Improving preclinical research through rigorous study design and transparent reporting

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Beware the creeping cracks of bias

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

Evaluation of Excess Significance Bias in Animal Studies of Neurological Diseases

Raise standards for preclinical cancer research

Why animal research needs to improve

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

When Mice Mislead

Helping editors, peer reviewers and authors improve the clarity, completeness and transparency of reporting health research

Bringing rigour to translational medicine

Drug targets slip-sliding away

Unreliable research

Trouble at the lab

Translating animal research into clinical benefit

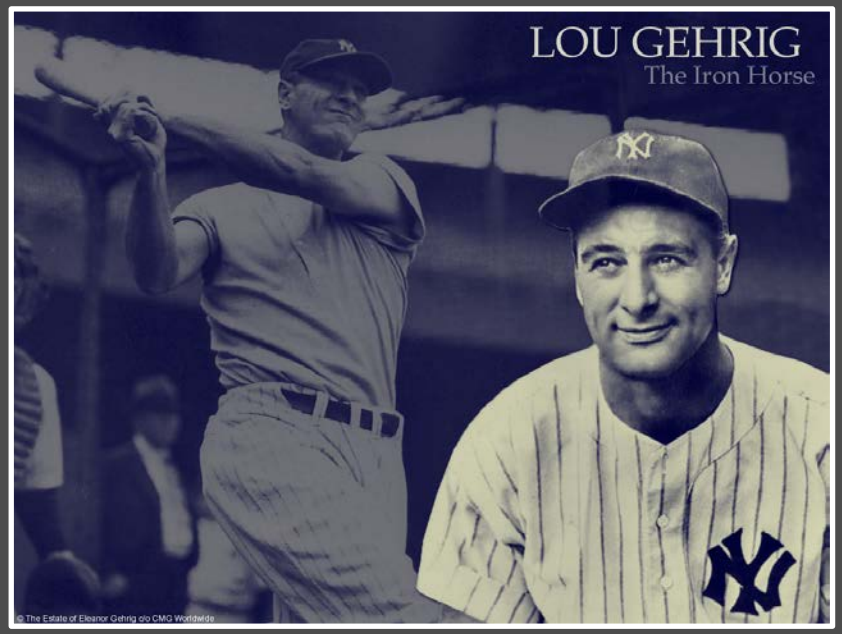
Amyotrophic lateral sclerosis (ALS)

- Death within 5 years of diagnosis
- Central pathological finding: motor neuron death
- Rodents over-expressing SOD1 gene recapitulate ALS

2002: Minocycline reported to extend survival of SOD1 mice

2003: Randomized placebo controlled trial (412 patients treated for 9 months)

2007: Results of the trial are published - minocycline found to have a harmful effect on patients with ALS



Design, power, and interpretation of studies in the standard murine model of ALS

ALS Therapy Development Institute (ALS TDI)

- Screened more than 70 drugs in 18000 mice across 221 studies
- Used rigorous and appropriate statistical methodologies
- No statistically significant effects for any of the drugs, including several previously reported as efficacious.

Scott *et al., Amyotroph Lateral Scler* 2008; 9: 4-15

How to improve reproducibility?

Lack of transparency in reporting	Review	Transparency in reporting
Lack of experimental rigor Unconscious bias	Education	Good experimental design Attentiveness to bias
Publication bias and Chance	Culture	Focus on rigor not glitter

Publish or perish!

Impact factor

Grant support

Novelty

Significance

Innovation

First action taken by NINDS: Notice in the NIH Guide

Improving the Quality of NINDS-Supported Preclinical and Clinical Research through Rigorous Study Design and Transparent Reporting

Notice Number: NOT-NS-11-023
Release Date: August 10, 2011
Issued by: National Institute of Neurological Disorders and Stroke (NINDS)

Purpose:

> …..NINDS believes that applications that propose preclinical research, or that are based on previous preclinical data, will be greatly strengthened if the design, execution, and interpretation of the proposed studies and supporting data are adequately described. NINDS encourages investigators, whenever possible, to address these elements directly in their applications.

