THE NIH PERSPECTIVE ON RIGOR AND REPRODUCIBILITY

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IS THERE A REPRODUCIBILITY CRISIS?

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

1,576 researchers surveyed

The Reproducibility Challenge

Noted by research community in multiple publications

- Across research areas
- Especially in preclinical research

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.

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.

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.

Raise standards for preclinical cancer research
C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

Reforming Science: Methodological and Cultural Reforms
THE NIH RESPONSE TO THE REPRODUCIBILITY ISSUE
One goal is to “exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.”
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.
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 the lay public is demanding a change in the discovery process. The system is broken. In the rush to publish, researchers at NIH have discovered that the credibility of experiments is constantly being questioned, leading to inconsistent or outlandish results. NIH is working to rebalance the peer review, and other measures to enhance reproducibility.

NIH to balance sex in cell and animal studies

Janice A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

NIH Publications on the Issue
New Journal Policies to Enhance Reproducibility

Journals unite for reproducibility

R

reproducibility, transparency, and inde-
pendent verifications are cornerstones of the
scientific enterprise. When the results of a
study fail to replicate, it affects the trustworthi-
ness of scientific work and the validity of the
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The press release states that journals, along with other communities, are working to improve the reproducibility of research. The release mentions that the new policies are designed to encourage transparency and independent verification in research. The policies are intended to promote a culture of accountability and responsibility among researchers.
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

• Standards
• Replicates
• Statistics
• Randomization
• Blinding
• Sample size estimation
• Inclusion/exclusion criteria

http://www.nih.gov/about/reporting-preclinical-research.htm
APPLICATION, REVIEW, AND PROGRESS REPORT UPDATES
Enhancing Reproducibility through Rigor and Transparency

Rigor + Transparency $\rightarrow$ Reproducibility

- Easy to measure
- Difficult to measure

Short-term focus to achieve long-term goal
# RPG Application and Review

<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>
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<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>
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Research Performance Progress Reports (RPPR)

Reporting on rigor and transparency:

• Evaluate rigor for past year and upcoming year,
• Prepare non-competing renewals for the next competitive renewal, and
• Help NIH implement and evaluate the policy for both current and new awards.
TRAINING TO ENHANCE REPRODUCIBILITY
Training

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

• 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 helping to ensure unbiased outcome measures. This module presents the principles of blinding and randomization.

Module 3: Replicating Experiments
Reproducible research is a core component of scientific research. This module describes how to design experiments to allow others to reproduce your results.

Module 4: Reproducibility Evaluation Checklist
This module provides a checklist to help researchers assess the reproducibility of their experiments.

Related Information

- Administrative Supplements to NIGMS Predoctoral Training Grants
- NIH Web Portal on Rigor and Reproducibility
- NIH Grants & Funding Web Site on Rigor and Reproducibility in Grant Applications
- NIH Reproducibility Workshops
  - Cell Biology
  - Structural Biology
  - Genome Technology
  - Cell Culture Studies
- Videocast [Day 1 | Day 2]
"Graduate schools ‘mostly teach facts the first year,’ said Jon Lorsch, director of the National Institute of General Medical Sciences at the NIH. ‘They should teach methods.’”

Projects Funded Under PA-16-060

Listed below are the details of the projects funded under PA-16-060.

- Training in Experimental Rigor and Reproducibility
- Open Source Training in Computational Competence and Hands-on Data Analysis
- Experimental Design, Biostatistics and Quantitative Analysis
- Fundamental Concepts of Study Design, Statistics and Informatics
- Ensuring Rigor and Reproducibility: A Team Based Approach
- Promotion of Strong Foundations in Research Design and Methods Towards Reproducible and Rigorous Research
- Development of an Online Course on Statistical and Computational Tools for Reproducible Science
- Improved Reagent Verification as a Means for Enhanced Research Reproducibility
- Experimental Design, Biostatistics and Biological Variable Consideration
- Rigor and Reproducibility Training for Cellular and Molecular Medicine Research
- Integrating Concepts of Rigor, Repeatability and Reproducibility in Molecular Biology
- Training in Design of Research Methods for Reproducibility and Rigor
- Adoption of Good Research Practices
- Integrated Introduction to Biostatistics and Computation

