THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Knowledge that will change your world

New Year, New NIH Expectations: *Are You Ready?*

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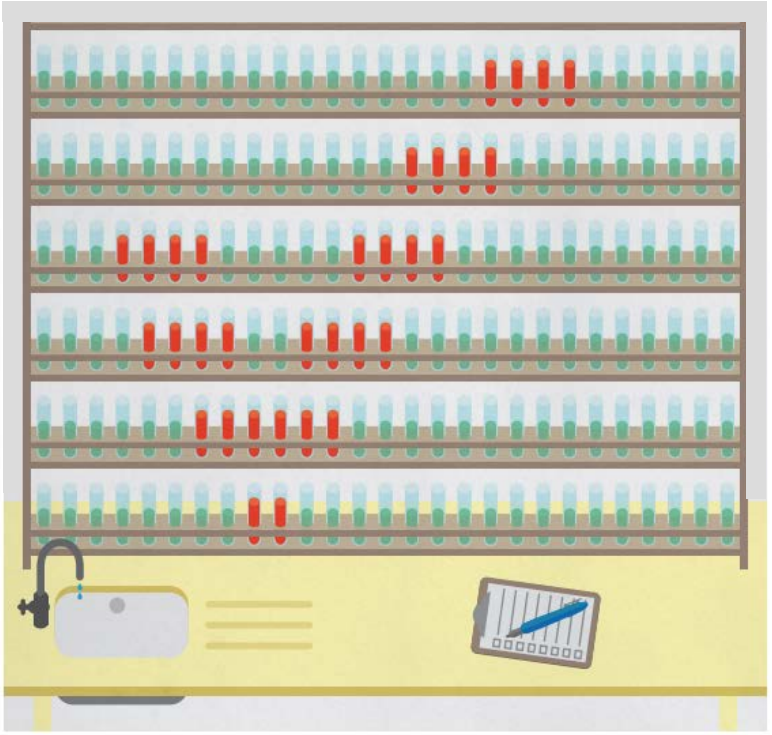
NIH plans to Enhance Reproducibility

Policy: NIH plans to enhance reproducibility

Francis Collins & Lawrence Tabak.
Nature. 2014 Jan 30; 505 (7485): 612-3.

Proposed NIH Actions

1. Training Module with an emphasis on good experimental design
2. Review Processes
   a. Checklist for analytic approach
   b. Scientific Premise review
   c. Unconscious Bias
3. Data Discovery Index (Big Data Initiative) for unpublished, primary data
4. PubMed Commons - open discourse about published articles



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.

Enhancing Reproducibility through Rigor and Transparency

Released: October 9, 2015 (1st communication June 9, 2015)

Implementing Rigor and Transparency in NIH & AHRQ Research Grant Applications
Notice Number: NOT-OD-16-011
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-011.html

Implementing Rigor and Transparency in NIH & AHRQ Career Development Applications
Notice Number: NOT-OD-16-012
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-012.html

When
These updates will take effect for due dates **on or after January 25, 2016**.

What is the goal of these changes?

Purpose

Applications (research and career development activity codes), progress reports and peer review expectations will incur changes intended to enhance the reproducibility of research findings through increased scientific rigor and transparency.

Updates Include:

- Revisions to application guide instructions for preparing your research strategy attachment
- Use of a new "Authentication of Key Biological and/or Chemical Resources" attachment
- Additional rigor and transparency questions reviewers will be asked to consider when reviewing (and SCORING!) applications

How will this affect the review of my grant?

Application Review Information

Scored Criteria:

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

Additional Considerations:

- **Authentication of Key Biological and/or Chemical Resources:** 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.

Enhancing Reproducibility through Rigor and Transparency

Preparing your Research Strategy

Newly revised grant application instructions will:

- 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 revised review criteria.

These new instructions and revised review criteria will focus on four areas deemed important for enhancing rigor and transparency:

1. the **scientific premise** of the proposed research,
2. **authentication** of key biological and/or chemical resources,
3. consideration of **relevant biological variables**, and
4. **rigorous experimental design** for robust and unbiased results.

Enhancing Reproducibility through Rigor and Transparency

Scientific Premise

Scientific Premise for an application is the research that is used to form the basis for the proposed research question;

Moving forward, NIH expects applicants to describe the general strengths and weaknesses of the prior research being *cited by the investigator as crucial to support the application*. This could include attention to the rigor of the previous experimental designs, as well as the incorporation of relevant biological variables and authentication of key resources.

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Enhancing Reproducibility through Rigor and Transparency

Authentication of Key Biological and / or Chemical Resources

NIH expects that key biological and/or chemical resources will be regularly authenticated to ensure their identity and validity for use in the proposed studies.

