

Society of Research Administrators International Webinars

What's New at the NIH? Requirements to Address Rigor and Reproducibility in Research

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This Webinar is being recorded.

Presenter



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<http://www.research.uky.edu/pdo/>

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Learning Objectives

1. Understand revisions to NIH proposal content requirements and peer review criteria to include assessment of rigor and reproducibility in research.
2. Become familiar with diverse resources available to help investigators meet new requirements to address key aspects of rigor and reproducibility in grant applications.

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Agency Perspective

- One of NIH's four stated goals in its mission...
 - To exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science (<https://www.nih.gov/about-nih/what-we-do/mission-goals>)
- Today's session covers topics that are integral to this goal.

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Preliminary Understandings

- What do we mean by *rigor* in research?
 - Close adherence to robust scientific standards/ methods in the *design* of studies and experiments
 - Careful application of the scientific method in the *conduct* of research
 - But even *before* these two facets...
 - Careful attention to *the rigor with which prior research has been conducted.*

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Preliminary Understandings

- What is *reproducibility*?
 - The ability to redo a study (either one's own or someone else's) and achieve comparable results.
- Replication of study results provides validity!

"Science has long been regarded as 'self-correcting', given that it is founded on the replication of earlier work."

<http://www.nature.com/news/policy-nih-plans-to-enhance-reproducibility-1.14586>
(Collins and Tabak, 2014)

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More on Reproducibility

- But, reproducibility is highly dependent on *transparency* of the research...
 - The scientific detail in both the proposal and the published research outcomes!
- Transparency relies on rigorously established lab procedures...
 - Careful *documentation* of study methods and processes
 - Careful *data handling* and *interpretation*.

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More on Reproducibility

- Transparency (of rigorous, unbiased research) is critical not only in the *proposal detail* but also in the *reporting processes!*
 - Progress reports to the sponsor
 - Publications reporting the discoveries
- Transparency lays the foundations to advance to later stages of research.

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What's Up with Research?

- Intensive ongoing 4+ year 'conversation'...
 - Focused on issues at play in the...
 - *Inability to reproduce or extend research findings* reported in some peer-reviewed literature
 - Commentary by NIH Director, Principal Deputy Director on possible causes and NIH actions
 - www.nature.com/news/policy-nih-plans-to-enhance-reproducibility-1.14586 (Collins and Tabak, 2014)
 - Commentary by NINDS convened stakeholders
 - www.nature.com/nature/journal/v490/n7419/full/nature11556.html (Landis, et al., 2012)

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Why the Alarm?

- The *inability to reproduce or extend research findings* based on reported study details...
 - Has been frustratingly widespread
 - Has ranged across the spectrum of research
 - Has even extended to efforts by the original study team to replicate their own studies
 - Has hindered advancement of promising research results to the next stages of discovery.



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The Results?

- New initiatives to develop strategies to address *rigor and reproducibility* in research, particularly on the part of the *National Institutes of Health and Agency for Healthcare Research and Quality*...
 - Workshops
 - Videocasts and training modules
 - Successful NIH pilots to inform new proposal and review guidelines.

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The Results?

- These collective efforts...
 - All culminated in implementation of *new requirements to address rigor and reproducibility in research* applications...

- Submitted on or after January 25, 2016.



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What is NIH Saying? (What's Not New)

- *Cornerstones* of science advancement are....
 - Rigor in designing and performing scientific research for...
 - Robust and unbiased design
 - The ability to reproduce biomedical research findings for...
 - Validity of the results and readiness to progress to the next phase of research

<https://www.nih.gov/research-training/rigor-reproducibility>

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What is NIH Saying? (What's Not New)

- Newly revised research grant application instructions...
 - *Clarify* long-standing expectations to ensure that *NIH funds the best and most rigorous science*.
 - *Highlight* the need for...
 - Applicants to describe details that may have been previously overlooked
 - Reviewers to consider such details in their review.

<https://www.nih.gov/research-training/rigor-reproducibility/updated-application-instructions-enhance-rigor-reproducibility>

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So What's New?

- While NIH *expectations* for rigor and reproducibility have not changed...
 - Application requirements have for...
 - National Institutes of Health
 - Agency for Healthcare Research and Quality
 - Revisions to 2 of 5 peer review criteria – Significance and Approach
- New NIH and other resources

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What Exactly Has Changed?

