OVERVIEW

• Why the concern about reproducibility?
• The NIH response
• Updates to grant applications
• Training and Resources
OVERVIEW

• Why the concern about reproducibility?
  • The NIH response
  • Updates to grant applications
  • Training and Resources
THE REPRODUCIBILITY CHALLENGE

Why animal research needs to improve
Many of the studies that use animals to model human diseases are too small and too prone to bias to be trusted, says Malcolm Macleod.

• Noted by research community in multiple publications

Beware the creeping cracks of bias
Evidence is mounting that research is riddled with systematic errors. Left unchecked, this could erode public trust, warns Daniel Sarewitz.

• Across research areas

• Especially in preclinical research

False-Positive Psychology: Undisclosed Flexibility in Data Collection and Analysis Allows Presenting Anything as Significant

Drug targets slip-sliding away
The starting point for many drug discovery programs is a published report on a new drug target. Assessing the reliability of such papers requires a nuanced view of the process of scientific discovery and publication.

Reforming Science: Methodological and Cultural Reforms
Believe it or not: how much can we rely on published data on potential drug targets?

Prinz, Schlange and Asadullah  
Bayer HealthCare  

_Nature Reviews Drug Discovery_  
2011; 10:712-713
A call for transparent reporting to optimize the predictive value of preclinical research


The US National Institute of Neurological Disorders and Stroke convened major stakeholders in June 2012 to discuss how to improve the methodological reporting of animal studies in grant applications and publications. The main workshop recommendation is that at a minimum studies should report on sample-size estimation, whether and how animals were randomized, whether investigators were blind to the treatment, and the handling of data. We recognize that achieving a meaningful improvement in the quality of reporting will require a concerted effort by investigators, reviewers, funding agencies and journal editors. Requiring better reporting of animal studies will raise awareness of the importance of rigorous study design to accelerate scientific progress.
DUE Diligence, Overdue

Results of rigorous animal tests by the Amyotrophic Lateral Sclerosis Therapy Development Institute (ALS TDI) are less promising than those published. All these compounds have disappointed in human testing.

*Although riluzole is the only drug currently approved by the US Food and Drug Administration for ALS, our work showed no survival benefit.
†References for published studies can be found in supplementary information at go.nature.com/hf4j6.
IS THERE A REPRODUCIBILITY CRISIS?

- 7% Don’t know
- 52% Yes, a significant crisis
- 38% Yes, a slight crisis
- 3% No, there is no crisis

1,576 researchers surveyed

CHALLENGES TO RIGOR AND TRANSPARENCY IN REPORTING SCIENCE

• Science often viewed as self-correcting
  • Immune from reproducibility problems?
  • Principle remains true over the long-term

• In the short- and medium-term, interrelated factors can short-circuit self-correction
  • Leads to reproducibility problem
  • Loss of time, money, careers, public confidence
FACTORS THAT “SHORT CIRCUIT” SELF-CORRECTION

Current “hyper-competitive” environment fueled, in part, by:

- Historically low funding rates
- Grant review and promotion decisions depend too much on “high profile” publications
FACTORS THAT “SHORT CIRCUIT” SELF-CORRECTION

Publication practices:

• Difficulty in publishing negative findings
• Overemphasis on the “exciting, big picture” finding sometimes results in publications leaving out necessary details of experiments
FACTORS THAT “SHORT CIRCUIT” SELF-CORRECTION

Poor training

• Inadequate experimental design
• Inappropriate use of statistics ("p-hacking")
• Incomplete reporting of resources used and/or unexpected variability in resources
OVERVIEW

• Why the concern about reproducibility?
• The NIH response
• Updates to grant applications
• Training and Resources
NIH plans to enhance reproducibility

Francis S. Collins and Lawrence A. Tabak discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

A growing chorus of concern, from scientists and laypeople, contends that the complex system for ensuring shorter term, however, the checks and balances that once ensured scientific fidelity have been hobbled. This has compromised outnumbered by the hundreds of thousands published each year in good faith.