Optimizing the Predictive Value of Preclinical Research

June 20 – 21, 2012
Washington Plaza Hotel
Washington DC

Editors

Funders

Investigators

Reviewers

Workshop Recommendations (examples)

- All relevant stakeholders share the responsibility of bringing about meaningful improvement in the quality of reporting.

- Grant applications and scientific publications which include *in vivo* animal experiments should, at a minimum, report on:
  - Randomization
  - Blinding
  - Sample size estimation
  - Handling of all data

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.

Landis, et al., *Nature* 2012; 490: 187-191

nature

ANNOUNCEMENT

Reducing our irreproducibility

"To ease the interpretation and improve the reliability of published results we will more systematically ensure that key methodological details are reported, and we will give more space to methods sections. We will examine statistics more closely and encourage authors to be transparent, for example by including their raw data."

nature structural & molecular biology

Raising standards

nature cell biology

Raising reporting standards

nature neuroscience

Raising standards

nature immunology

Raising standards

EDITORIAL NATURE MEDICINE

Raising standards

COMMENT

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.

A growing chorus of concern, from scientists and laypeople, contends that the complex system for ensuring the reproducibility of biomedical research is failing and is in need of restructuring[1,2]. As leaders of the US National Institutes of Health (NIH), we share this concern and here explore some of the significant interventions that we are planning.

Science has long been regarded as 'self-correcting', given that it is founded on the replication of prior work. Over the long term, that principle remains true. In the shorter term, h
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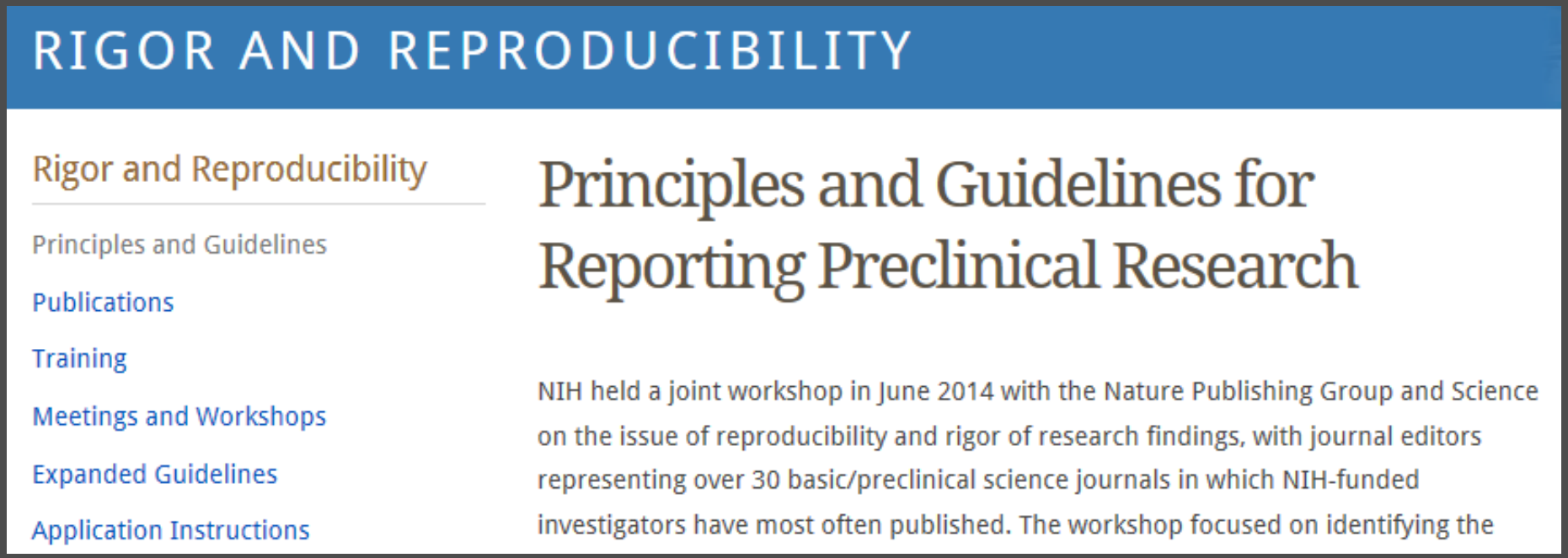
"Efforts by the NIH alone will not be sufficient to effect real change in this unhealthy environment."

