

New NIH Grant Application Rigor and Transparency Requirements: *Reviewer Perspectives*

May 9, 2016



Survey Drawing



Credits for thoughts, input and considerations for today's presentation

- **Gary Miller, PhD**, Professor, Emory University
 - Navigating the New NIH Guidelines on Rigor & Reproducibility
 - Research Resources 101, 4/30/16
- **Janet Gross, PhD, CEO**, Research Solutions
 - Navigating the New NIH Guidelines on Rigor & Reproducibility
- **Judy Hewitt, PhD**, Office of Extramural Research
 - NIH Regional Seminar: Rigor & Reproducibility: Back to Basics, 10/17/15
- **Russ Price, PhD**, Professor, Emory University
 - Reviewer instructions and templates
- **Li Wu, PhD**, Professor, Ohio State University
 - Example of authentication of key resources
- **Paul Spearman, MD**, Professor, Emory University
 - Example of authentication of key resources
- **Scott Gillespie, MS**, Biostatistician Sr.
 - Interesting philosophical statistical considerations

Today's K-Club Panelists



Paul Spearman, MD, Chief Research Officer,
Children's Healthcare of Atlanta, Nahmias-Schinazi
Research Professor & Vice Chair for Research, Dept.
of Pediatrics



Ralph DiClemente, PhD, Charles Howard Candler
Professor of Public Health & Co-Director of the CFAR
Developmental Core



Courtney, McCracken, PhD, Director, Pediatric
Biostatistics Core, Dept. of Pediatrics

Nomenclature

Enhancing **reproducibility**
through **rigor** and **transparency**

Rigor + **Transparency** =
Reproducibility

The Reproducibility Challenge

- Noted by research community; in multiple publications
 - Across research areas
 - Especially in preclinical research



Unreliable research

Trouble at the lab

Scientists like to think of science as self-correcting. To an alarming degree, it is not

Oct 19th 2013

<http://www.economist.com/news/briefing/21588057-scientists-think-science-self-correcting-alarming-degree-it-not-trouble>

The idea that the same experiments always get the same results, no matter who performs them, is one of the cornerstones of science's claim to objective truth. If a systematic campaign of replication does not lead to the same results, then either the original research is flawed (as the replicators claim) or the replications are (as many of the original researchers on priming contend). Either way, something is awry.

It is tempting to see the priming fracas as an isolated case in an area of science—psychology—easily marginalised as soft and wayward. But irreproducibility is much more widespread. A few years ago scientists at Amgen, an American drug company, tried to replicate 53 studies that they considered landmarks in the basic science of cancer, often cooperating closely with the original researchers to ensure that their experimental technique matched the one used first time round. According to a piece they wrote last year in *Nature*, a leading scientific journal, they were able to reproduce the original results in just six.

The Reproducibility Crisis

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 Mackoid.

- **Noted by 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.

- Across research areas
- Especially in areas where we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Rhasru Asadullah

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.

Reforming Science: Methodological and Cultural Reforms



Unreliable research

Trouble at the lab

Scientists like to think of science as self-correcting. To an alarming degree, it is not. Oct 10th 2013 | From the print edition

Like 146 | Tweet 1,227



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.

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

Story C. Landis¹, Susan G. Amara², Khusru Asadullah³, Chris P. Austin⁴, Robi Blumenstein⁵, Eileen W. Bradley⁶, Ronald G. Crystal⁷, Robert B. Darnell⁸, Robert J. Ferrante⁹, Howard Fillit¹⁰, Robert Finkelstein¹, Marc Fisher¹¹, Howard E. Gendelman¹², Robert M. Golub¹³, John L. Goudreau¹⁴, Robert A. Gross¹⁵, Amelie K. Gubitzi¹, Sharon E. Hesterlee¹⁶, David W. Howells¹⁷, John Huguenard¹⁸, Katrina Kelner¹⁹, Walter Koroshetz¹, Dimitri Krainc²⁰, Stanley E. Lazic²¹, Michael S. Levine²², Malcolm R. Macleod²³, John M. McCall²⁴, Richard T. Moxley III²⁵, Kalyani Narasimhan²⁶, Linda J. Noble²⁷, Steve Perrin²⁸, John D. Porter¹, Oswald Steward²⁹, Ellis Unger³⁰, Ursula Utz¹ & Shai D. Silberberg¹

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.