Instead, a complex array of other factors seems to have contributed to the lack of reproducibility. Factors include poor training of researchers in experimental design; increased emphasis on making provocative statements rather than presenting technical details; and publications that do not report basic elements of experimental design. Crucial experimental design elements that are all too frequently ignored include blinding, randomization, replication, sample-size calculation and the effect of sex differences.

And some says sauce to make and withhold to describe them as divisive edge. W scientists will be to further biomcounting and attitudes of centres and sci agencies of the overvaluation high-profile jour nalists also provide in such journal tenure, and in e rewards.

Then there is not published. Researchers to papers that poisory published work. Further compounding the problem is the difficulty of accessing unpublished data and the failure of funding agencies to establish or enforce policies that insist on data access.

PRECLINICAL PROBLEMS Reproducibility is potentially a problem in all scientific disciplines. However, human clinical trials seem to be less at risk because they are already governed by various regulations that stipulate rigorous design and independent oversight — including randomization, blinding, power estimates, pre-registration of outcome measures in standardized, public databases such as ClinicalTrials.gov and oversight by institutional review boards and data safety monitoring boards. Furthermore, the clinical trials community has taken important steps towards adopting standard reporting elements.
“Over the course of FY 2015, NIH plans to roll out policies that will require applicants to address inclusion of both sexes in biomedical research.”
BIOLOGICAL/DISEASE IMPACT OF EXPERIMENTAL DESIGN

Disease Impact, %

- Control
- Treatment

Male Female

Aggregated

Office of Extramural Programs
Since the 1960s, more than 400 widely used cell lines worldwide have been shown to have been misidentified.

A 2011 study of 122 different head and neck cancer cell lines revealed that 37 (30%) were misidentified.

Studies using just two misidentified cell lines were included in 3 grants funded by the NIH, two clinical trials, 11 patents, and >100 papers.
NEW JOURNALPOLICIES TO ENHANCE REPRODUCIBILITY

Journals unite for reproducibility

Reproducibility, rigor, transparency, and independent verification are cornerstones of the scientific method. Of course, just because a result is reproducible does not necessarily make it right, and just because it is not reproducible does not necessarily make it wrong. A transparent and rigorous approach, however, can almost always shine a light on issues of reproducibility. This light ensures that science moves forward, through independent verifications as well as the course corrections that come from refutations and the objective examination of the resulting data.

It was with the goal of strengthening such approaches in the biomedical sciences that a group of editors representing over 30 major journals, representatives from funding agencies, and scientific leaders assembled at the AAAS headquarters in June 2014 to discuss principles and guidelines for preclinical and clinical research. The gathering was convened by the U.S. National Institutes of Health, National Cancer Institute.

The discussion ranged from what journals were already doing to address reproducibility and the effectiveness of those measures to the compounding of the problem and the cost of solutions. The attendees agreed on a common set of Principles and Guidelines in Reporting Preclinical Research (www.nih.gov/about/reporting-preclinical-research.htm) that list proposed journal policies and author reporting requirements to promote transparency and reproducibility.

The new guidelines encourage that journals include in their information for authors their policies for statistical analysis and how they review the statistical accuracy of work under consideration. Any imposed page limits should not discourage reproducibility. The guidelines encourage using a checklist to ensure the reporting of important experimental parameters, such as standards used, number and type of replicates, statistics, method of randomization, whether experiments are blinded, and how the sample size was determined and what criteria were used to include or exclude any data. Journals should recommend the deposition of data in public repositories where available and link data bidirectionally to the published paper. Journals should strongly encourage, as appropriate, that all materials used in the experiment be shared with those who wish to replicate the experiment. Once a journal publishes a paper, it assumes the obligation to consider publication of a refutation of that paper, subject to its usual standards of quality.

The more open-ended portion of the guidelines suggests that journals establish best practices for image-based data (such as screening for manipulation and storing full-resolution archival versions) and how to describe experiments more completely. An example for animal experiments is requiring the source, species, strain, sex, age, health status, and strain characteristics. For cell lines, one might report the source, authentication, and mycoplasma contamination status. The editor of these guidelines does not obviate the need for authors or independent verification of research results, but should make it easier to perform such replication.

