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

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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 co-operating 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 Reproducibilit

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 Macleod**.

- 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**.

publications

  - Across research areas
  - Especially i

Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah

False-Positive Psychology: Undisclosed Flexibility in Data Collection and Analysis Allows Presenting Anything as Significant

The Economist | World politics | Business & finance | Economics | Science & technology | Culture

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 | From the print edition

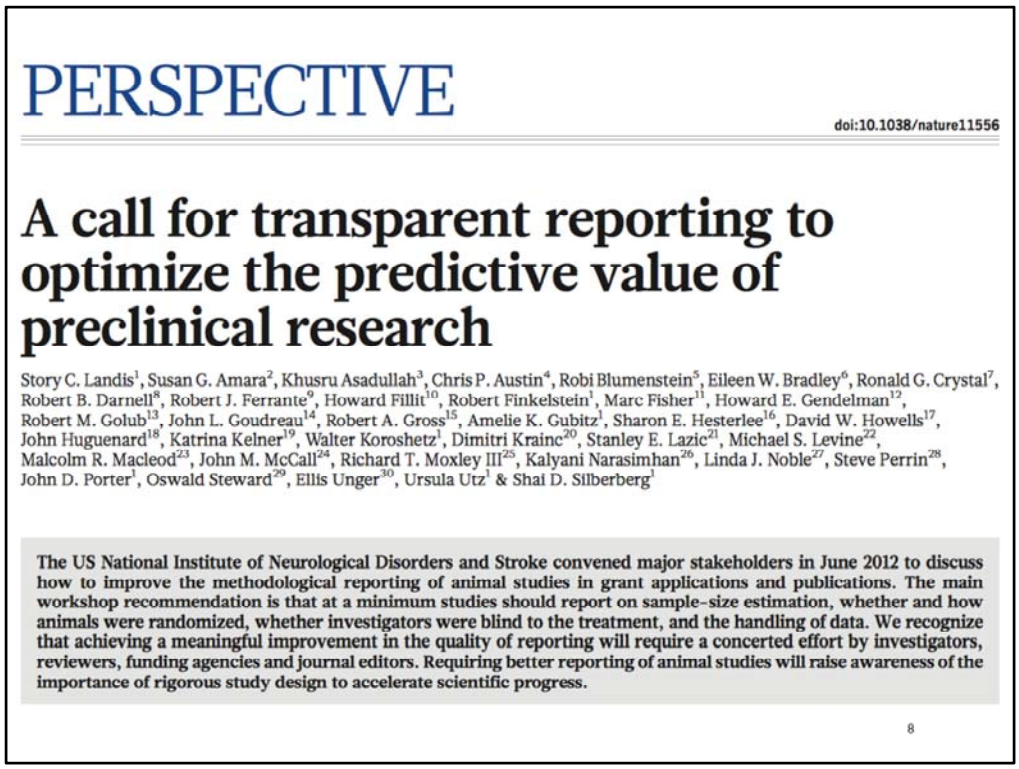
Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

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



PERSPECTIVE

doi:10.1038/nature11556

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

Story C. Landis[1], Susan G. Amara[2], Khusru Asadullah[3], Chris P. Austin[4], Robi Blumenstein[5], Eileen W. Bradley[6], Ronald G. Crystal[7], Robert B. Darnell[8], Robert J. Ferrante[9], Howard Fillit[10], Robert Finkelstein[1], Marc Fisher[11], Howard E. Gendelman[12], Robert M. Golub[13], John L. Goudreau[14], Robert A. Gross[15], Amelie K. Gubitz[1], Sharon E. Hesterlee[16], David W. Howells[17], John Huguenard[18], Katrina Kelner[19], Walter Koroshetz[1], Dimitri Krainc[20], Stanley E. Lazic[21], Michael S. Levine[22], Malcolm R. Macleod[23], John M. McCall[24], Richard T. Moxley III[25], Kalyani Narasimhan[26], Linda J. Noble[27], Steve Perrin[28], John D. Porter[1], Oswald Steward[29], Ellis Unger[30], Ursula Utz[1] & Shai D. Silberberg[1]

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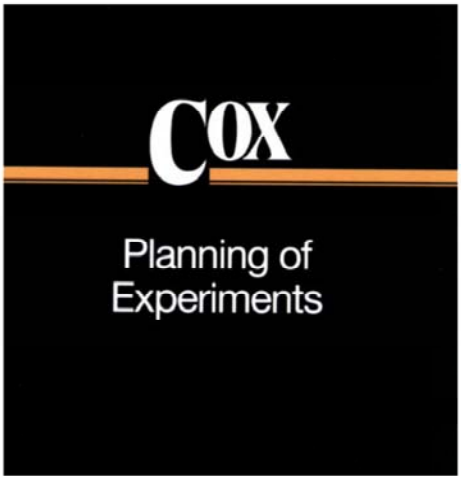
http://www.nature.com/nature/journal/v490/n7419/full/nature11556.html

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."