Nature, Vol. 505, pp. 612-13, 30 January 2014

How will NIH increase rigor and transparency?

1. Raise community awareness.
2. Enhance formal training.
3. Improve the review and evaluation of grant applications.
4. Increase stability for investigators.

RIGOR AND REPRODUCIBILITY



- Rigorous statistical analysis
- Transparency in reporting
- Data and material sharing
- Consideration of refutations
- Consider establishing best practice guidelines

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

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Clearinghouse for Training Modules to Enhance Data Reproducibility

In January 2014, NIH launched a series of initiatives to enhance rigor and reproducibility in research. As a part of this initiative, NIGMS, along with nine other NIH institutes and centers, issued the funding opportunity announcement RFA-GM-15-006 to develop, pilot and disseminate training modules to enhance data reproducibility. Graduate students, postdoctoral fellows and early stage investigators are the primary audiences for these training modules.

For the benefit of the scientific community, we will be posting the products of these grants on this Web site as they become available in the future.

In addition, we are sharing here a series of four training modules developed by NIH. These modules focus on integral aspects of rigor and reproducibility in the research endeavor, such as bias, blinding and exclusion criteria. The modules are not meant to be comprehensive, but rather are intended as a foundation to build on and a way to stimulate conversations, which may be facilitated by the use of the accompanying discussion materials. Currently, the modules are being integrated into NIH intramural training activities.

NIH Rigor and Reproducibility Training Modules

Introduction to the Modules [PDF, 110KB]

Module 1: Lack of Transparency
In order to reproduce someone else's findings adequately, the experimental methods, rationale and other pertinent information must be accessible and understandable. This module highlights the need to include all relevant details in publications to ensure that other studies are able to build upon the research appropriately and accurately.
Lack of Transparency Discussion Material [PDF, 97.2KB]

Related Information

NIH Reproducibility Workshops on Modern Technologies: Potentials and Pitfalls
- Cell Biology
- Structural Biology

Google: NIGMS clearinghouse

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4. Increase funding stability for investigators.

New Biographical Sketch Format Required for NIH Grant Applications Submitted on or after May 25, 2015

- Increased page limit (5 pages).
- Researchers describe up to five of their most significant contributions to science, along with the background that framed their research.
- Investigators can outline the central findings of prior work and the influence of those findings on the investigator's field.