Some of the journals at the meeting also had implemented all or most of these principles and guidelines. The important point is that a large number of scientific journals are standing together in their conviction that reproducibility and transparency are important.

As partners to the research enterprise in the communication and dissemination of research results, journals want to do their part to raise the standards of benefit to all scientists and the benefit of society. The hope is that these guidelines will not be viewed as onerous, but as part of the quality control that justifies the public trust in science.
PRINCIPLES AND GUIDELINES FOR REPORTING PRECLINICAL RESEARCH

- Rigorous statistical analysis
- Transparency in reporting
- Data and material sharing
- Consideration of refutations
- Consider establishing best practice guidelines for:
  - Antibodies
  - Cell lines
  - Animals

http://www.nih.gov/about/reporting-preclinical-research.htm
# TRANS – NIH PILOTS

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<th>Types of Efforts Being Developed</th>
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<td>New Funding Opportunities with additional review criteria regarding scientific premise</td>
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<td>Changes to Biosketch</td>
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<td>Approaches to reduce &quot;perverse incentives&quot; to publish</td>
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<td>Other efforts</td>
<td>Use of Prize Challenges to encourage reproducibility of results, PubMed Commons</td>
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</table>
OUR GUIDING PRINCIPLES FOR RIGOR & TRANSPARENCY

• **Clarify** NIH’s long-standing expectations regarding rigor and transparency in applications

• Raise awareness and begin culture shifts in the scientific community

• Prompt applicants to consider issues that they may have previously down-played or ignored
OUR GUIDING PRINCIPLES FOR RIGOR & TRANSPARENCY

• Improve the way that applicants describe their work; provide sufficient information for reviewers

• Demonstrate to our public stakeholders that NIH is seriously considering their concerns

• As always, ensure that NIH is investing in the best science and minimizing unnecessary burden
• Policy named “Enhancing Reproducibility through Rigor and Transparency”
• Short-term focus to achieve long-term goal
• Rigor + Transparency --&gt; Reproducibility

Easy to measure  Difficult to measure
Enhancing Reproducibility in NIH-supported Research through Rigor and Transparency

Dr. Larry Tabak is the Principal Deputy Director of NIH.

Nothing could be more important to our enterprise than research rigor, assuring that the results of our work are reproducible. Our conversation with you on this topic began early last year with a commentary in Nature by Francis Collins and today’s guest blogger, Larry Tabak, on the importance of reproducibility and how NIH plans to enhance it. As described in a follow-up Rock Talk post, the topic of reproducibility is not new. Evidence has shown that too many biomedical-research publications are irreproducible. Thus this topic demanded our community’s immediate attention and we have had continued dialog with and participation by you over the course of the last 18 months to describe the issue, request information, launch
OVERVIEW

• Why the concern about reproducibility?
• The NIH response
• Updates to grant applications
• Training and Resources
FOUR AREAS OF CLARIFICATION

• Scientific premise
• Scientific rigor
• Relevant Biological Variables, Such as Sex
• Authentication of Key Biological and/or Chemical Resources
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<th>Section of Application</th>
<th>Criterion Score</th>
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<th>Contribute to Overall Impact?</th>
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<tbody>
<tr>
<td>Scientific Premise</td>
<td>NA</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>Approach</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>
SCIENTIFIC PREMISE

The research used to form the basis for the proposed research question

- observations,
- preliminary data, or
- published literature

Consideration may include

- attention to the rigor of the previous experimental designs
- incorporation of relevant biological variables and authentication of key resources
SCIENTIFIC PREMISE
RESEARCH STRATEGY: SIGNIFICANCE

• Explain the importance of the problem or critical barrier to progress in the field that the proposed project addresses.

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

• Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.

• Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.
SCIENTIFIC PREMISE
SIGNIFICANCE – REVIEW QUESTIONS

• Does the project address an important problem or a critical barrier to progress in the field?

• Is there a strong scientific premise for the project?

• If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?