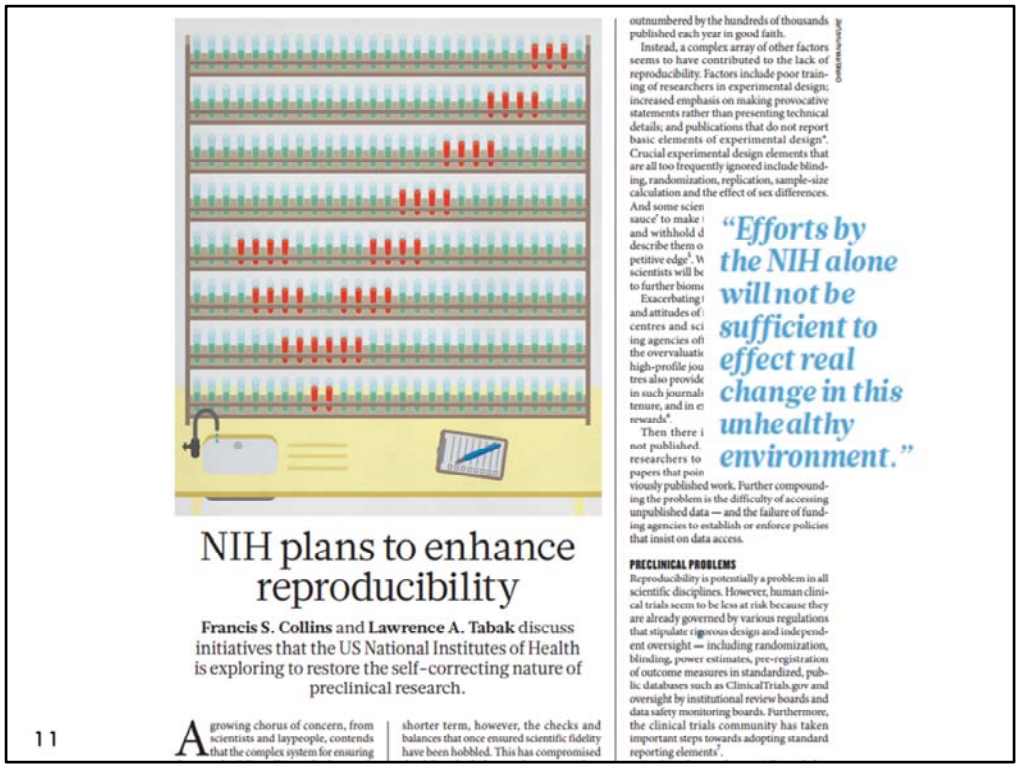
Free from systematic error

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 design*. 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 scien sauce' to make and withhold d describe them o petitive edge[3]. W scientists will be to further biom

Exacerbating and attitudes of centres and sci ing agencies oft the overvaluatic high-profile jou tres also provide in such journals tenure, and in e rewards[4].

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

Then there i not published. researchers to papers that poin viously 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 elements[5].