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<http://www.nature.com/nature/journal/v490/n7419/full/nature11556.html>

Nature 490, 187–191 (11 October 2012) doi:10.1038/nature11556



Overarching point – Rigor and transparency have always been expected in science. While these requirements are touted as “new” and they may be for some, for many they may be a “reorganization or expansion” of information and justification already included. The change is now that the NIH is requesting that these components be specifically stated and the sections highlighted or expanded.

Good Experimental Design (and Reporting) Underlies Rigor and Reproducibility of Findings



Five requirements for a
“good” experimental design:

- Free from systematic error
- Have high precision
- Have a wide range of validity/applicability
- Simple experiments
- Have the ability to calculate uncertainty

COX, D.R. *Planning Experiments*, John Wiley and Sons, New York, 1958.

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This book is about the planning of experiments in which the effects under investigation tend to be masked by fluctuations outside the experimenter's control.

It was designed by its author "to give a comprehensive nonmathematical course on the design and analysis of experiments...in conjunction with a textbook on statistical analysis [and]... to avoid statistical and mathematical technicalities and to concentrate on a treatment that will be intuitively acceptable to the experimental worker, for whom the book is primarily intended."

Free from systematic error

Should be made sufficiently precise

Conclusion should have a wide range of validity

Experimental arrangement should be as simple as possible

Uncertainty in the conclusions should be assessable

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.

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A growing chorus of concern, from scientists and laypeople, contends that the complex system for ensuring shorter term, however, the checks and balances that once ensured scientific fidelity have been hobbled. This has compromised

outnumbered by the hundreds of thousands published each year in good faith. Instead, a complex array of other factors seems to have contributed to the lack of reproducibility. Factors include poor training of researchers in experimental design; increased emphasis on making provocative statements rather than presenting technical details; and publications that do not report basic elements of experimental design¹. Crucial experimental design elements that are all too frequently ignored include blinding, randomization, replication, sample-size calculation and the effect of sex differences. And some scientists are reluctant to 'make sauce' to make and withhold and describe them on a competitive edge². Without scientists will be to further bloom: Exacerbating and attitudes of centres and scientific agencies of the overvaluation of high-profile journals also provide in such journals tenure, and in rewards³. Then there is not published, researchers to papers that previously published work. Further compounding the problem is the difficulty of accessing unpublished data — and the failure of funding agencies to establish or enforce policies that insist on data access.

PRECLINICAL PROBLEMS

Reproducibility is potentially a problem in all scientific disciplines. However, human clinical trials seem to be less at risk because they are already governed by various regulations that stipulate rigorous design and independent oversight — including randomization, blinding, power estimates, pre-registration of outcome measures in standardized, public databases such as ClinicalTrials.gov and oversight by institutional review boards and data safety monitoring boards. Furthermore, the clinical trials community has taken important steps towards adopting standard reporting elements⁴.

“Efforts by the NIH alone will not be sufficient to effect real change in this unhealthy environment.”

Policy: NIH plans to enhance reproducibility

[Francis S. Collins](#)

& [Lawrence A. Tabak](#)

27 January 2014

Nature 505, 612–613 (30 January 2014) doi:10.1038/505612a

<http://www.nature.com/news/policy-nih-plans-to-enhance-reproducibility-1.14586>

New Journal Policies to Enhance Reproducibility

EDITORIAL

Science

Journals unite for reproducibility

Reproducibility, 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 means 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 AAAI headquarters in June of 2014 to discuss principles and guidelines for preclinical biomedical research. The gathering was convened by the US 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 need of solutions. The attendees agreed on a common set of Principles and Guidelines to Reporting Preclinical Research (see www.guidelinesforreporting-preclinicalresearch.com) that set 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, statistical methods of randomization, whether experi-

ments 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 intentionally to the published paper. Journals should strongly encourage, or 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 portion of the guidelines suggests that journals establish best practices for image-based data (such as screening for manipulation and storing full-resolution original images) and how to describe experiments more completely. An example for animal experiments in reporting the mouse, species, strain, sex, sex/husbandry related and strain characteristics, or transgenic animals, etc. 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 already had implemented all or most of these principles and guidelines, but the important point is that a large number of scientific journals are standing together in their conviction that reproducibility and transparency are important issues. As partners in our 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 these guidelines will not be viewed as an exercise, but as part of the quality control that justifies the public trust in science.



Marsha McHugh
Editor-in-Chief
Science Journals



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

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nature

EDITORIALS

ENVIRONMENT Saving species is far from a walk in the park **8**

PSYCHOLOGY Psychology goes up to check its workbooks **9**



SCIENCE Climate plan goes up to check its workbooks **9**

Journals unite for reproducibility

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

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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, but partners in the research enterprise in the communication and dissemination of research results, want to do their part to raise the standards for the benefit of all scientists and the benefit of society. The hope is that these guidelines will not be viewed as an exercise, but as part of the quality control that justifies the public trust in science.