• How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?
FAQ: WILL ATTENTION TO SCIENTIFIC PREMISE IMPEDE INNOVATION?

• Scientific premise refers to the key data introduced by the applicant to justify the project

• If preliminary data are not provided in an application, a critical assessment of the scientific literature that supports and/or contradicts the research question(s) can be provided

• Consideration of scientific premise can help investigators identify the risks and develop a research strategy that enhances the opportunity for success
SCIENTIFIC RIGOR

• The strict application of the scientific method

• Robust results
  • obtained with solid, well-controlled experiments
  • capable of being reproduced under well-controlled conditions, using reported experimental details.

• Methods to reduce bias (examples)
  • multiple individuals record assessments,
  • define terminology in advance,
  • independent, blinded assessors, etc.
SCIENTIFIC RIGOR
RESEARCH STRATEGY: APPROACH

• Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. Describe the experimental design and methods proposed and how they will achieve robust and unbiased results. Unless addressed separately in Item 15 (Resource Sharing Plan), include how the data will be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate.

• Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.

• If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high risk aspects of the proposed work.
**SCIENTIFIC RIGOR APPROACH – REVIEW QUESTIONS**

- Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
- Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?
- Are potential problems, alternative strategies, and benchmarks for success presented?
- If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?
FAQ: HOW MUCH DETAIL DO I NEED TO INCLUDE TO ADDRESS SCIENTIFIC RIGOR?

• Succinctly state what is planned
  • Include information on samples numbers, blinding, powered studies, statistical analyses…

• Be transparent about your plans for analysis

• Stay within page limits
CONSIDERATION OF RELEVANT BIOLOGICAL VARIABLES, SUCH AS SEX

- Affect health or disease
  - sex,
  - age,
  - weight, and
  - underlying health conditions

- Should be factored into research designs, analyses, and reporting in vertebrate animal and human studies.

- Proposing to study one sex?
  - Need strong justification from the scientific literature, preliminary data, or other relevant considerations
RELEVANT BIOLOGICAL VARIABLES
RESEARCH STRATEGY: APPROACH

• Explain how relevant biological variables, such as sex, are factored into research designs and analyses for studies in vertebrate animals and humans. For example, strong justification from the scientific literature, preliminary data, or other relevant considerations, must be provided for applications proposing to study only one sex.

• If your study(s) involves human subjects, the sections on the Inclusion of Women and Minorities and Inclusion of Children can be used to expand your discussion on inclusion and justify the proposed proportions of individuals (such as males and females) in the sample, but it must also be addressed here in the Approach section.

• Please refer to NOT-OD-15-102 for further consideration of NIH expectations about sex as a biological variable.
RELEVANT BIOLOGICAL VARIABLES
APPROACH – REVIEW QUESTIONS

• Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?
FAQ: WILL I HAVE TO DOUBLE MY ANIMAL NUMBERS?

• Policy requires that you consider sex as a biological variable

• Justification should be provided if the application proposes to study one sex
  • sex-specific condition of phenomenon (e.g., ovarian or prostate cancer),
  • acutely scarce resources, or
  • sex-specific hypotheses possible due to known differences between males and females.

• Cost and absence of known sex differences are inadequate justifications for not addressing sex.
AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES

• 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

• Key biological and/or chemical resources may or may not be generated with NIH funds and:
  • may differ from laboratory to laboratory or over time;
  • may have qualities and/or qualifications that could influence the research data; and
  • are integral to the proposed research.
AUTHENTICATION OF KEY RESOURCES
OTHER RESEARCH PLAN SECTIONS – INSTRUCTIONS

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 may or may not be generated with NIH funds and: 1) may differ from laboratory to laboratory or over time; 2) may have qualities and/or qualifications that could influence the research data; and 3) are integral to the proposed research. These 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 ATTACHMENT

## PHS 398 Research Plan

### 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 POPII 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
AUTHENTICATION OF KEY RESOURCES
ADDITIONAL REVIEW CONSIDERATION

• For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.
FAQ: WHAT SHOULD I INCLUDE IN MY AUTHENTICATION PLAN?