Policy: NIH plans to enhance reproducibility

Francis S. Collins

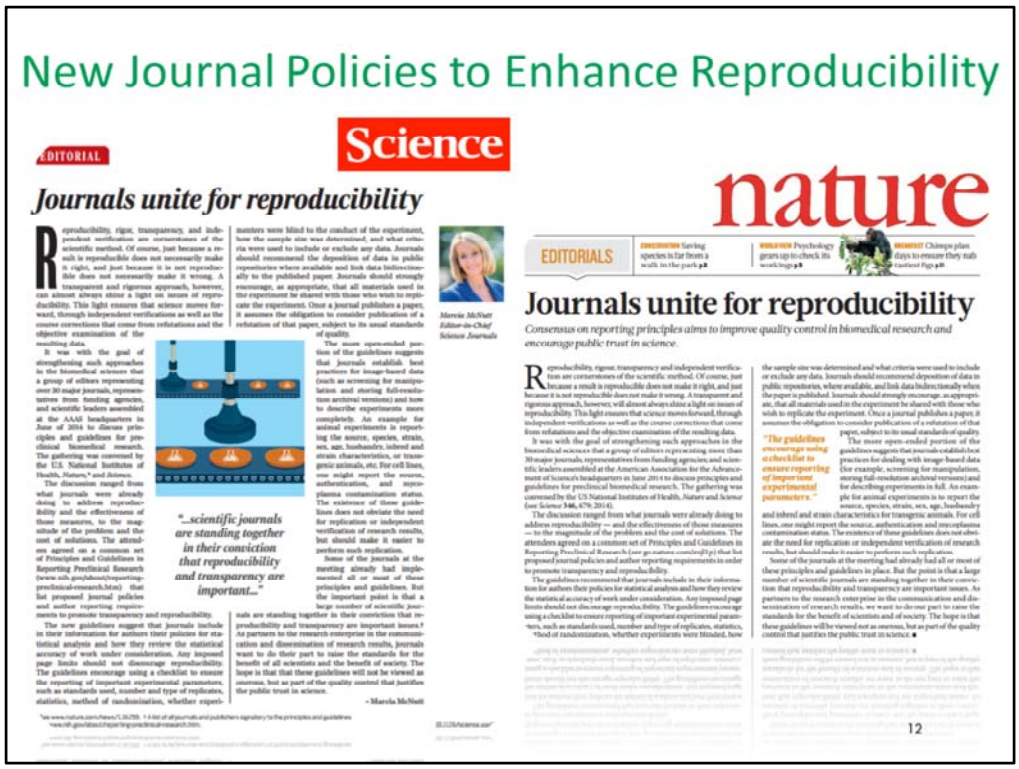
& **Lawrence A. Tabak**

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



Science

EDITORIAL

Journals unite for reproducibility

nature

EDITORIALS

Journals unite for reproducibility

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

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

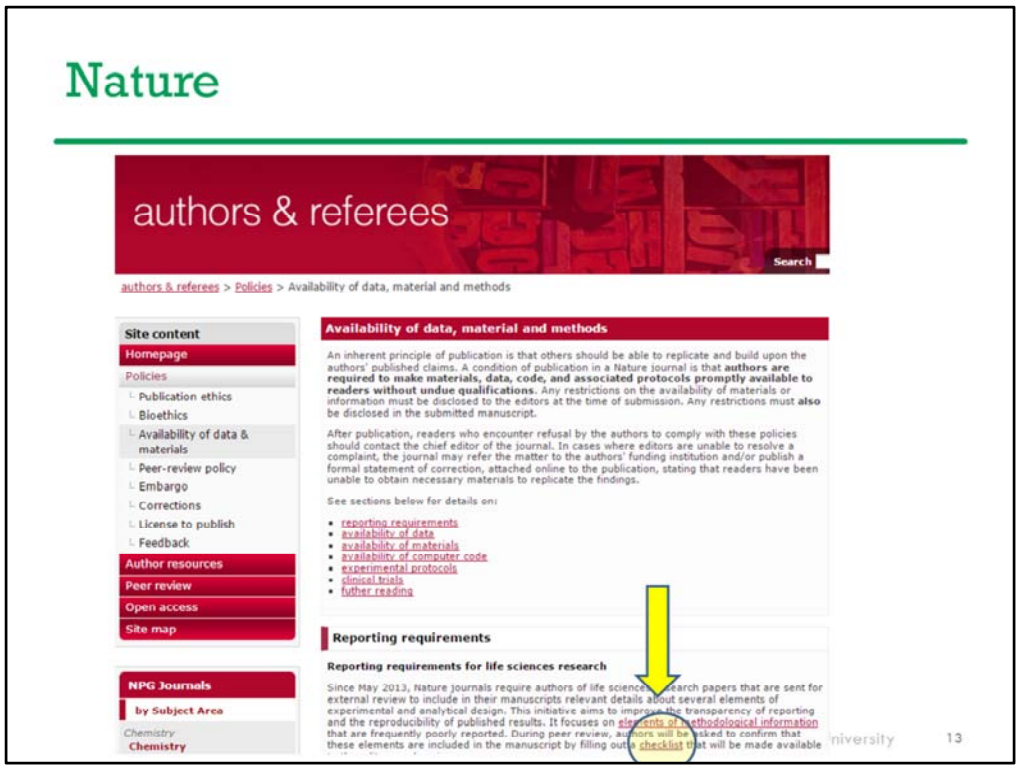
Science 7 November 2014

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 to facilitate these goals and over 135 journals have endorsed 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

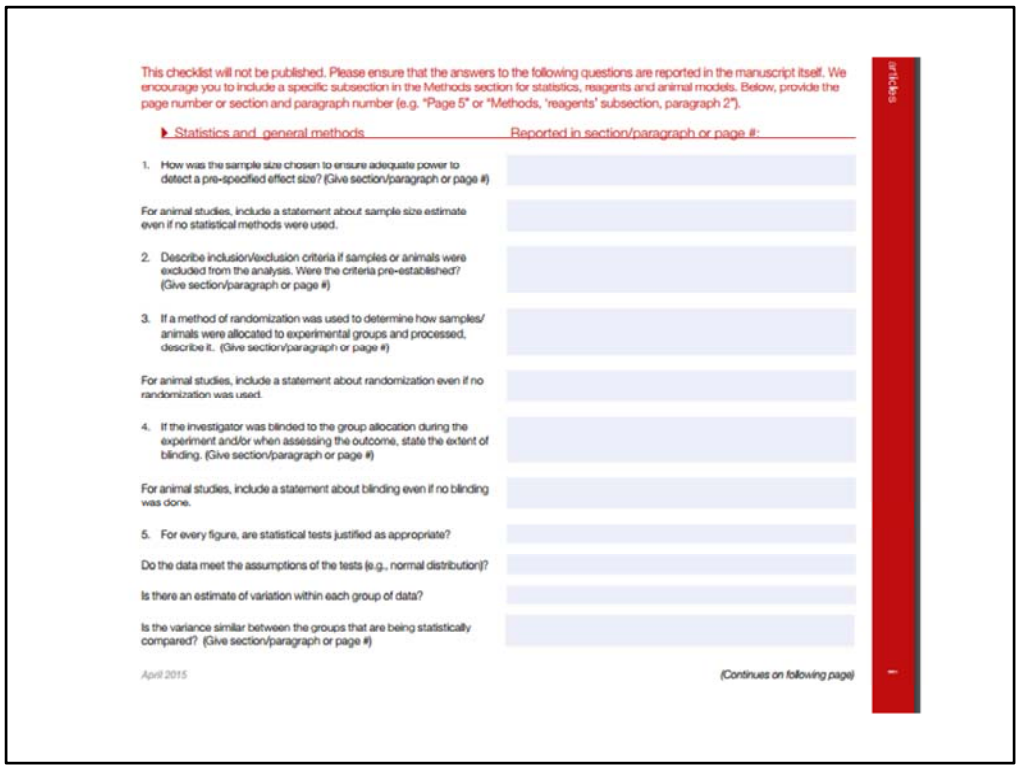


http://www.nature.com/authors/policies/availability.html

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



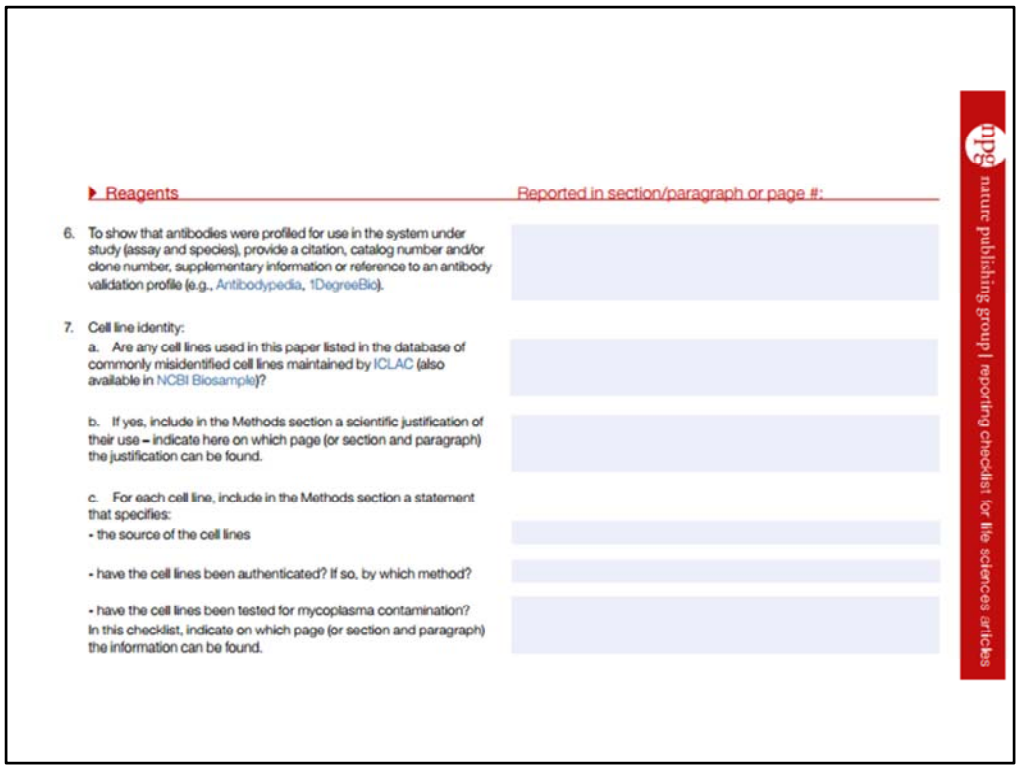
This checklist will not be published. Please ensure that the answers to the following questions are reported in the manuscript itself. We encourage you to include a specific subsection in the Methods section for statistics, reagents and animal models. Below, provide the page number or section and paragraph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