NOT-OD-15-032

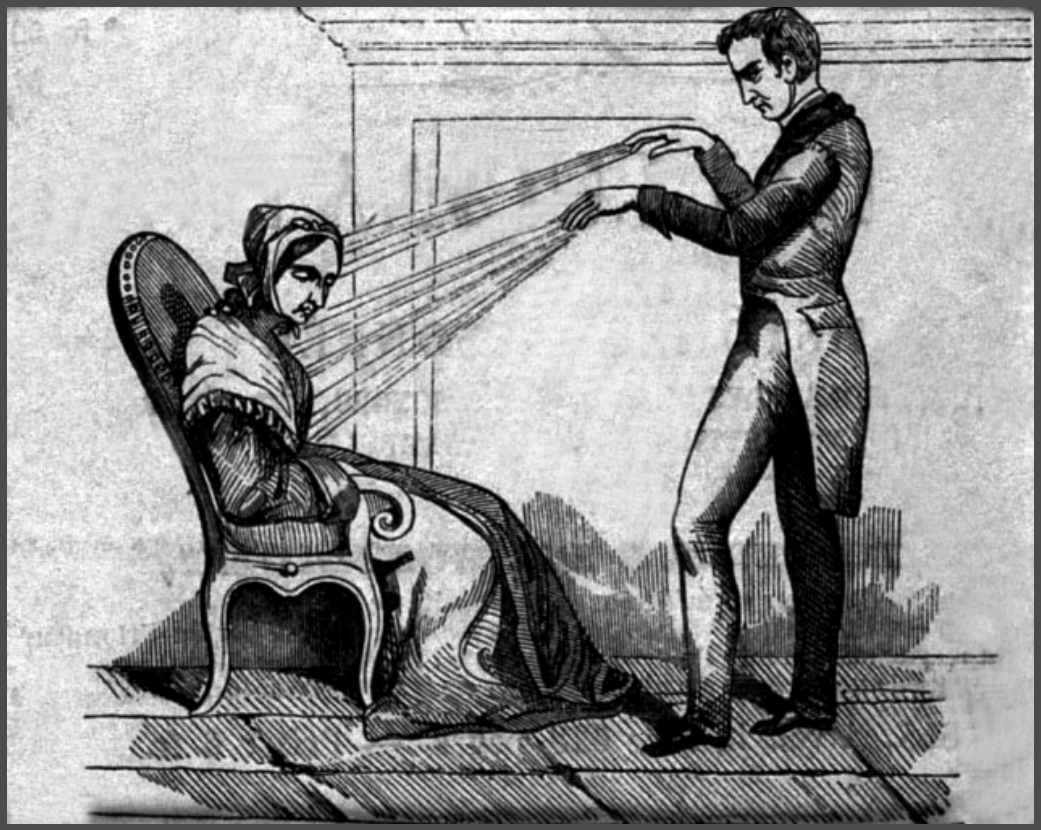
Applicants must also address…

NOT-OD-16-011

Rigorous Experimental Design

NIH expects applicants to describe how they will achieve robust and unbiased results when describing the experimental design and proposed methods.

Robust results are obtained using methods designed to avoid bias and can be reproduced under well-controlled and reported experimental conditions.



Animal Magnetism
Friedrich Anton Mesmer

“The investigators were blinded to the group allocation during the entire test. We randomized mice to control for potential age, gender and litter effects. The sample size was predetermined on the basis of our unpublished data and a recent report.”

“Using ImageJ, the area of the dorsal hippocampus was measured on each of the low-resolution images by an investigator who was blinded to treatment status.”

Scientific Premise of Proposed Research

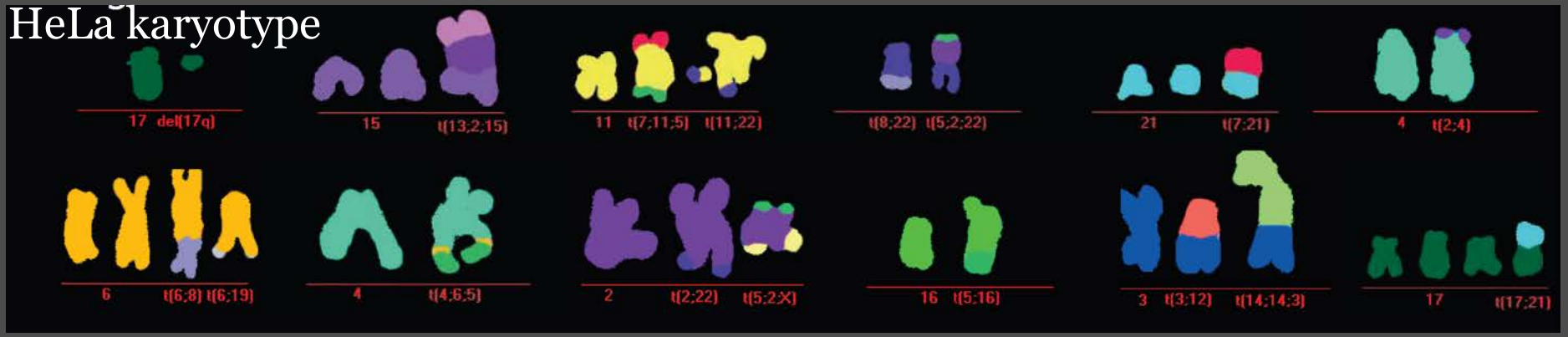
The scientific premise for an application is the research that is used to form the basis for the proposed research question.

NIH expects applicants to describe the general strengths and weaknesses of the prior research being cited by the investigator as crucial to support the application.