- Within SF424 Application Guide (currently “Forms-D”)
 - Updated *application instructions* for Research Strategy
 - Updates to peer review – Significance, Approach
 - New ‘Authentication Plan’
 - New Additional consideration for review – Authentication
- PIs “*strongly encouraged*” to discuss revised instructions with NIH program staff prior to submitting an application

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Implementation

- Who?
 - PIs submitting *research* proposals to NIH and AHRQ, but stay tuned!
 - New training and fellowship application requirements!
- When?
 - Effective for due dates on or after January 25, 2016
- Why?
 - To enhance rigor + transparency → reproducibility

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Four New Requirements

- New requirements in grant applications...
 - Scientific premise forming the basis of the proposed research
 - Rigorous experimental design for robust and unbiased results
 - Consideration of relevant biological variables
 - Authentication of key biological and/or chemical resources
- Research Strategy page limit has *not* changed!

NOT-OD-15-103 – Enhancing Reproducibility through Rigor and Transparency

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Updates to Research Strategy

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Updates to SF424 On Significance

1. Significance

- Explain the importance of the problem or critical barrier to progress in the field....
- 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.

NEW!

SF424 instructions '*map*' to the review criterion – “Describe the scientific premise....”

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Updates to SF424 On Significance

1. Significance (cont.)

- Explain how the 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....

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Review Criterion – Significance

- **Significance**
 - Does the project address an important problem or a critical barrier to progress in the field?
 - Is there a strong scientific premise for the proposed project?
 - If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved?

NEW!

SF424 instructions '*map*' to the review criterion – “Describe the scientific premise....”

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Review Criterion – Significance

- **Significance (cont.)**
 - How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Existing review questions still apply!

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A Word about Scientific Premise

- *Scientific premise* refers to **two** aspects...
 - **Prior research** that is crucial to the support the proposed research
 - Preliminary data
 - Published literature
 - NIH expects applicants to describe...
 - **Strengths** and **weaknesses** of **prior research cited**, such as rigor of previous experimental designs.

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A Word about Scientific Premise

- **Strengths** and **weaknesses** may include...
 - Appropriate statistical power
 - Justified sample sizes
 - Use of control groups
 - Important biological variables, e.g., both sexes
 - Authentication of key resources, e.g., cell lines
 - Data handling – missing data, outliers
 - Blinding/ randomization

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More on Scientific Premise

- *Not identifying strengths and/or weaknesses* could be considered a weakness in review.
- Conclusions based on flawed prior research may not support the next phase of research.
- See more on value of scientific premise and core reporting standard...

www.nature.com/nature/journal/v490/n7419/full/nature11556.html (Landis, et al., 2012)

NOT-OD-15-103 – Enhancing Reproducibility through Rigor and Transparency

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Updates to SF424 on Approach

3. 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....
- Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.

NEW!

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Updates to SF424 on Approach

3. Approach (cont.)

- If the project is in the early stages of development, describe any strategy to establish feasibility....
- 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.

NEW!
MEM!

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Updates to SF424 on Approach

3. Approach (cont.)

- 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 and justify the proposed proportions of individuals (such as males and females) in the sample, but it must also be addressed here...

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Updates to SF424 on Approach

3. Approach (cont.)

- Please refer to NOT-OD-15-102 for further consideration of NIH expectations about sex as a biological variable.
- Point out any procedures, situations, or materials that may be hazardous to personnel and precautions to be exercised.
- If research on Human Embryonic Stem Cells (hESCs) is proposed but an approved cell line...cannot be identified, provide a strong justification....

NEW!
MEM!

NOT-OD-15-102 Consideration of Sex as a Biological Variable

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Review Criterion – Approach

- **Approach**
 - 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?

NEW!
MEM!

SF424 instructions '*map*' to the review criterion – "...achieve robust unbiased results."

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Review Criterion – Approach

- **Approach cont.**
 - 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?

Existing review questions still apply!

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Review Criterion – Approach

- **Approach cont.**
 - If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed?
 - Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

NEW!
MEMO!

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Review Criterion – Approach

- **Approach cont.**
 - If the project involves human subjects and/or NIH-defined clinical research, are the plans for 1) Protection of Human Subjects, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children, justified in terms of the scientific goals and research strategy proposed?