Statistics and general methods	Reported in section/paragraph or page #:
1. How was the sample size chosen to ensure adequate power to detect a pre-specified effect size? (Give section/paragraph or page #)	
For animal studies, include a statement about sample size estimate even if no statistical methods were used.	
2. Describe inclusion/exclusion criteria if samples or animals were excluded from the analysis. Were the criteria pre-established? (Give section/paragraph or page #)	
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 #)	
For animal studies, include a statement about randomization even if no randomization was used.	
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 #)	
For animal studies, include a statement about blinding even if no blinding was done.	
5. For every figure, are statistical tests justified as appropriate?	
Do the data meet the assumptions of the tests (e.g., normal distribution)?	
Is there an estimate of variation within each group of data?	
Is the variance similar between the groups that are being statistically compared? (Give section/paragraph or page #)	

April 2015

(Continues on following page)

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



▸ Reagents — Reported in section/paragraph or page #:

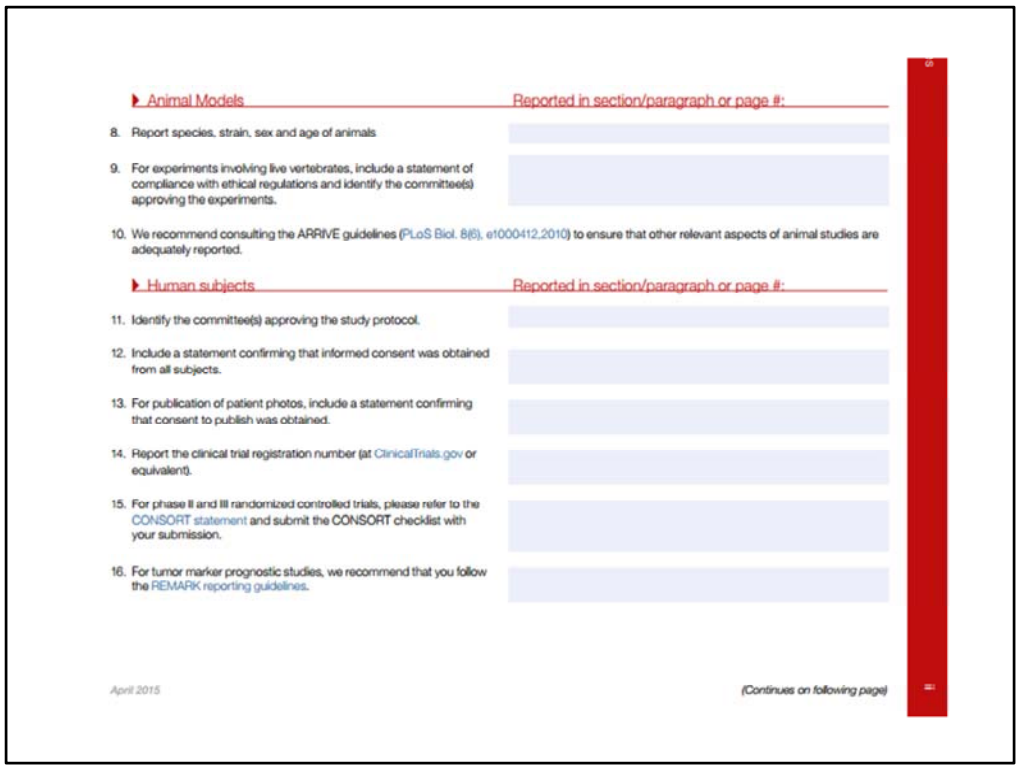
6. To show that antibodies were profiled for use in the system under study (assay and species), provide a citation, catalog number and/or clone number, supplementary information or reference to an antibody validation profile (e.g., Antibodypedia, 1DegreeBio).

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.

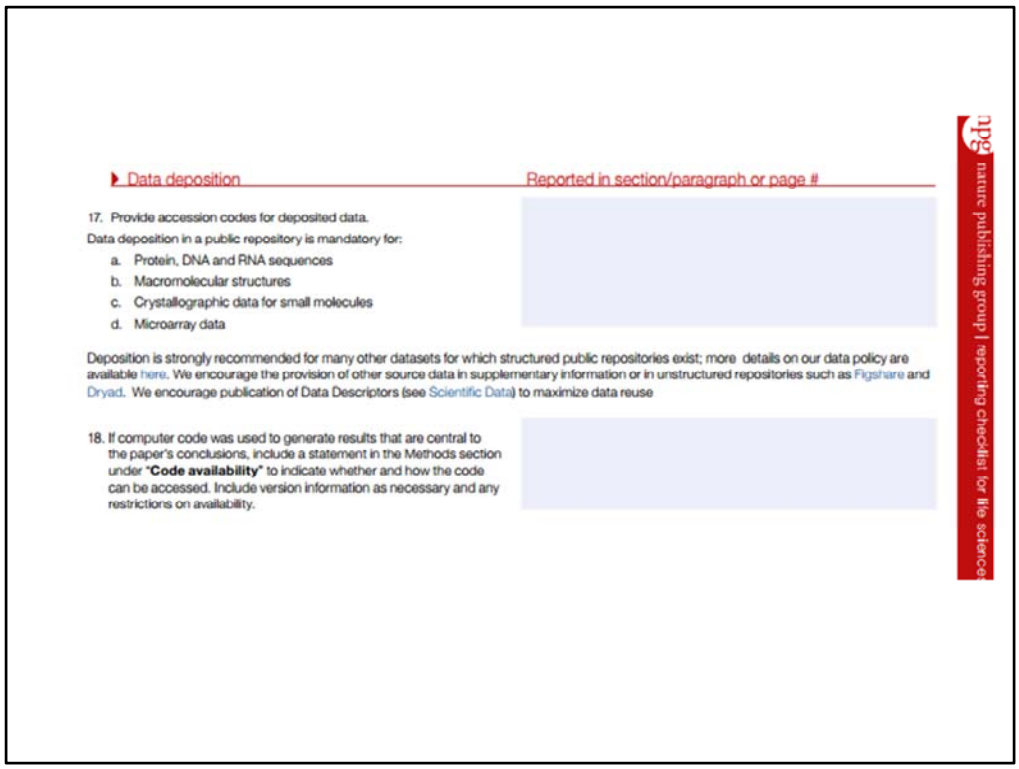
http://www.nature.com/authors/policies/checklist.pdf



Animal Models	Reported in section/paragraph or page #:
8. Report species, strain, sex and age of animals	
9. For experiments involving live vertebrates, include a statement of compliance with ethical regulations and identify the committee(s) approving the experiments.	
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.	

