NIH Update Following ACD Recommendations on Enhancing Rigor, Transparency, and Translatability in Animal Research

Michael S Lauer, MD
NIH Deputy Director for Extramural Research

NIH Advisory Committee to the Director (ACD) Meeting (Virtual)
June 9, 2022
ACD Enhancing Rigor, Transparency, and Translatability in Animal Research Working Group Members

EXTERNAL MEMBERS

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Bren Professor of Molecular Biology
Merkin Institute for Translational Research
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Johns Hopkins School of Medicine

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University of Ottawa Heart Institute
CHU Bordeaux, IHU Liryc

Karen Svenson, PhD
Senior Scientific Program Manager and Research Scientist
Jackson Laboratory
# ACD Enhancing Rigor, Transparency, and Translatability in Animal Research Working Group Members

## USG MEMBERS

<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Affiliation</th>
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<tbody>
<tr>
<td>Lawrence A. Tabak, DDS, PhD (Co-Chair)</td>
<td>Principal Deputy Director, NIH</td>
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<tr>
<td>Brian Berridge, DVM, PhD, DACVP</td>
<td>Associate Director, National Toxicology Program; Scientific Director Division National Toxicology Program; National Institute of Environmental Health Science, NIH</td>
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<td>Paul Brown, PhD</td>
<td>Associate Director for Pharmacology and Toxicology; Office of New Drugs, Center for Drug Evaluation and Research, FDA</td>
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<td>Janine Clayton, MD</td>
<td>Director; Office of Research on Women's Health, NIH</td>
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<tr>
<td>Joshua A. Gordon, MD, PhD</td>
<td>Director; National Institute of Mental Health, NIH</td>
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<tr>
<td>Michael Lauer, MD</td>
<td>Deputy Director for Extramural Research; Office of Extramural Research, NIH</td>
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<tr>
<td>Robyn Lee-Stubbs, MS, CPIA, PStat®</td>
<td>IACUC Chair/Statistician; United States Army Medical Research Institute of Chemical Defense</td>
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<tr>
<td>Glenn Merlino, PhD</td>
<td>Scientific Director for Basic Research; Center for Cancer Research, National Cancer Institute, NIH</td>
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<tr>
<td>Shai Silberberg, PhD</td>
<td>Director for Research Quality; National Institute of Neurological Disorders and Stroke, NIH</td>
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<tr>
<td>Carrie Wolinetz, PhD</td>
<td>Acting Chief of Staff; Associate Director; Office of Science Policy, NIH</td>
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Recommendations: Five Themes

1. Improve Study Design and Analytic Rigor
2. Address Bias, Incomplete Reporting and Questionable Research Practices
3. Improve Relevance and Use of Animal Models
4. Improve Methodologic and Results Reporting
5. Measure and Evaluate Effectiveness and Costs
Overview

• EAWG detailed review of recommendations
• DPCPSI ORIP NOSI and concept clearance on rigor, reproducibility, and translatability of animal research
• Planned workshops
• Existing resources and opportunities to better leverage them
• Ongoing efforts to enhance rigor and peer review
• Shorter-term considerations for discussion

EAWG = Extramural Activities Working Group
DPCPSI ORIP = Division of Program Coordination, Planning, and Strategic Initiatives
NOSI = Notice of Special Interest
Notice of Special Interest (NOSI): Development of Resources and Technologies for Enhancing Rigor, Reproducibility, and Translatability of Animal Models in Biomedical Research

Notice Number:
NOT-OD-22-039

Key Dates

Release Date: December 7, 2021
First Available Due Date: February 16, 2022
Expiration Date: May 08, 2024

Related Announcements
PAR-21-167 - Development of Animal Models and Related Biological Materials for Research (R21 Clinical Trial Not Allowed)

Issued by
Division of Program Coordination, Planning and Strategic Initiatives, Office of Research Infrastructure Programs (ORIP)

ORIP NOSI Goals

• Exploratory/developmental and highly innovative projects aimed at developing broadly applicable technologies, tools, and resources for validating animal models and enhancing the rigor, reproducibility, and translatability of animal research

• [Proposals] ... must either address research interests of multiple NIH ICs, explore multiple body or organ systems, or be applicable to diseases and processes that impact multiple body or organ systems.