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A Word about Robust, Unbiased Design

- Robust and unbiased design...
 - NIH expects applicants to describe...
 - Methods designed to avoid bias
 - Well-controlled and reported experimental conditions.
 - NIH expects applicants to include **full transparency in reporting experimental details** so that others (and you!) may reproduce and extend the findings.

NOT-OD-15-103 – Enhancing Reproducibility through Rigor and Transparency

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A Word about Robust, Unbiased Design

- Check for Institute-specific guidance!
 - “*Examples of the most critical elements for a well-designed study are summarized....*”
 - NINDS (NOT-NS-11-023)
http://www.ninds.nih.gov/funding/grant_policy.htm
 - NIMH (NOT-MH-14-004)
<http://www.nimh.nih.gov/research-priorities/policies/enhancing-the-reliability-of-nimh-supported-research-through-rigorous-study-design-and-reporting.shtml>
 - NIDA (NOT-DA-14-007)
<http://www.drugabuse.gov/offices/office-nida-director-od/office-translational-initiatives-program-innovations-otipi/nih-initiative-enhancing-research-reproducibility-transparency>

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Example – Guidance from NIDA

- Points to consider...
 - **Experimental design**
 - Rationale for selected models, endpoints
 - Adequacy of the controls
 - Route, dosing and timing of treatment
 - Sample size estimates, including power calculation
 - Statistical methods to be use in analysis and interpretation...

Office of the NIDA Director: NIH Initiative on Enhancing Research Reproducibility...Transparency

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Example – Guidance from NIDA

- More points to consider...
 - **Minimizing bias**
 - Methods of blinding
 - Inclusion and exclusion criteria
 - Strategies for randomization and/ or stratification
 - Procedures for dealing with missing data...
 - Reporting all results (negative and positive)

Office of the NIDA Director: NIH Initiative on Enhancing Research Reproducibility...Transparency

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Example – Guidance from NIDA

- More points to consider...
 - **Results**
 - Reporting of independent validation/ replication
 - Robustness and reproducibility of observed results, including whether replicates used different lots of animals, drugs, reagents, experimenters
 - Dose-response results
 - Verification that interventional drug or biologic reached and engaged the target

Office of the NIDA Director: NIH Initiative on Enhancing Research Reproducibility...Transparency

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Summary - Additions to Scored Review

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

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New 'Authentication' Attachment

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Updates to SF424 on 'Authentication'

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

NEW!
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Updates to SF424 on 'Authentication'

- 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;
 - Have qualities and/or qualifications that could influence the research data;
 - Be integral to the proposed research.

NEW!
MEM!

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Updates to SF424 on 'Authentication'

- 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;
 - Have qualities and/or qualifications that could influence the research data;
 - Be integral to the proposed research.

NEW!
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Updates to SF424 on 'Authentication'

- **Authentication (cont.)**
 - [These resources] include, but are not limited to, *cell lines, specialty chemicals, antibodies, and other biologics*.
 - Standard reagents that aren't expected to vary (e.g. buffers, and other common biologics or chemicals) need not be included in the plan.

NEW!
MEM!

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Review Criterion – Authentication

- Additional Review Considerations
 - Reviewers will assess the information provided in the Authentication section. Any reviewer questions associated with key biological and/or chemical resource authentication will need to be addressed prior to award.
 - Information presented in this section must focus only on authentication and/or validation of key resources to be used in the study

NEW!
MEM!

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A Word on ‘Authentication Plan’

- *NIH caution!*
 - Do not use this added section to circumvent the page limits of the Research Strategy.
- Attach the Plan (one page or less) where designated in the application package.
- “No clear consensus guidelines” – NIH has not defined specifically how to address authentication of specific resources but is looking to the research community to shape development.

NOT-OD-15-103 – Enhancing Reproducibility through Rigor and Transparency

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A Word on 'Authentication Plan'

- Do not include actual authentication data; instead provide...
 - *Plans* for independent verification
 - Frequency, particularly for long-term use as regards stability.
- My caution!
 - Policy states 'biological' or 'chemical' – do not use this attachment for other types of resources.

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Summary - Additional Review Criterion

- Under *Additional Review Considerations*
 - **Authentication of Key Biological/Chemical Resources:** Where applicable, reviewers will comment on the plans proposed for identifying and ensuring the validity of those resources.