Human subjects	Reported in section/paragraph or page #:
11. Identify the committee(s) approving the study protocol.	
12. Include a statement confirming that informed consent was obtained from all subjects.	
13. For publication of patient photos, include a statement confirming that consent to publish was obtained.	
14. Report the clinical trial registration number (at ClinicalTrials.gov or equivalent).	
15. For phase II and III randomized controlled trials, please refer to the CONSORT statement and submit the CONSORT checklist with your submission.	
16. For tumor marker prognostic studies, we recommend that you follow the REMARK reporting guidelines.	

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



Data deposition | Reported in section/paragraph or page #

17. Provide accession codes for deposited data.

Data deposition in a public repository is mandatory for:

a. Protein, DNA and RNA sequences
b. Macromolecular structures
c. Crystallographic data for small molecules
d. Microarray data

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

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.

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

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- 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

NIH to balance sex in cell and animal studies

Fixing problems with cell lines

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

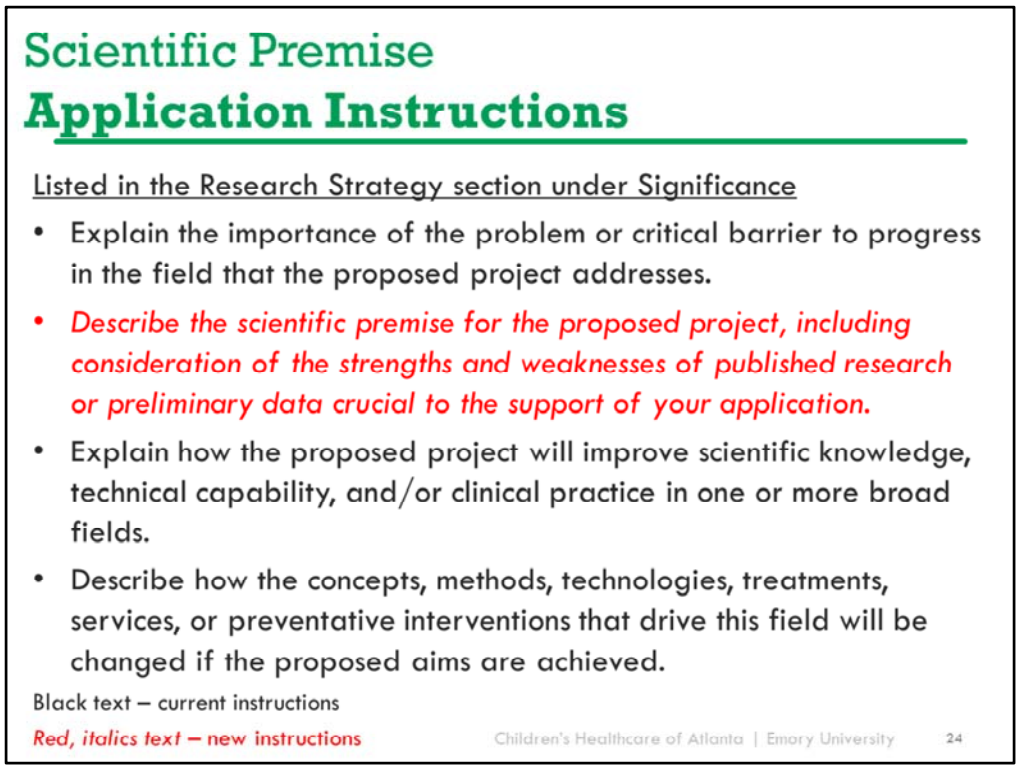
Mentored Career Development Award (K) Applications and Review

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

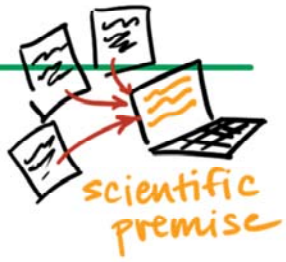
1) Scientific Premise
2) Scientific Rigor
3) Consideration of Relevant Biological Variables

