21st Century Cures Act Update: Research Rigor and Reproducibility

Michael Lauer, MD (for the ACD WG) Deputy Director for Extramural Research National Institutes of Health

114th Meeting of the Advisory Committee to the Director (ACD) National Institutes of Health Porter Neuroscience Building, Building 35 A, Rooms 620/630, Bethesda, Maryland June 8, 2017 Disclosures: None



Section 2039 requires the NIH Director to convere a workinggroup under the ACD to develop and issue recommendations through the ACD for a formal policy, which may incorporate or be informed by relevant existing and ongoing activities to enhance rigor and reproducibility of scientific research funded by NIH.



ACD Working Group

- ACD
 - Russ Altman (Chair)
 - Mary Sue Coleman
 - Lisa Cooper
 - Jose Florez
 - Linda Griffith
 - Peter MacLeish

• NIH

- Michael Lauer
- Pritty Joshi
- Jennifer Plank-Bazinet
- Patricia Valdez



Few Years Ago

PERSPECTIVE

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A call for transparent reporting to optimize the predictive value of preclinical research

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Pilots



NIH to balance sex in cell and animal studies



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Fixing problems with cell lines

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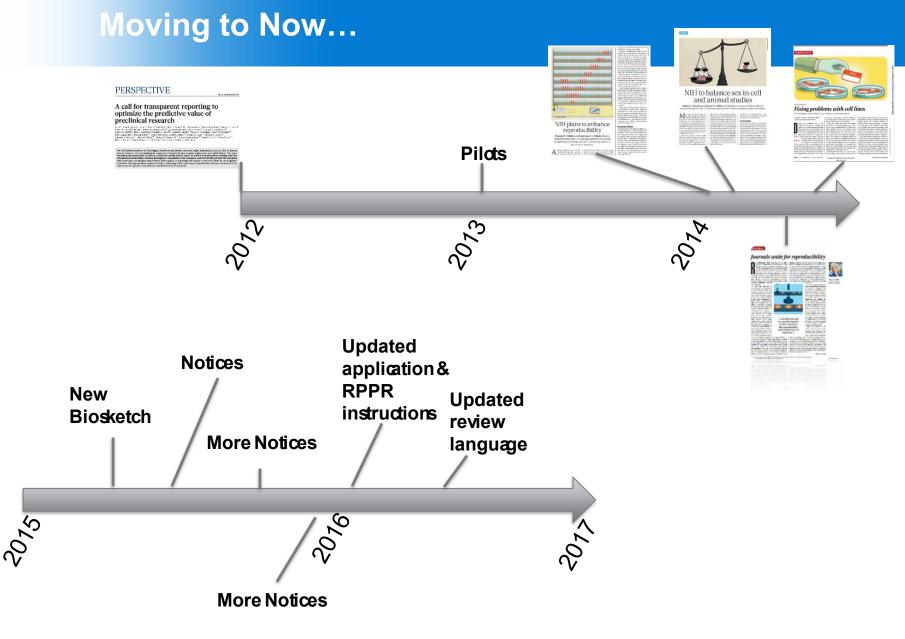
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(See handout for links to notices)

Multi-Stakeholder Approach

EDITORIAL

Science

Journals unite for reproducibility

eproducibility, 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 of 2014 to discuss principles and guidelines for preclinical biomedical research. The gathering was convened by the U.S. National Institutes of Health, Nature,* and Science.

The discussion ranged from what journals were already doing to address reproducibility and the effectiveness of those measures, to the magnitude 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/reportingpreclinical-research.htm) that list proposed journal policies and author reporting requirements to promote transparency and reproducibility.

The new guidelines suggest 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 experi-

menters were blind to the conduct of the experiment, 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 por-

tion of the guidelines suggests

that journals establish best

practices for image-based data

(such as screening for manipu-

lation and storing full-resolu-

tion archival versions) and how

to describe experiments more

completely. An example for

animal experiments is report-

ing the source, species, strain,

sex, age, husbandry, inbred and

strain characteristics, or trans-

genic animals, etc. For cell lines,

one might report the source,

authentication, and myco-

plasma contamination status.

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lines does not obviate the need

for replication or independent

verification of research results.

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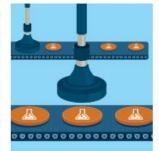
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"...scientific journals are standing together in their conviction that reproducibility and transparency are important ... "

> nals are standing together in their conviction that reproducibility and transparency are important issues.[†] As partners to the research enterprise in the communication and dissemination of research results, journals want to do their part to raise the standards for the benefit of all scientists and the benefit of society. The hope is that that these guidelines will not be viewed as onerous, but as part of the quality control that justifies the public trust in science.

- Marcia McNutt

See www.nature.com/news/1.16299. 1 A list of all journals and publishers signatory to the principles and guidelines aww.nih.gow/about/reporting-preclinical-research.htm.