<http://www.nature.com/news/journals-unite-for-reproducibility-1.16259>

Science 7 November 2014

Vol 346 no 6210 p. 679

Investigators are expected to report on approaches taken to ensure robust and unbiased results in their progress report as well as in their submitted manuscripts. A set of guidelines for reporting preclinical research in publications was developed during an NIH sponsored joint workshop with the Nature Publishing Group and Science in June 2014 on the issue of reproducibility and rigor of research findings. Journal editors representing over 30 basic/preclinical science journals agreed on a set of [principles and guidelines for reporting preclinical research](http://www.guidelinesforreporting-preclinicalresearch.com) to facilitate these goals and [over 135 journals have endorsed](http://www.guidelinesforreporting-preclinicalresearch.com) the principles.

<https://www.nih.gov/research-training/rigor-reproducibility/principles-guidelines-reporting-preclinical-research>

<https://www.nih.gov/sites/default/files/research-training/initiatives/reproducibility/rigor-reproducibility-endorsements.pdf>

authors & referees

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Site content

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NPG Journals

by Subject Area

Chemistry
Chemistry

Availability of data, material and methods

An inherent principle of publication is that others should be able to replicate and build upon the authors' published claims. A condition of publication in a Nature journal is that **authors are required to make materials, data, code, and associated protocols promptly available to readers without undue qualifications**. Any restrictions on the availability of materials or information must be disclosed to the editors at the time of submission. Any restrictions must also be disclosed in the submitted manuscript.

After publication, readers who encounter refusal by the authors to comply with these policies should contact the chief editor of the journal. In cases where editors are unable to resolve a complaint, the journal may refer the matter to the authors' funding institution and/or publish a formal statement of correction, attached online to the publication, stating that readers have been unable to obtain necessary materials to replicate the findings.

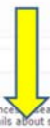
See sections below for details on:

- [reporting requirements](#)
- [availability of data](#)
- [availability of materials](#)
- [availability of computer code](#)
- [experimental protocols](#)
- [clinical trials](#)
- [further reading](#)

Reporting requirements

Reporting requirements for life sciences research

Since May 2013, Nature journals require authors of life sciences research papers that are sent for external review to include in their manuscripts relevant details about several elements of experimental and analytical design. This initiative aims to improve the transparency of reporting and the reproducibility of published results. It focuses on **elements of methodological information** that are frequently poorly reported. During peer review, authors will be asked to confirm that these elements are included in the manuscript by filling out a **checklist** that will be made available



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<http://www.nature.com/authors/policies/availability.html>

Nature Journal Article Reporting Requirements

This initiative aims to improve the transparency of reporting and the reproducibility of published results. It focuses on elements of methodological information that are frequently poorly reported. **During peer review, authors will be asked to confirm that these elements are included in the manuscript by filling out a checklist that will be made available to the editors and reviewers.**

<http://www.nature.com/authors/policies/checklist.pdf>

This checklist will not be published. Please ensure that the answers to the following questions are reported in the manuscript itself. We encourage you to include a specific subsection in the Methods section for statistics, reagents and animal models. Below, provide the page number or section and paragraph number (e.g. "Page 5" or "Methods, 'reagents' subsection, paragraph 2").

▶ Statistics and general methods Reported in section/paragraph or page #:

<p>1. How was the sample size chosen to ensure adequate power to detect a pre-specified effect size? (Give section/paragraph or page #)</p> <p>For animal studies, include a statement about sample size estimate even if no statistical methods were used.</p>	<p>_____</p> <p>_____</p>
<p>2. Describe inclusion/exclusion criteria if samples or animals were excluded from the analysis. Were the criteria pre-established? (Give section/paragraph or page #)</p>	<p>_____</p>
<p>3. If a method of randomization was used to determine how samples/animals were allocated to experimental groups and processed, describe it. (Give section/paragraph or page #)</p> <p>For animal studies, include a statement about randomization even if no randomization was used.</p>	<p>_____</p> <p>_____</p>
<p>4. If the investigator was blinded to the group allocation during the experiment and/or when assessing the outcome, state the extent of blinding. (Give section/paragraph or page #)</p> <p>For animal studies, include a statement about blinding even if no blinding was done.</p>	<p>_____</p> <p>_____</p>
<p>5. For every figure, are statistical tests justified as appropriate?</p> <p>Do the data meet the assumptions of the tests (e.g., normal distribution)?</p> <p>Is there an estimate of variation within each group of data?</p> <p>Is the variance similar between the groups that are being statistically compared? (Give section/paragraph or page #)</p>	<p>_____</p> <p>_____</p> <p>_____</p> <p>_____</p>