Training in Experimental Rigor and Reproducibility

Principal Investigator: Christopher J. Cheng, Ph.D., University of California, Berkeley
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.

https://grants.nih.gov/reproducibility/
Ongoing Evaluation

Program Development
- Needs Assessment

Program Implementation
- Process Evaluation

Program Outcomes
- Outcomes Evaluation
Instruction in the Responsible Conduct of Research

Requirements:
- At least 8 contact hours
- Minimum of once every four years
- Training at each career stage
Thank You!

reproducibility@nih.gov
Appendix Slides
RESEARCH STRATEGY: SIGNIFICANCE
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.

SIGNIFICANCE – REVIEW QUESTION
Is there a strong scientific premise for the project?
GUIDANCE

• FAQs on Scientific Premise
  – Excerpt: “Scientific premise concerns the quality and strength of the research used to form the basis for the proposed research question. NIH expects applicants to describe the general strengths and weaknesses of the prior research being cited by the applicant as crucial to support the application.”

• Reviewer Guidance on Scientific Premise
  – Excerpt: “A weak scientific premise, or the failure to address scientific premise adequately, may affect criterion and overall impact scores.”

• Blog Post on Scientific Premise
RESEARCH STRATEGY: APPROACH
Describe the experimental design and methods proposed and how they will achieve robust and unbiased results.

APPROACH – REVIEW QUESTIONS
Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?
GUIDANCE

• **FAQs on Scientific Rigor**
  – Excerpt: “Scientific rigor is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. This includes full transparency in reporting experimental details so that others may reproduce and extend the findings.”

• **Reviewer Guidance on Scientific Rigor**
  – Excerpt: “The applicant should describe experimental controls, plans to reduce bias (blinding, randomization, subject inclusions and exclusion criteria, etc.), power analyses, and statistical methods, as appropriate.”

• **Blog Post on Scientific Rigor**
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.

APPROACH – REVIEW QUESTION

Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?
GUIDANCE

• FAQs on Biological Variables
  – Excerpt: “Addressing the influence of sex in biomedical research with animals does not necessarily imply an increase in costs. Rather, well-designed research either tests or controls for variables that might influence outcomes, and sex is one such variable among many that must be considered to obtain valid results.”

• Reviewer Guidance on Biological Variables
  – Excerpt: “A justification is expected if the application proposes to study one sex, for example in the case of a sex-specific condition or phenomenon (e.g., ovarian or prostate cancer), acutely scare resources, or sex-specific hypotheses when there are known differences between males and females.”

• SABV Flowchart

• Blog Post on Biological Variables, and here, and here.
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 are characterized as follows.

- 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.

- See NIH's page on Rigor and Reproducibility for more information.
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.
• **FAQs on Authentication**
  – Excerpt: “The new application instructions and review language on authentication of key biological and/or chemical resources are intended for applications proposing use of *established* research resources that should be authenticated prior to and during use.”

• **Reviewer Guidance on Authentication**
  – Excerpt: “Reviewers will discuss the authentication plan after scoring; comments on key resource authentication should not affect scores.”

• **Blog Post on Authentication**, [and here](#), [and here](#).
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
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.
GUIDANCE

• **FAQs on Progress Reports**
  – Excerpt: “Investigators will be directed to emphasize the approaches taken to ensure robust and unbiased results, including any developments affecting the proposed experimental design, methodology, analysis and interpretation in the NIH Research Performance Progress Report (RPPR). If sufficient information is not provided in the progress report, program officials may request the additional information needed to assess progress.”

• **Training module for Program Officers** (NIH-only)
  – Excerpt: “During their review of scientific progress reports, program staff should ensure that the research was conducted in accordance with the updated policy on rigor and transparency.”