• Each investigator determines which resources are key to the proposed research.

• Scientific societies and the research community encouraged to develop standard approaches.

• Key resources refer to *established resources*.

• If key resources have been obtained from an outside source, the investigator is still expected to provide their own plans.

• Authentication plan is not scored, so if the application is meritorious, applicant may work with PO to address any deficiencies prior to award.
POLICY APPLIES TO:  
Research  
• Career Development  
• Centers  
• People-based  
• Program Projects  
• Small Business  
• Resource-Related

Training *(coming soon - see NOT-OD-16-034)*  
• Individual Fellowships  
• Institutional Training  
• Institutional Career Dev

DOES NOT APPLY TO:  
• Administrative supplements  
• Conferences  
• Construction  
• Instrumentation  
• Publication support
RPPR

• NOT-OD-16-005 on Post Award changes
• Rigor addition to RPPR instructions: 1/25/2016
• NOT-OD-16-031 (published12/15/2015)
• These RPPR updates for rigor and transparency:
  • prepare non-competing renewals for the next competitive renewal, and
  • will help NIH implement and evaluate the policy for both current and new awards.
B.2 What was accomplished under these goals?

Goals are equivalent to specific aims. In the response, emphasize the approaches taken to ensure robust and unbiased results. Include the significance of the findings to the scientific field.

B.6 What do you plan to do for the next reporting period to accomplish the goals?

Include any important modifications to the original plans, including efforts to ensure that the approach is scientifically rigorous and results are robust and unbiased. Provide a scientific justification for any changes involving research with human subjects or vertebrate animals. A detailed description of such changes must be provided under Section F. Changes.
OVERVIEW

• Why the concern about reproducibility?
• The NIH response
• Updates to grant applications
• Training and Resources
TRAINING

• Need for more training on day-to-day basis
• Focus on rigor & transparency
• Separate from RCR
TRAINING

• NIH will require a description of instruction in the design and conduct of rigorous experiments.
  • Institutional training
  • Institutional career development
  • Individual fellowships

• Additional guidance on training requirements will be forthcoming; see NOT-OD-16-034
Clearinghouse for Training Modules to Enhance Data Reproducibility

In January 2014, NIH launched a series of initiatives to enhance rigor and reproducibility in research. As a part of this initiative, NIGMS, along with nine other NIH institutes and centers, issued the funding opportunity announcement RFA-GM-15-006 to develop, pilot and disseminate training modules to enhance data reproducibility. Graduate students, postdoctoral fellows and early stage investigators are the primary audiences for these training modules.

For the benefit of the scientific community, we will be posting the products of these grants on this Web site as they become available in the future.

In addition, we are sharing here a series of four training modules developed by NIH. These modules focus on integral aspects of rigor and reproducibility in the research endeavor, such as bias, blinding and exclusion criteria. The modules are not meant to be comprehensive, but rather intended as a foundation to build on and a way to stimulate conversations, which may be facilitated by the use of the accompanying discussion materials. Currently, the modules are being integrated into NIH intramural training activities.

NIH Rigor and Reproducibility Training Modules

Introduction to the Modules [PDF, 110KB]

Module 1: Lack of Transparency
In order to reproduce someone else’s findings adequately, the experimental methods, rationale and other pertinent information must be accessible and understandable. This module highlights the need to include all relevant details in publications to ensure that other studies are able to build upon the research appropriately and accurately.
Lack of Transparency Discussion Material [PDF, 97.2KB]

Module 2: Blinding and Randomization
Sample blinding and randomization are key elements in reducing selection and other biases as well as in permitting reliable statistical testing. This module presents the importance of blinding and randomization, as well as the impact of issues that may introduce bias, such as pressure to publish.
Blinding and Randomization Discussion Material [PDF, 104KB]

Module 3: Biological and Technical Replicates
Including replicates in the experimental process is essential to ensuring the most rigorous research approach. In this module, reviewers discuss a figure included in a grant application and the potential significance of the finding, which leads to a brief conversation about the differences between biological and technical replicates.
Projects Funded Under PA-15-136