April 2015 (Continues on following page)

5/10/15

<http://www.nature.com/authors/policies/checklist.pdf>

▶ Reagents	Reported in section/paragraph or page #:
6. To show that antibodies were profiled for use in the system under study (assay and species), provide a citation, catalog number and/or clone number, supplementary information or reference to an antibody validation profile (e.g., <i>Antibodypedia</i> , <i>1DegreeBio</i>).	
7. Cell line identity: a. Are any cell lines used in this paper listed in the database of commonly misidentified cell lines maintained by ICLAC (also available in NCBI Biosample)?	
b. If yes, include in the Methods section a scientific justification of their use – indicate here on which page (or section and paragraph) the justification can be found.	
c. For each cell line, include in the Methods section a statement that specifies:	
- the source of the cell lines	
- have the cell lines been authenticated? If so, by which method?	
- have the cell lines been tested for mycoplasma contamination? In this checklist, indicate on which page (or section and paragraph) the information can be found.	

<http://www.nature.com/authors/policies/checklist.pdf>

	<u>Reported in section/paragraph or page #:</u>
▶ Animal Models	
8. Report species, strain, sex and age of animals	<input type="text"/>
9. For experiments involving live vertebrates, include a statement of compliance with ethical regulations and identify the committee(s) approving the experiments.	<input type="text"/>
10. We recommend consulting the ARRIVE guidelines (PLoS Biol. 8(6), e1000412,2010) to ensure that other relevant aspects of animal studies are adequately reported.	<input type="text"/>
▶ Human subjects	
11. Identify the committee(s) approving the study protocol.	<input type="text"/>
12. Include a statement confirming that informed consent was obtained from all subjects.	<input type="text"/>
13. For publication of patient photos, include a statement confirming that consent to publish was obtained.	<input type="text"/>
14. Report the clinical trial registration number (at ClinicalTrials.gov or equivalent).	<input type="text"/>
15. For phase II and III randomized controlled trials, please refer to the CONSORT statement and submit the CONSORT checklist with your submission.	<input type="text"/>
16. For tumor marker prognostic studies, we recommend that you follow the REMARK reporting guidelines .	<input type="text"/>

April 2015 (Continues on following page)

<http://www.nature.com/authors/policies/checklist.pdf>

▶ Data deposition	Reported in section/paragraph or page #
<p>17. Provide accession codes for deposited data. Data deposition in a public repository is mandatory for:</p> <ol style="list-style-type: none"> Protein, DNA and RNA sequences Macromolecular structures Crystallographic data for small molecules Microarray data <p>Deposition is strongly recommended for many other datasets for which structured public repositories exist; more details on our data policy are available here. We encourage the provision of other source data in supplementary information or in unstructured repositories such as Figshare and Dryad. We encourage publication of Data Descriptors (see Scientific Data) to maximize data reuse</p>	
<p>18. If computer code was used to generate results that are central to the paper's conclusions, include a statement in the Methods section under "Code availability" to indicate whether and how the code can be accessed. Include version information as necessary and any restrictions on availability.</p>	

<http://www.nature.com/authors/policies/checklist.pdf>

NIH's Guiding Principles for Rigor & Transparency

- Raise awareness and begin culture shifts in the scientific community
 - Demonstrate to our public stakeholders that NIH is seriously considering their concerns
 - Ensure that NIH is investing in the best science and minimizing unnecessary burden
-
- Clarify NIH's long-standing expectations regarding rigor and transparency and how they would like to see this described in applications
 - Prompt applicants to consider issues that they may have previously down-played or ignored, which may have a detrimental effect on the quality of the science they produce
 - Improve the way that applicants describe their work; provide sufficient information for reviewers

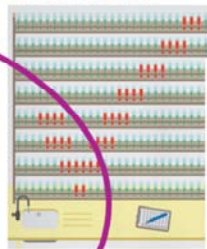
Four Areas of Clarification

- Scientific premise
- Scientific rigor
- Relevant Biological Variables, Such as Sex

Addressed within Research Strategy

- Authentication of Key Biological and/or Chemical Resources

Addressed as separate attachment



NIH plans to enhance reproducibility

Francis S. Collins and Lawrence A. Tabak discuss initiatives at the US National Institutes of Health to explore ways to restore the self-correcting nature of basic research.

introduction of the handbook of research practices and the importance of standardizing experimental procedures to enhance reproducibility. The handbook also provides a comprehensive overview of the field of reproducibility research and the challenges that researchers face in this area.