Concept Clearance

• DPCPSI ORIP presented to Council of Councils on May 19, 2022

• Grant mechanisms
  • 2-year R21
  • 5-year R01
  • 4-year R24 and U24
  • Small business

• Proposed projects must demonstrate how proposed resources and technologies will impact rigor and reproducibility of animal studies

Other Planned Workshops

• ORIP: animal models and related resources for COVID research
  • Leverages NIH-wide portfolio analysis

• ORIP: enhance rigor and reproducibility by managing extrinsic factors
  • Assess equipment, instrumentation, and extramural construction projects

• National Academies Institute for Laboratory Animal Research (ILAR) project on effective communication with the general public about scientific research that requires work with animals
Existing Resources

Statistical Topics for Reproducible Animal Research
Andrew W. Brown and David B. Allison, Indiana University School of Public Health-Bloomington; Tapan Mehta and Stephen Watts, University of Alabama at Birmingham, R25 GM116167

Preclinical research involving animal models can be improved when appropriate experimental, analytical, and reporting practices are used. We produced a series of animated vignettes with quantitative experts and laboratory scientists discussing aspects of study design, interpretation,

Controls in Animal Studies for Rigor and Reproducibility
Christina N. Bennett and Marsha Lakes Matyas, American Physiological Society, R25 GM116166

This teaching module was designed to help biomedical researchers understand the changing standards of practice for studies using animals as research models. This module is comprised of three sections that focus on developing strong skills in designing animal studies, analyzing results from those studies, and reporting findings that are reproducible. Modules are designed to be used by higher education institutions, laboratory groups, individuals, and professional societies.

Highlighting Other Resources

Resources for Preparing Your Application
Learn how to prepare a rigorous application with select excerpts of rigor from awarded applications, authentication plan examples, and resources like the experimental design assistant (EDA), guidance on sample size calculation, and more.

Training and Other Resources
Resources and training on many aspects of rigor and reproducibility, including sex as a biological variable, research methods, reviewer guidance and more.

https://www.nc3rs.org.uk/our-portfolio/experimental-design-assistant-eda
Alzheimer's Disease Preclinical Efficacy Database

AlzPED is a publicly available, searchable, data resource that aims to increase the transparency, reproducibility and translatability of preclinical efficacy studies of candidate therapeutics for Alzheimer's disease.

NIH ACD Working Group on Enhancing Reproducibility and Rigor in Animal Research

https://alzped.nia.nih.gov
## Experimental Design

<table>
<thead>
<tr>
<th>Item</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Is the following information reported in the study?:</td>
<td></td>
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<tr>
<td>✗ Power/Sample Size Calculation</td>
<td></td>
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<tr>
<td>✓ Blinded for Treatment</td>
<td>✓ Randomized into Groups</td>
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<tr>
<td>✓ Pharmacokinetic Measures</td>
<td>✓ Blinded for Outcome Measures</td>
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<tr>
<td>✓ Toxicology Measures</td>
<td>✓ Pharmacodynamic Measures</td>
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<tr>
<td>✓ Biomarkers</td>
<td>✓ ADME Measures</td>
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<tr>
<td>✓ Formulation</td>
<td>✓ Dose</td>
</tr>
<tr>
<td>✓ Duration of Treatment</td>
<td>✓ Route of Delivery</td>
</tr>
<tr>
<td>✓ Age of Animal at the Beginning of Treatment</td>
<td>✓ Frequency of Administration</td>
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<tr>
<td>✓ Sex as a Biological Variable</td>
<td>✓ Age of Animal at the End of Treatment</td>
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<tr>
<td>✗ Number of Premature Deaths</td>
<td>✓ Study Balanced for Sex as a Biological Variable</td>
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<tr>
<td>✓ Statistical Plan</td>
<td>✗ Number of Excluded Animals</td>
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<tr>
<td>✗ Inclusion/Exclusion Criteria Included</td>
<td>✓ Genetic Background</td>
</tr>
<tr>
<td>✓ Conflict of Interest</td>
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Ongoing Rigor Efforts

• CSR Advisory Council Workgroup on Simplifying Review Criteria
  • Focus on what’s important: five to three criteria
    • Should it be done? → Importance of the science
    • Can it be done well? → Feasibility and rigor
    • Will it be done? → Investigators and environment
  • Further ACD discussion later this year
• NIH Data Management and Sharing Policy (later this ACD)

## NINDS Activities

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<th>Funding Opportunity Title</th>
<th>Creating an Educational Nexus for Training in Experimental Rigor (CENTER) (UC2 Clinical Trial Not Allowed)</th>
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<tr>
<td>Funding Opportunity Title</td>
<td>Materials to Enhance Training in Experimental Rigor (METER) (UE5 Clinical Trial Not Allowed)</td>
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[These] Funding Opportunity Announcements (FOAs) ... together aim to facilitate teaching of fundamental principles of rigorous biomedical research by developing an innovative online educational resource for use by a broad range of researchers in an array of learning environments.

Catalyzing Communities of Research Rigor Champions
A Workshop Hosted by the NINDS Office of Research Quality

May 23-24, 2022
NIH Campus, Bethesda, MD

https://www.infinityconferences.org/ResearchRigorChampions

Co-Chairs:

Steven Goodman, Stanford University
Veronique M. Kiermer, PLOS

Possible Short to Intermediate Efforts

• Guide Notice to encourage use of ARRIVE Guidelines when reporting results of NIH-funded animal research
  • Many journals already encourage or require ARRIVE

• Fund statistical cores to support animal researchers at under-resourced institutions

• Non-monetary prize to highlight exemplary work in study design and analysis in animal research