S Office of Extramural Research 10.1126/science.aa>

Marcia McNutt

Editor-in-Chief

Science Journals



Consensus on reporting principles aims to improve quality control in biomedical research and encourage public trust in science.

eproducibility, rigour, transparency and independent verification are cornerstones of the scientific method. Of course, just N because a result is reproducible does not make it right, and just because it is not reproducible does not make it wrong. A transparent and rigorous approach, however, will 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.

EDITORIALS

CONCOMPTION Saving

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The discussion ranged from what journals were already doing to address reproducibility - and the effectiveness of those measures - to the magnitude of the problem and the cost of solutions. The attendees agreed on a common set of Principles and Guidelines in Reporting Preclinical Research (see go.nature.com/ezil1p) that list proposed journal policies and author reporting requirements in order to promote transparency and reproducibility.

The guidelines recommend 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 reporting of important experimental paramsters, such as standards used, number and type of replicates, statistics, shod of randomization, whether experiments were blinded, how

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nature

"The guidelines encourage using a checklist to ensure reporting of important experimental parumeters."

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and inbred and strain characteristics for transgenic animals. For cell lines, one might report the source, authentication and mycoplasma contamination status. The existence of these guidelines does not obviate the need for replication or independent verification of research results, but should make it easier to perform such replication.

Some of the journals at the meeting had already had all or most of these principles and guidelines in place. But the point is that a large number of scientific journals are standing together in their conviction that reproducibility and transparency are important issues. As partners to the research enterprise in the communication and dissemination of research results, we want to do our part to raise the standards for the benefit of scientists and of society. The hope is that these guidelines will be viewed not as onerous, but as part of the quality control that justifies the public trust in science.

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Multi-Stakeholder Approach





RPG Application and Review

Element of Rigor	Section of Application	Criterion Score	Additional Review Consideration	Contribute to Overall Impact?
Scientific Premise	Research Strategy	Significance	NA	Yes
Scientific Rigor		Approach	NA	Yes
Consideration of Relevant Biological Variables Such as Sex		Approach	NA	Yes
Authentication of Key Biological and/or Chemical Resources	New Attachment	NA	Adequate or Inadequate	No





National Institutes of Health

Grants & Funding

NIH's Central Resource for Grants and Funding Information



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Home » Policy & Compliance » Rigor and Reproducibility

About OER

NIH Grants Policy Statement

Notices of Policy Changes

Compliance & Oversight

Select Policy Topics

Rigor and Reproducibility



Scientific rig of knowledg to assist the

progress re Introduction to the Modules [PDF, 110KB]

Module 1: Lack of Transparency

In order to reproduce someone else's findings adequately, the exother pertinent information must be accessible and understandal to include all relevant details in publications to ensure that other research appropriately and accurately.

Ent

Lack of Transparency Discussion Material [PDF, 97.2KB]



Module 2: Blinding and Randomization

Sample blinding and randomization are key elements in reducing as in permitting reliable statistical testing. This module presents randomization, as well as the impact of issues that may introduc Blinding and Randomization Discussion Material [PDF, 104KB]

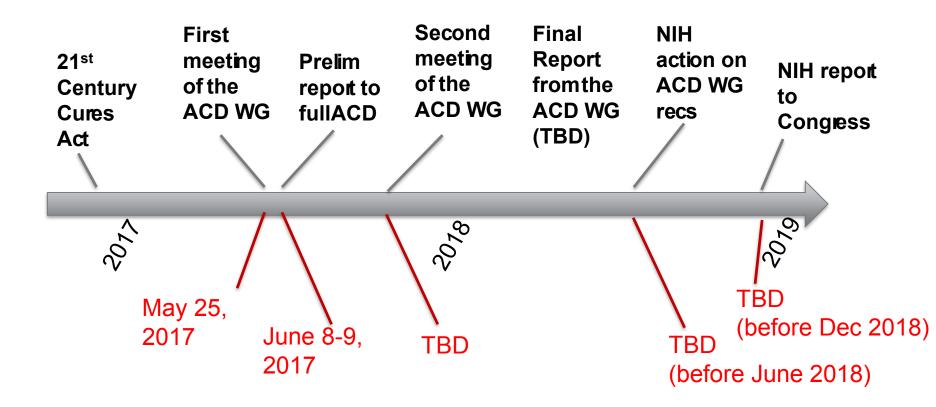
https://grants.nih.gov/reproducibility/index.htm

https://www.nigms.nih.gov/training/pages/clearinghouse-for-training-modules-to-enhance-data-reproducibility.aspx





Timeline for ACD WG





 Application 	Trial design	3a 3b
 Highlight what's important 	Participants	4a 4b
 Section(s) for rigor 	Interventions	5
 Not just authentication 	Outcomes	6a
– "CONSORT-like" checklist	Sample size	6b 7a
 Clarifies review priorities 	Randomisation:	7b
 Resources 	Sequence generation	8a 8b
- Validated, vetted materials	Allocation concealment mechanism	9
	Implementation	10

Blinding 11a

- Training
 - Ongoing funded projects (PA-16-060)
 - Incorporate into spectrum of ethics training
 - NAS: "detrimental research practices"



https://www.nap.edu/catalog/21896/fostering-integrity-in-research

