource Sharing Plan(s)		Add Attachment	Delete Attachment	View Attachment
15. Authentication of Key Biological and/or Chemical Resources		Add Attachment	Delete Attachment	View Attachment
Appendix				
16. Appendix	Add Attachments	Delete Attachments	View Attachments	

Read the instructions.

Contact Info

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References

Clayton JA & Collins FS. **NIH to balance sex in cell and animal studies.** *Nature*. 2014 May 15; 509(7500): 282-283. http://www.nature.com/news/policy-nih-to-balance-sex-in-cell-and-animal-studies-1.15195

Collins FS and Tabak LA. **NIH plans to enhance reproducibility.** *Nature*. 2014 Jan 30; 505(7485): 612–613. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4058759/

Landis SC, Amara SG, Asadullah K, Austin CP, Bumenstein R, et al. **A call for transparent reporting to optimize the predictive value of preclinical research.** *Nature*. 2012 Oct 11; 490(7419): 187-191. http://www.nature.com/nature/journal/v490/n7419/full/nature11556.html

Lorsch JR, Collins FS, Lippincott-Schwartz J. **Fixing problems with cell lines.** *Science.* 2014 Dec 19; 346(6216): 1452-1453. http://science.sciencemag.org/content/346/6216/1452

NIH Notice NOT-OD-15-102, **Consideration of Sex as a Biological Variable in NIH-funded Research.** http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html

NIH Rigor and Reproducibility. https://www.nih.gov/research-training/rigor-reproducibility; http://grants.nih.gov/reproducibility/index.htm#guidance; http://grants.nih.gov/reproducibility/faqs.htm#4827: Infographic http://grants.nih.gov/reproducibility/documents/grant-guideline.pdf

Russell SW and Morrison DC. **The Grant Application Writer's Workbook – Forms D Edition.** April 2016. Grant Writers' Seminars and Workshops, LLC: Buellton, CA.