- These include, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics. (See NOT-OD-15-103 for definition)

In the absence of clear guidelines, researchers should transparently report on what they have done to authenticate key resources, so that consensus can emerge.

Save this information in a single PDF file named "Authentication of Key Resources Plan," and attach it as Item 12, Other Attachments, on the R&R Other Project Information page of the application package.

Enhancing Reproducibility through Rigor and Transparency

Consideration of Sex and other Relevant Biologic Variables

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.

- Please refer to NOT-OD-15-102 for further consideration of NIH expectations about sex as a biological variable.

Investigators should consider other biological variables (e.g., age), as appropriate, in the design and analyses of their proposed studies. Research plans and findings should clearly indicate which biological variables are tested or controlled. Clear justification should be provided for exclusion of variables that may be relevant but are not considered in the research plan.

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Enhancing Reproducibility through Rigor and Transparency

Rigorous Experimental 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. NIH expects applicants to describe how they will achieve robust and unbiased results when describing the experimental design and proposed methods. Features of experimental design may include:

- Use of standards
- Sample size estimation
- Randomization
- Blinding
- Appropriate replicates
- Controlling for inter-operator variability

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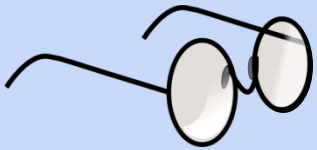
- Statistical methods planned
- Inclusion and exclusion criteria
- Subject retention and attrition
- How missing data will be handled
- And others, as appropriate to the science

HOW SCIENTISTS FOOL THEMSELVES – AND HOW THEY CAN STOP

Humans are remarkably good at self-deception. But growing concern about reproducibility is driving many investigators to seek ways to fight their own worst instincts.

COGNITIVE FALLACIES IN RESEARCH



HYPOTHESIS MYOPIA

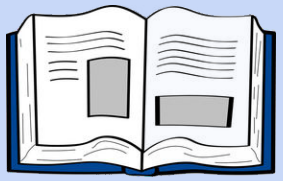
Collecting evidence to support a hypothesis, not looking for evidence against it, and ignoring other explanations.

TEXAS SHARPSHOOTER

Seizing on random patterns in the data and mistaking them for interesting findings.

ASYMMETRIC ATTENTION

Rigorously checking unexpected results, but giving expected ones a free pass.



JUST-SO STORYTELLING

Finding stories after the fact to rationalize whatever the results turn out to be.

Adapted from Nature (go.nature.com/nqyohl)

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DEBIASING TECHNIQUES

DEVIL'S ADVOCACY

Explicitly consider alternative hypotheses – then test them out head-to-head.

PRE-COMMITMENT

Publicly declare a data collection and analysis plan before starting the study.

TEAM OF RIVALS

Invite your academic adversaries to collaborate with you on a study.

BLIND DATA ANALYSIS

Analyze data that look real but are not exactly what you collected – and then lift the blind.

Adapted from Nature (go.nature.com/nqyohl)

Enhancing Reproducibility through Rigor and Transparency

Reproducibility through Archiving and Version Control

- As data are collected, each substantial iteration of the database should be archived in order to have a transparent history of data evolution. This technique is essentially version control of the database

- If the study has a small number of subjects and a small number of outcomes, consider double data entry and asking a statistician/methodologist to compare the databases. Allows for quick identification of data transcription errors.

- Try to avoid using statistical software that relies completely on a graphical user interface (GUI). GUIs (point and click software) lack documentation and transparency.

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Enhancing Reproducibility through Rigor and Transparency

Reproducibility through Archiving and Version Control

- When a paper is being submitted, it is imperative that the final raw dataset, a documented program that prepared the analysis ready dataset, a documented program that conducted the analysis, and the output from that program must be archived together.

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Enhancing Reproducibility through Rigor and Transparency

Reproducibility through Blinding and Peer Review.

- If you have conducted your own analyses, a wise approach is to pass a blinded dataset to a methodologist in order to do an independent analysis. When two independent researchers come to the same results, greater confidence in the conclusions is achieved.

- Another approach is to have a methodologist review the techniques used to analyze the data. It is very common for the UAB methodologists to request a colleague review their results and ask ‘Did I miss something?’ , ‘Would you have done it this way?’ , or ‘Is there other analysis you would do?’

Enhancing Reproducibility through Rigor and Transparency

Reproducibility through Reproducible Research Documents.

- In the past 5 years, numerous statistical software including R and SAS have developed systems designed to produce one ‘reproducible document’ from a master program that embeds the data, the analytic program, and the output into one document (LATEX pdf). The document is created such that when an analytic command is executed, the command is printed to the document AND the output from that command appears directly after the code.
- Within R/ R Studio, the KNITR package creates these documents.
- Within SAS, the StatRep Package creates these documents.