Authentication of Key Biological and/or Chemical Resources

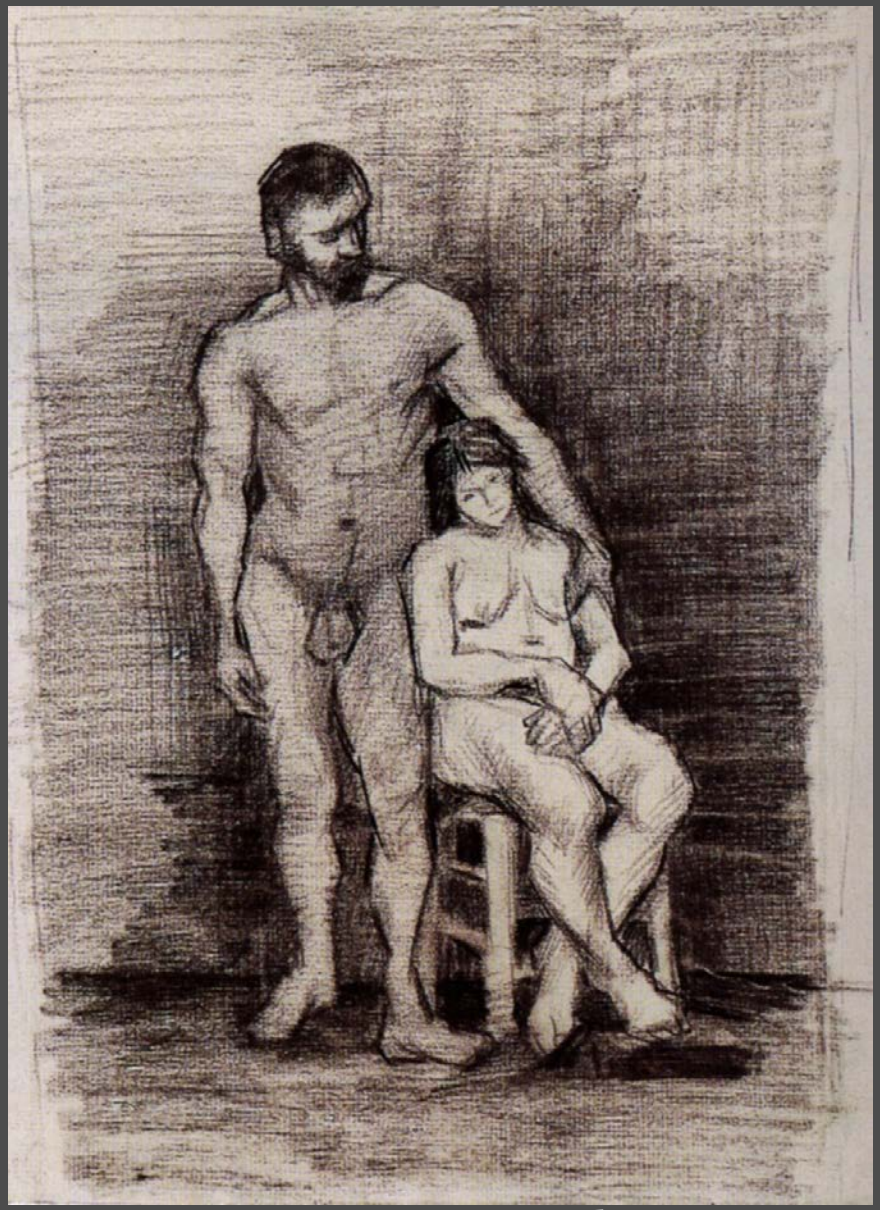
NIH expects that key biological and/or chemical resources will be regularly authenticated to ensure their identity and validity for use in the proposed studies.

Researchers should transparently report on what they have done to authenticate key resources, so that consensus can emerge.



Landry et al. *G3 (Bethesda)* 2013; 3: 1213-24

Consideration of Sex and Other Relevant Biological Variables



Vincent van Gogh

Research plans and findings should clearly indicate which biological variables are tested or controlled.

Clear justification should be provided for exclusion of variables that may be relevant but are not considered in the research plan.

Are the new NIH rigor criteria working?

- Various evaluations are ongoing and planned by the NIH Office of Extramural Research and the NINDS Director of Research Quality
- NINDS pilot study suggests that applicants/reviewers are paying more attention to rigor, but that…
  - The definition of Scientific Premise may need to be clarified
  - Applicant proposals for rigorous experimental design vary in quality – overcoming unconscious bias is often neglected

Questions?