4) Authentication of Biological/Chemical Resources

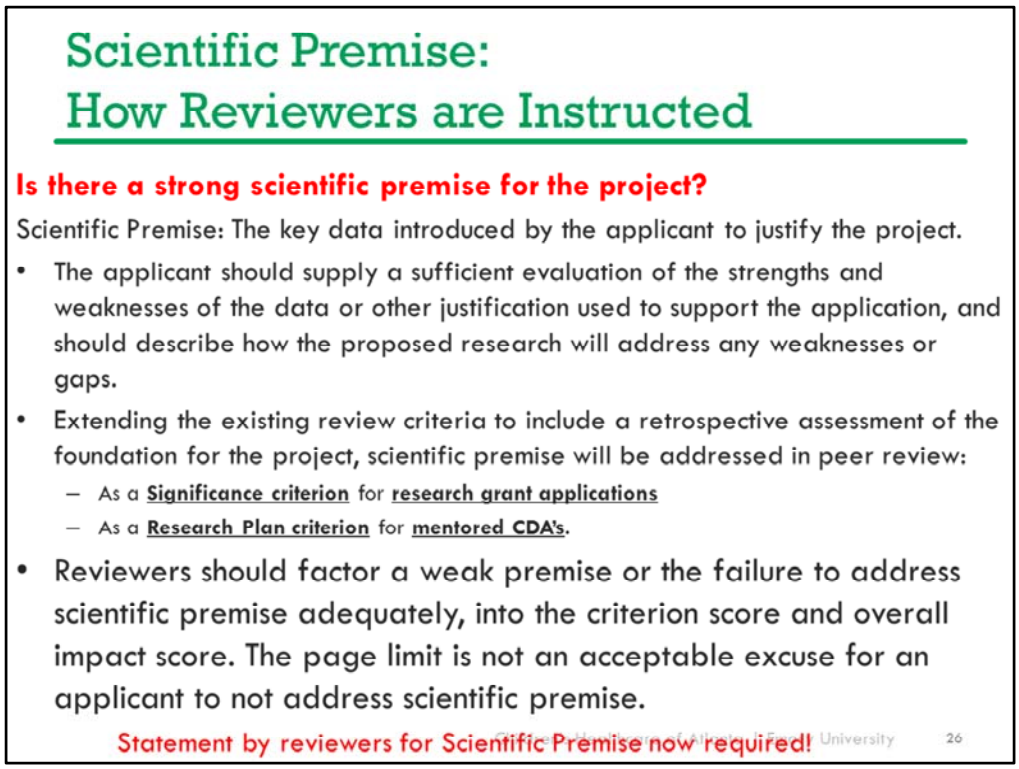


http://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/career-forms-d.pdf

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***



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

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

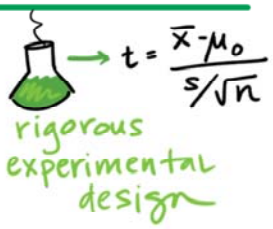
- Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. *Describe the experimental design and methods proposed and how they will achieve robust and unbiased results.* Unless addressed separately in the Resource Sharing Plan attachment below, 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

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

Fundamental Information on Vertebrate Animal Species

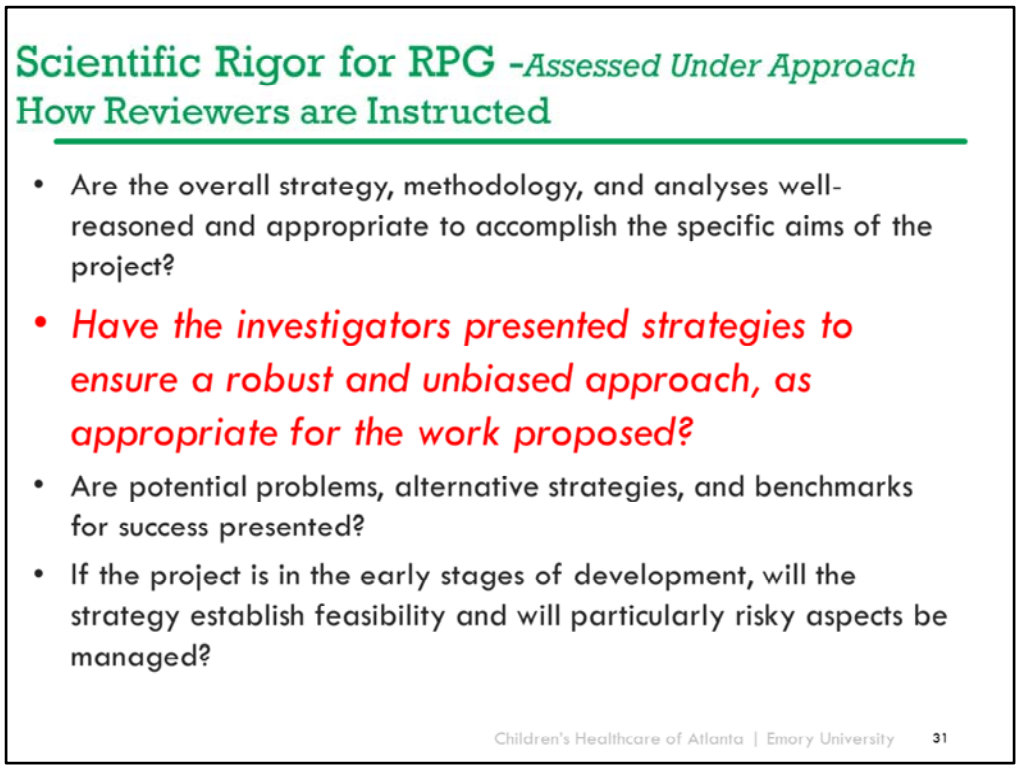
Fundamental Information on Human Subjects