NIH to balance sex in cell and animal studies

Janine 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.



Fixing problems with cell lines

Technology and policies can improve authentication

Researchers are using new technologies to improve the accuracy of cell line authentication. This is important because many cell lines used in research are contaminated with other cell lines, which can lead to misleading results. The NIH is working to develop new technologies and policies to improve authentication and ensure that researchers are using the correct cell lines for their studies.

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RPG Application and Review

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

Mentored Career Development Award (K) Applications and Review

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

The Four Focus Areas – one by one

- 1) Scientific Premise
- 2) Scientific Rigor
- 3) Consideration of Relevant Biological Variables
- 4) Authentication of Biological/Chemical Resources

Scientific Premise

Application Instructions

Listed in the Research Strategy section under Significance

- Explain the importance of the problem or critical barrier to progress in the field that the proposed project addresses.
- *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.*
- Explain how the proposed 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 if the proposed aims are achieved.

Black text – current instructions

Red, italics text – new instructions

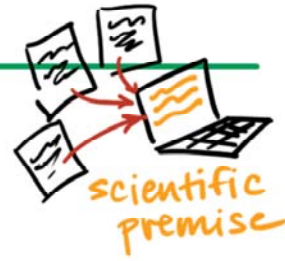
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<http://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/career-forms-d.pdf>

Scientific Premise

- All research builds upon prior research, whether observations, preliminary data, or published literature. The scientific premise for an application is **the research that is used to form the basis for the proposed research question.**
- Scientific premise includes a retrospective consideration of the foundation for the application
- The applicant should evaluate the strengths and weakness of the foundational research *including the rigor, relevant variables, and authentication of resources of said work*
- **The background**



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Scientific Premise: How Reviewers are Instructed

Is there a strong scientific premise for the project?

Scientific Premise: The key data introduced by the applicant to justify the project.

- The applicant should supply a sufficient evaluation of the strengths and weaknesses of the data or other justification used to support the application, and should describe how the proposed research will address any weaknesses or gaps.
- Extending the existing review criteria to include a retrospective assessment of the foundation for the project, scientific premise will be addressed in peer review:
 - As a **Significance criterion** for **research grant applications**
 - As a **Research Plan criterion** for **mentored CDA's**.
- Reviewers should factor a weak premise or the failure to address scientific premise adequately, into the criterion score and overall impact score. The page limit is not an acceptable excuse for an applicant to not address scientific premise.

Statement by reviewers for Scientific Premise now required! University 26

In the significance review criteria for R's -
http://grants.nih.gov/grants/peer/critiques/rpg_D.htm

In the Research Plan review criteria for K's -
http://grants.nih.gov/grants/peer/critiques/k_D.htm

Scientific Premise: Questions for the Panel



- What is the right length to address this?
- Do you recommend special formatting to highlight this for the reviewer?
- Will you write your own grants any differently now that this is being highlighted as a review criteria?
- What do you think of publications and formal efforts to formalize replication attempts?
 - Reproducibility Initiative (life scientists can pay to have their work validated by an independent lab)
 - Publishing negative results

For reference:

<http://grants.nih.gov/reproducibility/faqs.htm#4824>

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<http://journals.plos.org/plosone/s/criteria-for-publication>

The Four Focus Areas – one by one

- 1) Scientific Premise
- 2) Scientific Rigor
- 3) Consideration of Relevant Biological Variables
- 4) Authentication of Biological/Chemical Resources

Scientific Rigor

Application Instructions

Listed in the Research Strategy Section under 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 the Resource Sharing Plan attachment below, include how the data will be collected, analyzed, and interpreted.
- Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.
- If the project is in the early stages of development, describe any strategy to establish feasibility, and address the management of any high risk aspects of the proposed work.

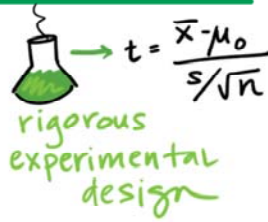
Black text – current instructions

Red, italics text – new instructions

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Scientific Rigor

- 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 the experimental design and methods proposed and how they will achieve robust and unbiased results
- Robust and unbiased results are obtained using methods designed to avoid bias and these results can be reproduced under well-controlled and reported experimental conditions
- This includes **transparency of experimental details to allow reproducibility**


$$t = \frac{\bar{x} - \mu_0}{s/\sqrt{n}}$$

rigorous
experimental
design

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Fundamental Information on Vertebrate Animal Species

Fundamental Information on Human Subjects

Experimental Design

Minimizing Bias

Results

Interpretation of Results

Scientific Rigor for RPG -Assessed Under Approach How Reviewers are Instructed

- 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?*
- 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?