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The First Reviewers Report...

- Reviewer training for most programs began in June 2016...
 - Reviewers *must* use the new terms from the revised review criteria in their review comments.
 - As we might expect, reviewers are *looking to find those precise phrases* in the proposal.
 - Reviews that aren't compliant with this instruction are being returned.

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Reviewers Report...

- Reviewer training varies across Institutes but covers the key points...
 - **Scientific Premise** – strengths, weaknesses in cited literature
 - **Rigor** – groups sizes, independent and blinded measurements, inclusion/ exclusion criteria, management of missing data, etc.

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What about Progress Reports?

- Annual non-competing (Type 5) *Research Performance Progress Reports* for research address rigor as of January 25, 2016.
 - Accomplishments section...
 - B.2 What was accomplished under these goals?
 - Include the approaches taken to ensure robust and unbiased results.

NOT-OD-16-031 – Updates to NIH, AHRQ Research Performance Progress Reports...

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What about Progress Reports?

- *Research Performance Progress Reports cont.*
 - Accomplishments section...
 - B.6. What do you plan to do for the next reporting period...?
 - Discuss efforts to ensure that the approach is scientifically rigorous and results are robust and unbiased.

NOT-OD-16-031 – Updates to NIH, AHRQ Research Performance Progress Reports...

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Stay Tuned!

- NIH has *delayed implementation* to FY 2017 of policies on rigor and reproducibility for...
 - Institutional training grants (e.g., T32, T15)
 - Institutional career development awards (e.g., K12, KL2)
 - Individual Fellowships (F31, F32)

NOT-OD-16-034 – Coming Requirements...Institutional Training Grants, etc.

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Stay Tuned!

- Delay is due to recognition of need for time and resources to develop...
 - Substantive, effective **instructional plans** and **curricula** in rigorous experimental design across different fields
- Training grant PD/PIs should be working on these features now!

NOT-OD-16-034 – Coming Requirements...Institutional Training Grants, etc.

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New for 'T' and 'K' Mechanisms

- New for 'T' (training) and 'K' (career) grants...
 - **Summary of the instruction** planned...to ensure knowledge and skills required to design and conduct rigorous, well-controlled experiments that...
 - Consider relevant biological variables
 - Use authenticated biological/ chemical resources
 - Apply appropriate statistical tests for data analyses.
 - **Separate attachment** detailing instructional/ curricular content

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New for 'F' Mechanisms

- New inclusions for 'F' (fellowship)...
 - **Summary of plans** (in Research Strategy) to ensure rigorous, well-controlled experiments that...
 - Consider all relevant biological variables
 - Use authenticated biological/ chemical resources
 - Apply appropriate statistical tests for data analyses.
 - Details on **instruction in rigorous experimental design** in Institutional Environment/ Commitment to Training section.

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Resources for Investigators

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Policy Details Explained

NIH Policy: Rigor and Transparency - Module 1 (08/04/16/17)