- Experimental Design for Biomedical Trainees
- Career Counseling and Networking Program for Biomedical Trainees
- Advanced Statistical Experimental Design, Ethics and Data Analysis
- Fundamentals of Professional Communication and Project Management
- Building Alternative Career Skills With “Science Communication in the Digital Age”
- Training in Experimental Design for Biomolecular Pharmacology
- Computational and Professional Skills for Biomedical Trainees
- Enhancing Research and Career Building Skills for Trainees in Cell and Molecular Biology
- Enhancing Research and Career Building Skills for Trainees in Computational Bioinformatics and Biostatistics
- Best Practices to Ensure Reproducibility and Rigor in Research
- Hypothesis, Design and Biostatistics
- Quantitative Approaches to Experimental Design and Intro to Individual Development
- Improving Rigor and Reproducibility in Big Data Research
- Using ORANGE to Improve Ricor and Reproducibility in the Analysis of Large Datasets
- Mastering the Art of Reproducible Science

Experimental Design for Biomedical Trainees
Principal Investigator: Joey Barret, Ph.D., Vanderbilt University Medical Center

This project aims to develop and implement a curriculum which includes topics such as experimental design, determining appropriate sample size, selection of exclusion criteria, awareness of bias and other statistical considerations. This curriculum will be delivered through lectures, small group discussions and “walk-in clinics” with opportunities for biostatistics consultation designed to prepare Vanderbilt T32 trainees, chemical biology graduate students and Meharry Medical College students training at Vanderbilt to address issues of reproducibility in science.
Department of Health and Human Services
Part 1. Overview Information

Participating Organization(s)
National Institutes of Health (NIH)

Components of Participating Organizations
National Institute of General Medical Sciences (NIGMS)
National Cancer Institute (NCI)
National Institute on Aging (NIA)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institute of Biomedical Imaging and Bioengineering (NIBIB)
National Institute of Dental and Craniofacial Research (NIDCR)
National Institute on Drug Abuse (NIDA)
National Institute of Neurological Disorders and Stroke (NINDS)
National Center for Advancing Translational Sciences (NCATS)
Division of Program Coordination, Planning and Strategic Initiatives, Office of Research Infrastructure Programs (ORIP)
Office of Research on Women's Health (ORWH)

Funding Opportunity Title
Tools for Cell Line Identification (SBIR [R43/R44])

Activity Code
R43/R44 Small Business Innovation Research (SBIR) Grant - Phase I, Phase II, and Fast-Track

Announcement Type
New

Related Notices
None

Funding Opportunity Announcement (FOA) Number
PA-16-186
Rigor and Reproducibility

Scientific rigor and transparency in conducting biomedical research is key to the successful application of knowledge toward improving health outcomes. The information provided on this website is designed to assist the extramural community in addressing rigor and transparency in NIH grant applications and progress reports.

On This Page:

- Goals
- Guidance: Rigor and Reproducibility in Grant Applications
- Resources
- News
- References

Goals

The NIH strives to exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science. Updates to grant applications instructions and review language are intended to:

- clarify long-standing expectations to ensure that NIH is funding the best and most rigorous science;
- highlight the need for applicants to describe details that may have been previously overlooked;
- highlight the need for reviewers to consider such details in their reviews through updated review language, and
- minimize additional burden.

Guidance: Rigor and Reproducibility in Grant Applications

The NIH is committed to promoting rigorous and transparent research in all areas of science supported by a variety of grant programs. Updates to application instructions and review language intended to enhance reproducibility through
NIH POLICY: ENHANCING REPRODUCIBILITY THROUGH RIGOR AND TRANSPARENCY

Module 1: General Policy Overview
RIGOR UPDATES INFOGRAPHIC

NEW GRANT GUIDELINES
what you need to know

WHY UPDATE THE GUIDELINES?
The updates focus on four areas deemed important for enhancing rigor and transparency:

1. PREMISE
The scientific premise forming the basis of the proposed research

2. DESIGN
Rigorous experimental design for robust and unbiased results

3. VARIABLES
Consideration of relevant biological variables

4. AUTHENTICATION
Authentication of key biological and/or chemical resources

Send inquiries to reproducibility@nih.gov
See also NIH Notice NOT-OD-16-011

WHAT ARE THE UPDATES?