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http://grants.nih.gov/grants/peer/critiques/rpg_D.htm

Reviewer Guidance on Rigor and Transparency: Research Project Grant and Mentored Career Development Applications:

https://grants.nih.gov/grants/peer/guidelines_general/Reviewer_Guidance_on_Rigor_and_Transparency.pdf

Scientific Rigor for K23 – *Assessed Under Research Plan* How Reviewers are Instructed

- Are the proposed research question, design, and methodology of significant scientific and technical merit?
- Is the research plan relevant to the candidate's research career objectives?
- Is the research plan appropriate to the candidate's stage of research development and as a vehicle for developing the research skills described in the career development plan?
- Is there a strong scientific premise for the project?
- ***Has the candidate presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?***
- Has the candidate presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

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http://grants.nih.gov/grants/peer/critiques/k_D.htm

Reviewer Guidance on Rigor and Transparency: Research Project Grant and Mentored Career Development Applications:

https://grants.nih.gov/grants/peer/guidelines_general/Reviewer_Guidance_on_Rigor_and_Transparency.pdf

Scientific Rigor: Questions for the Panel



- How will you change your approach to grant writing?
- Will your own grant strategy review process change in light of this newly worded requirement? How can applicants best highlight this?
- What are some common statistical pitfalls that researchers should avoid?
 - P-hacking, HARKing, fishing expeditions
 - Using poorly defined/unvalidated outcome measures
 - Not addressing statistical power
- Does this jeopardize exploratory research?

For Reference:

<http://grants.nih.gov/reproducibility/faqs.htm#4828> | Emory University

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P-hacking is when researchers analyse their results in multiple ways or multiple times until they get their desired result

<http://blogs.plos.org/sciomm/2015/05/19/p-hacking-megan-head-on-why-its-not-good-for-science/>

HARKing - Hypothesis After the Results are Known

When researchers formulate or change their hypothesis after they have seen the results of their statistical analyses

<http://goodsciencebadscience.nl/?p=347>

The Four Focus Areas – one by one

- 1) Scientific Premise
- 2) Scientific Rigor
- 3) Consideration of Relevant Biological Variables
- 4) Authentication of Biological/Chemical Resources

Relevant Biological Variables Application Instructions

Listed in the Research Strategy Section under 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.*
 - *Please refer to [NOT-OD-15-002](#) for further consideration of NIH expectations about sex as a biological variable.*

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<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html>

Consideration of Relevant Biological Variables, Such as Sex

- Biological variables, such as sex, age, weight, and underlying health conditions, are often critical factors affecting health or disease
- 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**



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In clinical research: This has previously applied to conducting research with children and pregnant women, where limitation to these populations has required justification, so for researchers conducting research in limited populations, this component is not really new.

The Four C's of Studying Sex to Strengthen Science

1. **Consider** - Design studies that take sex into account, or explain why it isn't incorporated
2. **Collect** - Tabulate sex-based data
3. **Characterize** - Analyze sex-based data
4. **Communicate** - Report (via progress reports) and publish sex-based data



Relevant Biological Variables *–Assessed Under Approach* How Reviewers are Instructed

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

Consideration of Relevant Biological Variables: Questions for the Panel



- How will you handle this in your own research?
- Will this requirement double research budgets?
- Will this involve more foundational work before a study is even started?
- What are your expectations as a reviewer?

For Reference:

<http://grants.nih.gov/reproducibility/faqs.htm#4835>

Strong justification from the scientific literature, preliminary data, or other relevant considerations must be provided for applications proposing to study only one sex.

The Four Focus Areas – one by one

- 1) Scientific Premise
- 2) Scientific Rigor
- 3) Consideration of Relevant Biological Variables
- 4) Authentication of Biological/Chemical Resources

Authentication of Key Resources

Application Instructions – own attachment

Briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.