Experimental Design

Minimizing Bias

Results

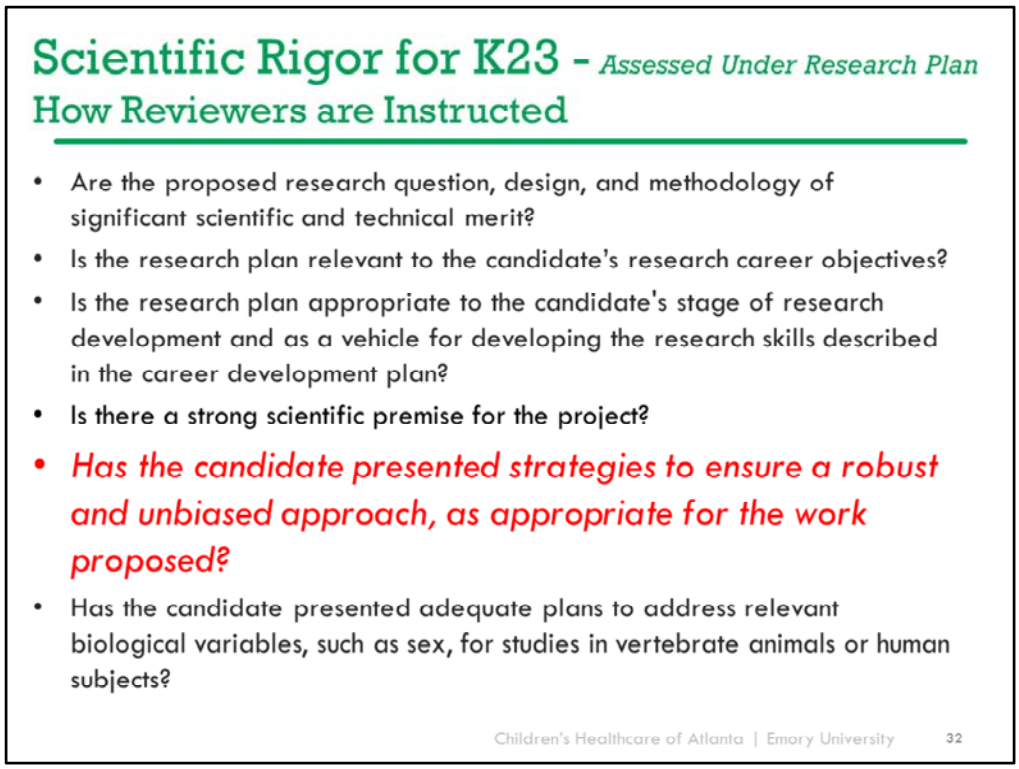
Interpretation of Results



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

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

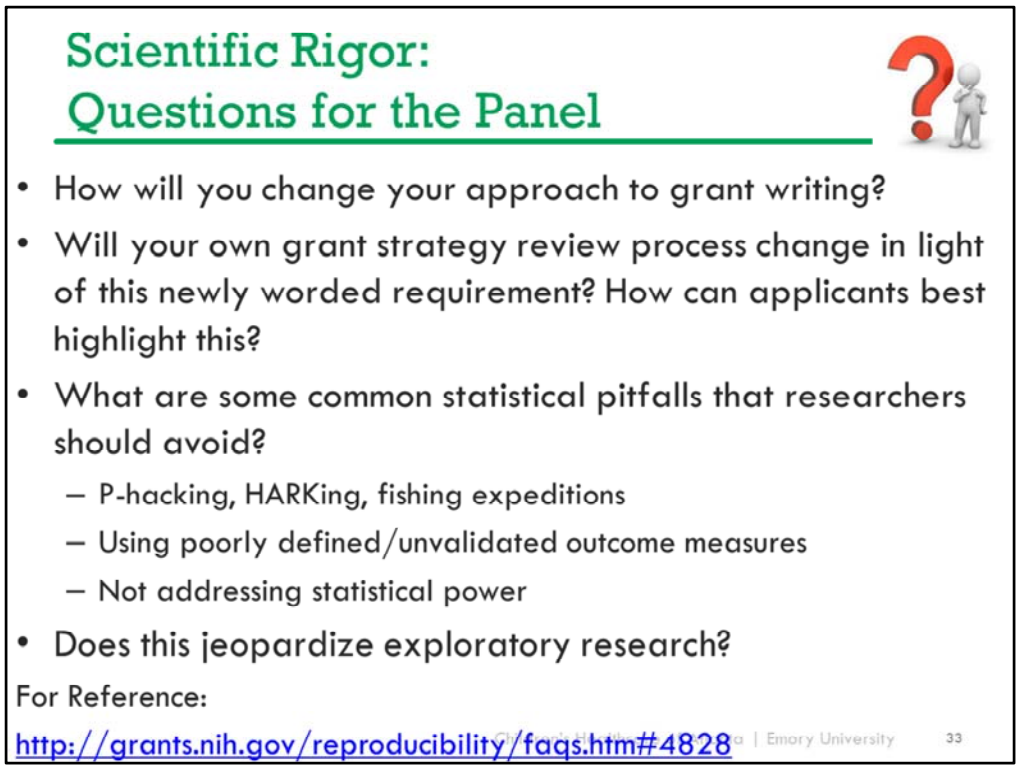
https://grants.nih.gov/grants/peer/guidelines_general/Reviewer_Guidance_on_Rigor_and_Transparency.pdf



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



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

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

HARKing - Hypothesis After the Results are Known

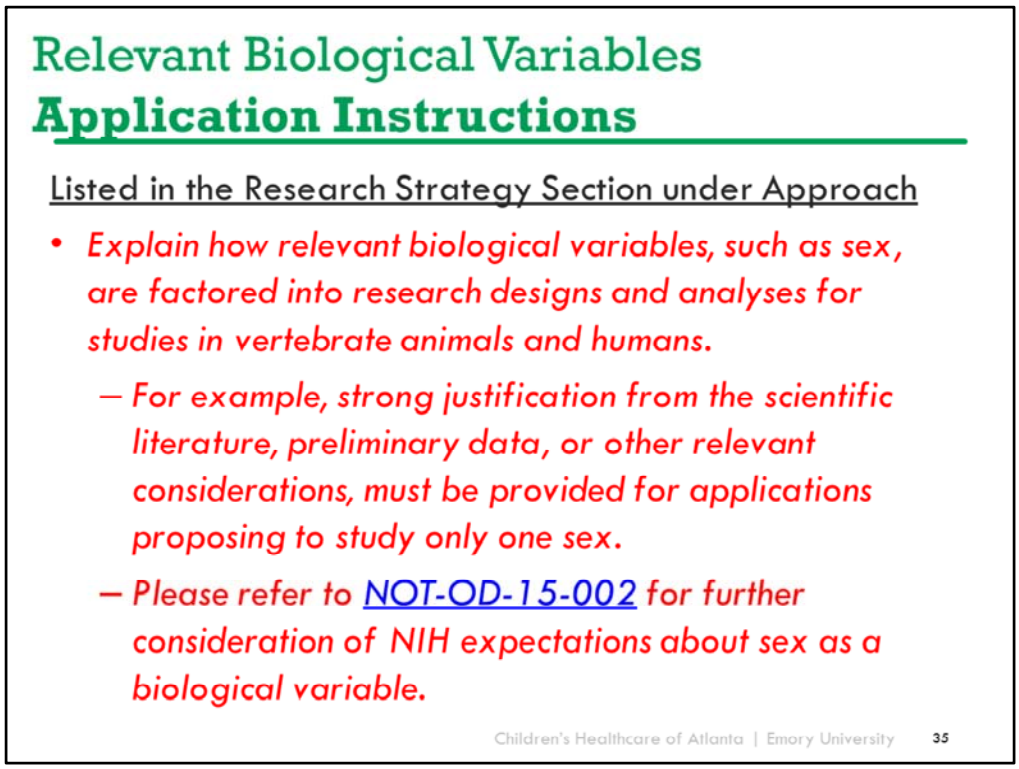
When researchers formulate or change their hypothesis after they have seen the results of their statistical analyses