1. UPDATES TO RESEARCH STRATEGY GUIDANCE
The research strategy is where you discuss the significance, innovation, and approach of your research plan. Let’s look at an R01, for example:

The new research strategy guidelines require that you:
- State the strengths and weaknesses of published research or preliminary data crucial to the support of your application
- Describe how your experimental design and methods will achieve robust and unbiased results
- Explain how biological variables, such as sex, are factored into research design and provide justification if only one sex is used

2. NEW ATTACHMENT FOR AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES
From now on, you must briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.

These include, but are not limited to:
- CELL LINES
- ANTIBODIES
- SPECIALTY CHEMICALS
- 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.

DO NOT put experimental methods or preliminary data in this section

DO focus on authentication and validation of key resources

3. NEW REVIEWER GUIDELINES
Here are the additional criteria the reviewers will be asked to use:

- Is there a strong scientific premise for the project?
- Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?
- Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?

Reviewers will also be asked to comment on that new attachment (see Update 2)!
<table>
<thead>
<tr>
<th>4 AREAS OF FOCUS</th>
<th>WHAT DOES IT MEAN?</th>
<th>WHERE SHOULD IT BE INCLUDED IN THE APPLICATION?</th>
</tr>
</thead>
</table>
| Scientific Premise | The **scientific premise** for an application is the research that is used to form the basis for the proposed research question(s). Describe the general strengths and weaknesses of the prior research being cited as crucial to support the application. Consider discussing the rigor of previous experimental designs, as well as the incorporation of relevant biological variables and authentication of key resources. | **Research Strategy**  
➤ Significance  
*See related FAQs, blog post* |
| Scientific Rigor (Design) | **Scientific rigor** is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. Emphasize how the experimental design and methods proposed will achieve robust and unbiased results. | **Research Strategy**  
➤ Approach  
*See related FAQs, blog post, examples from pilots* |
| Biological Variables | **Biological variables**, such as sex, age, weight, and underlying health conditions, are often critical factors affecting health or disease. In particular, sex is a biological variable that is frequently ignored in animal study designs and analyses, leading to an incomplete understanding of potential sex-based differences in basic biological function, disease processes and treatment response. Explain how relevant biological variables, such as the ones noted above, are 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. | **Research Strategy**  
➤ Approach  
*See related FAQs, blog posts, article* |
| Authentication | **Key biological and/or chemical resources** include, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics. Briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies. These resources may or may not be generated with NIH funds and:  
• may differ from laboratory to laboratory or over time;  
• may have qualities and/or qualifications that could influence the research data;  
• are integral to the proposed research. The authentication plan should state in one page or less how you will authenticate key resources, including the frequency, as needed for your research. Note: Do not include authentication data in your plan. | **Other Research Plan Section**  
➤ Include as an attachment  
➤ Do not include in the Research Strategy  
*See related FAQs, blog post* |
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

  Acknowledge as a weakness in the critique and discussion and score accordingly

  Is strong justification provided for the single sex study? (2)

  NO

  No

  Acknowledge as a weakness in the critique and discussion and score accordingly

  YES

  Does the proposal demonstrate plans to report data disaggregated by sex? (4)

  NO

  No

  Acknowledge as a weakness in the critique and discussion and score accordingly

  YES

  Are both sexes included in the study?

  NO

  No

  Acknowledge as a weakness in the critique and discussion and score accordingly

  YES

  Is the study intended to test for sex differences?

  NO

  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?

  NO

  No

  Acknowledge as a weakness in the critique and discussion and score accordingly

  YES

  Acknowledge as a strength 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.
EVALUATION PLANS

- Needs Assessment
- Process Evaluation
- Outcomes Evaluation
THANK YOU!

QUESTIONS?

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