- *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.*
- *Reviewers will assess the information provided in this Section. Any reviewer questions associated with key biological and/or chemical resource authentication will need to be addressed prior to award.*

Authentication: May 25, 2016 and beyond

PHS 398 Research Plan

OMB Number: 0925-0001

Introduction			
1. Introduction to Application (Resubmission and Revision)	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
Research Plan Section			
2. Specific Aims	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
3. *Research Strategy	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
4. Progress Report/Publication List	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
Human Subjects Section			
5. Protection of Human Subjects	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
6. Data Safety Monitoring Plan	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
7. Inclusion of Women and Minorities	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
8. Inclusion of Children	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
Other Research Plan Section			
9. Vertebrate Animals	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
10. Select Agent Research	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
11. Multiple PDP/ Leadership Plan	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
12. Consortium/Contractual Arrangements	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
13. Letters of Support	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
14. Resource Sharing Plan(s)	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
15. Authentication of Key Biological and/or Chemical Resources	<input type="text"/>	Add Attachment	Delete Attachment View Attachment
Appendix			
16. Appendix	Add Attachments Delete Attachments View Attachments <input type="checkbox"/>		

Authentication of Key Biological and/or Chemical Resources

- The quality of the resources used to conduct research is critical to the ability to reproduce the results. 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.



- Key biological and/or chemical resources are those that: 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 and may or may not be generated with NIH funds. **These include, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics.**

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Authentication of Key Resources How Reviewers are Instructed

- *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.*

Not part of the impact score!

Authentication of Key Resources Example

We understand the importance of authenticating resources used in this project, as part of our overall laboratory quality assurance (QA) program. The intent of our QA program is to ensure reproducibility of our results, so that our findings can make a real and continued impact in the field. Part of our QA program includes requiring a minimum of three replicates for all submitted/published experiments, and validation of all key results by an independent, blinded laboratory member. Another important aspect of QA is the documentation of the quality and activity of all key reagents developed in our research program. Here we detail our current procedures for key reagents.

Authentication of Key Resources Example

Standard laboratory reagents. We purchase high quality chemicals from Sigma, Fisher, VWR, and other very established biological/chemical suppliers. For these, we rely upon the analysis conducted by the manufacturer and supplier.

Authentication of Key Resources

Example

Purchased/acquired antibodies. We purchase from multiple vendors, and rely on published reports plus documentation from the vendor to ensure specificity initially. However, for key experiments we validate specificity using knockdown/knockout cell lines as controls and validated preparations of antigen to evaluate specificity. We generally acquire more than one antibody for each antigen as further means of establishing the correct reactivity.

Authentication of Key Resources Example

We will deposit our published reagents, including DNA constructs, cell lines, and other unique reagents to the NIH AIDS Research and Reference Reagent Program to share with other researchers and to facilitate similar research in the field.

Authentication of Key Resources Example

We will provide appropriate training for new members in our lab to understand the importance of authentication of key biological and chemical resources and practice above procedures during research.

Authentication of Key Resources Example

We will publish detailed information of materials and methods used in the studies to ensure reproducibility of assays by other researchers.

Authentication of Key Biological and/or Chemical Resources: Questions for the Panel



- What should be included/excluded?
- Should labs establish stronger internal quality controls?
- Does this apply to clinical research and/or clinical trials?

For reference:

<http://grants.nih.gov/reproducibility/faqs.htm#4846>

<http://grants.nih.gov/reproducibility/faqs.htm#4846>



Appendix

Addressing Rigor

Some of the best links regarding how to address Rigor:

Examples for satisfying Rigor Requirement:

- http://www.ninds.nih.gov/funding/transparency_in_reporting_guidance.pdf
- <http://www.nimh.nih.gov/research-priorities/policies/enhancing-the-reliability-of-nimh-supported-research-through-rigorous-study-design-and-reporting.shtml>
- <https://www.drugabuse.gov/offices/office-nida-director-od/office-translational-initiatives-program-innovations-otipi/nih-initiative-enhancing-research-reproducibility-transparency>

Resources including examples of Rigor used in real, awarded applications:

- <http://grants.nih.gov/reproducibility/index.htm>

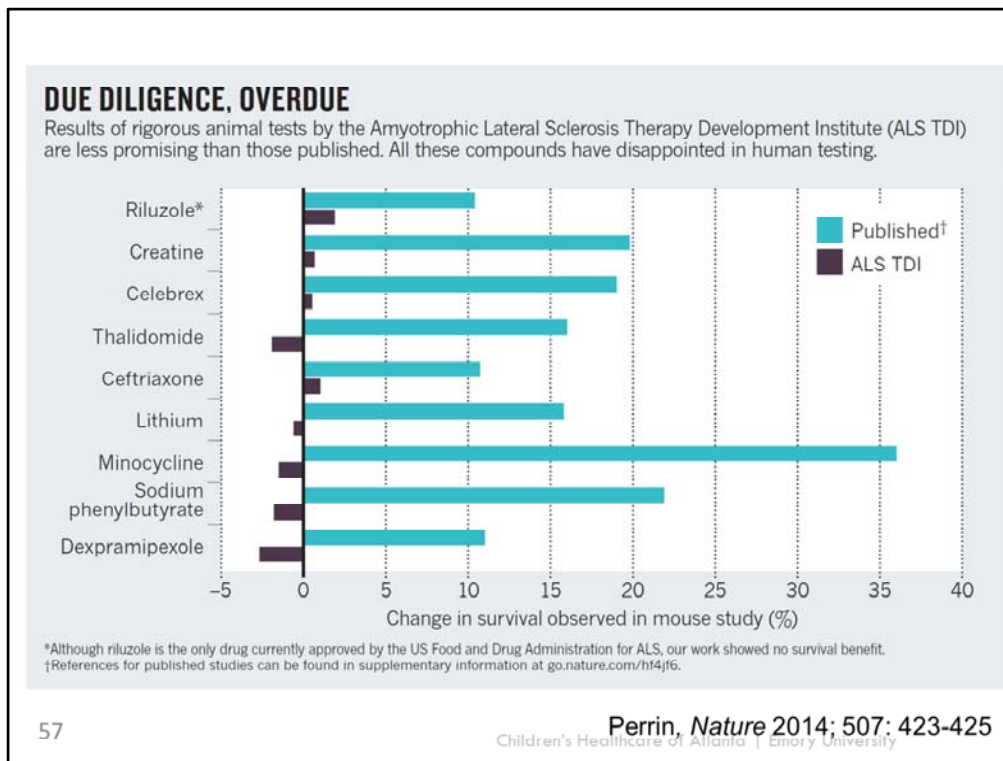
Authentication of Key Resources

Additional Example

Primary cells. Primary cells are routinely used in our laboratory and can vary from donor to donor. We utilize standard SOPs for preparation of T lymphocytes and for monocyte purification and differentiation into monocyte-derived macrophages. We rely primarily on replicates performed on multiple donors to ensure reproducibility of results with primary cell preparations.

Authentication of Key Resources Additional Example

We will purchase or obtain cell lines that will be used in the study from reliable resources to ensure the identity of the cell lines, such as the American Type Culture Collection (ATCC) or the NIH AIDS Research and Reference Reagent Program. We will freeze initial cell line stocks and use early passages of cell lines in all experiments. We will perform genotyping of the cell lines using established methods if required for a specific experiment as we described (Wu L. *et al.* Raji B cells, misidentified as THP-1 cells, stimulate DC-SIGN-mediated HIV transmission. *Virology*. 2004; 318:17-23).



<http://www.nature.com/news/preclinical-research-make-mouse-studies-work-1.14913>

Mice take the blame for one of the most uncomfortable truths in translational research. Even after animal studies suggest that a treatment will be safe and effective, more than 80% of potential therapeutics fail when tested in people. Animal models of disease are frequently condemned as poor predictors of whether an experimental drug can become an effective treatment. Often, though, the real reason is that the preclinical experiments were not rigorously designed.

One such group of patients is those with amyotrophic lateral sclerosis (ALS), the fatal neurodegenerative condition also known as Lou Gehrig's or motor neuron disease. Over the past decade, about a dozen experimental treatments have made their way into human trials for ALS. All had been shown to ameliorate disease in an established animal model. All but one failed in the clinic, and the survival benefits of that one are marginal.

At the ALS Therapy Development Institute (TDI) in Cambridge, Massachusetts, we have tested more than 100 potential drugs in an established mouse model of this disease (mostly unpublished work). Many of these drugs had been reported to slow down disease in that same mouse model; none was found to be beneficial in our experiments (see ['Due diligence, overdue'](#)). Eight of these compounds ultimately failed in clinical trials, which together involved thousands of people. One needs to look no further than potential blockbuster indications such as Alzheimer's and cancer to see that the problem persists across diseases.

After nearly a decade of validation work, the ALS TDI introduced guidelines that should reduce the number of false positives in preclinical studies and so prevent unwarranted clinical trials. The recommendations, which pertain to other diseases too, include: rigorously assessing animals' physical and biochemical traits in terms of human disease; characterizing when disease symptoms and death occur and being alert to unexpected variation; and creating a mathematical model to aid experimental design, including how many mice must be included in a study. It is astonishing how often such straightforward steps are overlooked. It is hard to find a publication, for example, in which a preclinical animal study is backed by statistical models to minimize experimental noise.