Resources Exit

NIH Policy: Enhancing Reproducibility through Rigor and Transparency

Module 1: General Policy Overview



reproducibility@nih.gov

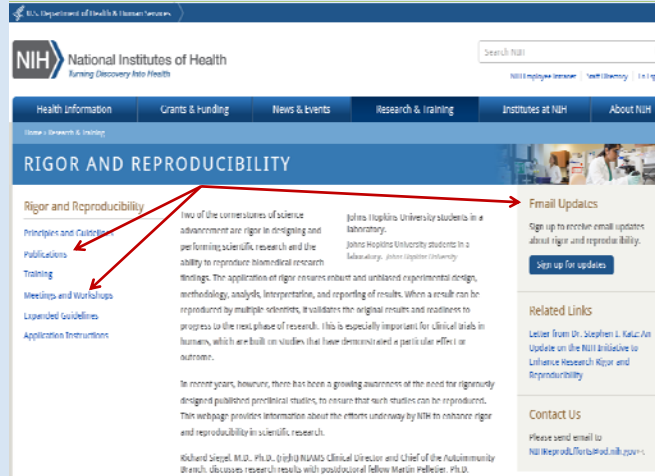
Menu Notes

1. NIH Policy: Enhancing Reproducibility through Rigor and Transparency
2. How to Navigate This Presentation
3. Training Objectives
4. NIH Policy
5. The Problem
6. Sex as a Biological Variable
7. Resource Authentication
8. Deliberative Efforts
9. Principles and Guidelines for Reporting Preclinical Research
10. Pilot Programs
11. Communicating NIH Policies
12. Key Areas
13. Scientific Prevision
14. Example: Amyotrophic Lateral Sclerosis (ALS)
15. Apparent Effects (Noise) vs. Fishnet Size
16. POPOR: A Call for Transparent Reporting
17. Scientific Prevision
18. Scientific Prevision for Biomimetic Research
19. Updated Application Instructions: Scientific Prevision
20. Elucidated Evidence: Language: Scientific Prevision

https://grants.nih.gov/reproducibility/module_1/presentation.html

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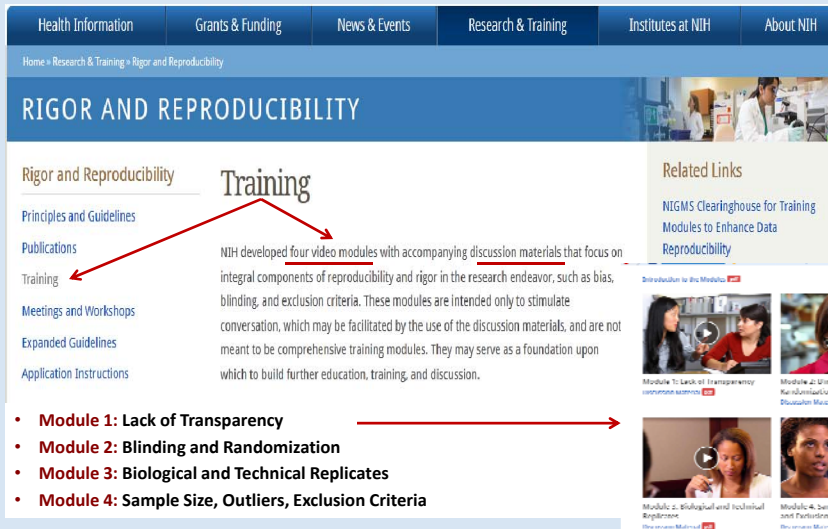
Get to Know the NIH Rigor Web Portal!



<http://www.nih.gov/research-training/rigor-reproducibility>

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Training Resources



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Check Out *Open Mike!*



NIH Extramural
Nexus blog for
clarifications on...

- Scientific Premise
- Biological Variables
- Scientific Rigor
- Authentication of Resources!

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Resources!

- Learn more...
 - Archived NIH videocasts
<http://www.nih.gov/research-training/rigor-reproducibility/meetings-workshops>
 - Publications from NIH authors on...
 - the issue of reproducibility
 - NIH's actions to enhance reproducibility<http://www.nih.gov/research-training/rigor-reproducibility/publications>

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Broader Guidance

- Learn more...
 - Code of Federal Regulations
 - Food and Drug Administration 21 CFR Part 58 – Good Clinical Practice for Nonclinical Laboratory Studies
 - [Subpart F \(Test and Control Articles\)](#)
 - [Subpart J \(Records and Reports\)](#)
 - Insights from other organizations
 - [Center for Open Science: Transparency and Openness Promotion \(TOP\) Guidelines](#)

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Your Questions!

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References

- Collins, Francis and Tabak, Lawrence. Policy: NIH plans to enhance reproducibility. *Nature* 505, 612–613 (30 January 2014)
doi:10.1038/505612a. <http://www.nature.com/news/policy-nih-plans-to-enhance-reproducibility-1.14586>
- Landis, et al. A call for transparent reporting to optimize the predictive value of preclinical research. *Nature*. Oct 11, 2012; 490(7419): 187–191.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3511845/>
- NIH Policy: Enhance Reproducibility through Rigor and Transparency, Module 1: General Policy Overview, (source for images used in slides)
https://grants.nih.gov/reproducibility/module_1/presentation.html
- NIH Notices (NOT-OD-15-102, NOT-OD-15-103, NOT-OD-16-031, NOT-OD-16-034, NOT-DA-14-007, NOT-NS-11-023, NOT-MH-14-004)

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Thank you!

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