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

The Four Focus Areas – one by one

1) Scientific Premise
2) Scientific Rigor
3) Consideration of Relevant Biological Variables

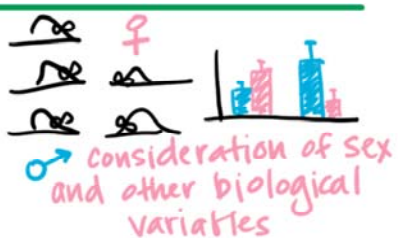
4) Authentication of Biological/Chemical Resources



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

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

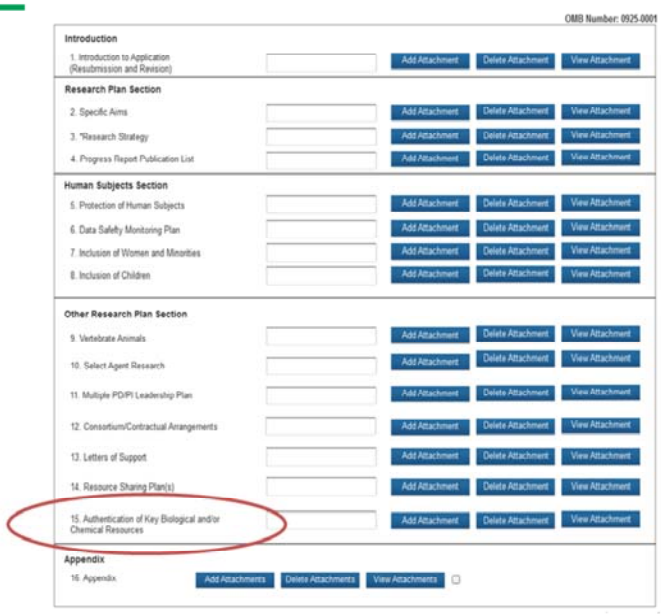
4) Authentication of Biological/Chemical Resources

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) — Add Attachment | Delete Attachment | View Attachment

Research Plan Section

2. Specific Aims — Add Attachment | Delete Attachment | View Attachment
3. *Research Strategy — Add Attachment | Delete Attachment | View Attachment
4. Progress Report Publication List — Add Attachment | Delete Attachment | View Attachment

Human Subjects Section

5. Protection of Human Subjects — Add Attachment | Delete Attachment | View Attachment
6. Data Safety Monitoring Plan — Add Attachment | Delete Attachment | View Attachment
7. Inclusion of Women and Minorities — Add Attachment | Delete Attachment | View Attachment
8. Inclusion of Children — Add Attachment | Delete Attachment | View Attachment

Other Research Plan Section

9. Vertebrate Animals — Add Attachment | Delete Attachment | View Attachment
10. Select Agent Research — Add Attachment | Delete Attachment | View Attachment
11. Multiple PD/PI Leadership Plan — Add Attachment | Delete Attachment | View Attachment
12. Consortium/Contractual Arrangements — Add Attachment | Delete Attachment | View Attachment
13. Letters of Support — Add Attachment | Delete Attachment | View Attachment
14. Resource Sharing Plan(s) — Add Attachment | Delete Attachment | View Attachment
15. Authentication of Key Biological and/or Chemical Resources — Add Attachment | Delete Attachment | View Attachment

Appendix

16. Appendix — Add Attachments | Delete Attachments | View Attachments

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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.**

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


A.BACALL
"There's a flaw in your experimental design.
All the mice are scorpios."

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:

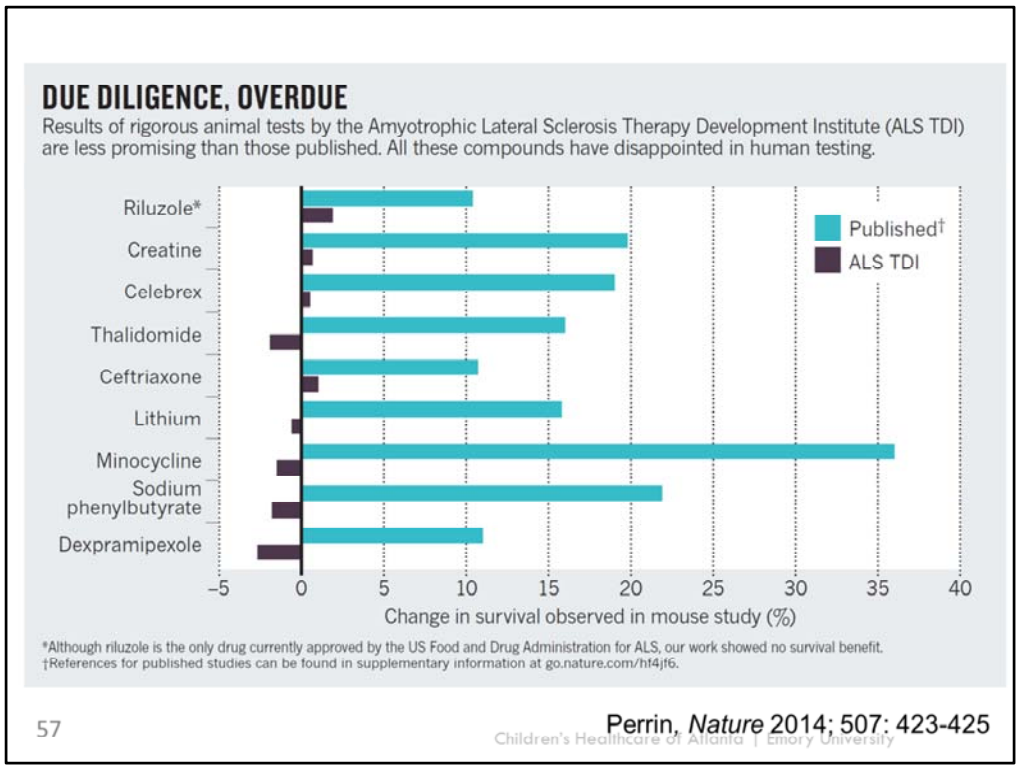
- http://grants.nih.gov/reproducibility/index.htm

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.