The Growing Challenge

- Noted by research community; in multiple publications
- Across research areas
- Especially in preclinical research
A call for transparent reporting to optimize the predictive value of preclinical research

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.
December 7, 2012:
- Workshop held by NCI, in partnership with FDA and NIST
- Focused on:
  - “State of the science” in standardization of molecular diagnostics
  - Survey of what has been successful and what remains challenging
  - Presentations of real and mock submissions to the FDA
  - Discussions of future priorities
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, however, the checks and balances that once ensured scientific fidelity have been hobbled. This has compromised the ability of today’s researchers to reproduce others’ findings.

Let’s be clear: with rare exceptions, we have no evidence to suggest that irreproducibility is about scientific misconduct. In 2011, the Office of Research Integrity of the US Department of Health and Human Services pursued only 12 such cases\(^3\). Even if this represents only a fraction of the actual problem, such papers are vastly...
Challenges to Ensuring Rigor and Transparency in Reporting Science: Science and “Self-Correction”

- Science often viewed as “self-correcting”; immune from reproducibility problems
  - Principle remains true over the long-term
- Checks and balances for reproducibility in the short- and medium-term are hobbled by interrelated factors
  - Results in compromised ability to reproduce findings of others, particularly in preclinical research studies involving animal models of disease
DUE DILIGENCE, OVERDUE

Results of rigorous animal tests by the Amyotrophic Lateral Sclerosis Therapy Development Institute (ALS TDI) are less promising than those published. All these compounds have disappointed in human testing.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in survival observed in mouse study (%)</th>
</tr>
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<tbody>
<tr>
<td>Riluzole*</td>
<td></td>
</tr>
<tr>
<td>Creatine</td>
<td></td>
</tr>
<tr>
<td>Celebrex</td>
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<tr>
<td>Thalidomide</td>
<td></td>
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<tr>
<td>Ceftriaxone</td>
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<td>Minocycline</td>
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<td>Dexpramipexole</td>
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*Although riluzole is the only drug currently approved by the US Food and Drug Administration for ALS, our work showed no survival benefit.
†References for published studies can be found in supplementary information at go.nature.com/hf4jf6.
Challenges to Ensuring Rigor and Transparency in Reporting Science: Factors that “Short Circuit” Self-Correction

- Current “hyper-competitive” environment is fueled, in part, by:
  - historically low funding rates
  - over-dependence on “high profile” publications when grants are reviewed; institutions are making appointment, promotion, and tenure decisions

- Publication practices that contribute:
  - Difficulty in publishing negative findings
  - Overemphasis on the “exciting, big picture” finding sometimes results in publications leaving out necessary details of experiments
Challenges to Ensuring Rigor and Transparency in Reporting Science: Factors that “Short Circuit” Self-Correction (cont.)

- Poor training leading to:
  - Inadequate experimental design – fundamental quality characteristics not reported/performed (e.g. blinded assessment, randomization, sample size calculations)
  - Inappropriate use of statistics ("p-hacking")
  - Incomplete reporting of resources used and/or unexpected variability in resources
NIH Response
## Trans-NIH actions

### Implementation of pilots

<table>
<thead>
<tr>
<th>Pilot Focus</th>
<th>Approaches</th>
<th>Types of Efforts Being Developed</th>
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| Training    | • Develop materials for training module to enhance transparency and reproducibility of scientific reporting | • RFI of courses in experimental design  
• RFA GM-15-006 to develop training modules—Ten ICs to support up to 21 awards at $150K each  
• Video training tools  
• Intramural workshops speaking to pitfalls with cutting edge technologies |
Development of Training Materials

- NIGMS funding opportunity (multiple ICs have signed on) supporting the development of training modules to enhance reproducibility
  - **RFA-GM-15-006**: Closed on November 21\(^{st}\), 2014
  - 10 ICs, $3.1M, ~20 awards
- NIH training materials on experimental design, rigor, and reproducibility
  - Release of modules expected in early 2015; will be made publicly available
Exclusive Preview!

- Sample Size and Exclusion Criteria
Development of Training Materials

- IRP workshops on data interpretation considerations for various experimental techniques
  - First workshop held on November 24\(^{th}\), 2014, 5 sessions covering imaging, FRET, FACS, and cell-based models
- Future sessions:
  - Structural Biology: March 2015
  - Genomics: April/May 2015
## Trans-NIH actions

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• Intramural workshops speaking to pitfalls with cutting edge technologies                                                                                     |
| Enhance grant application review | • Reviewer checklists on standards/scientific rigor  
• Evaluation of scientific premise/grant applications  
• Support replication studies  
• Consider sex as a biological variable  
• Identification of cell lines                                                                                                                                         | • Study section pilots  
• New FOAs with additional review criteria regarding scientific premise  
• Pilot use of contract service; replication centers being contemplated  
• RFI                                                                                                                                                                   |
Scientific Rigor: Review Criteria

- **Significance:**
  - Is the scientific premise of the project grounded in evidence from rigorously designed studies?

- **Approach:**
  - Have the investigators presented adequate plans to ensure the scientific rigor of experimental design, methodology, analysis, and interpretation by including strategies to ensure a robust and unbiased approach and to address biological variables, such as sex, as appropriate for the work proposed?
NIH Takes Steps to Address Sex Differences in Preclinical Research

May 14, 2014

Over the past two decades, we have learned a great deal about how men and women respond differently to treatments. This knowledge came after a concerted effort in the NIH-funded clinical research participants are cell and animal research.

research. But over half of NIH-funded clinical trials have followed suit. An over-reliance on male subjects to the sex of cells, can lead to conclusions that do not generalize to women. NIH is taking action to address this shortfall as outlined by Janine A. Clayton, M.D., Director of the NIH Office of Research on Women’s Health, and me in the Nature Comment below.

Francis S. Collins, M.D., Ph.D.
Director, National Institutes of Health

Director’s Page

Filling the Gaps: NIH Enacts New Policies to Address Sex Differences

Posted May 14, 2014

Today in Nature, National Institutes of Health (NIH) Director Dr. Francis Collins and I announce that NIH will be requiring applicants to report their cell and animal experimental design. By developing this policy, we are promoting a balanced approach to addressing male and female differences in cells and animals—just as we did years ago with women and men in NIH-funded clinical trials.

Janine Austin Clayton, M.D.
NIH Office of Research on Women’s Health

Clayton JA, Collins FS.
Biological/Disease Impact of Experimental Design

The graph compares the disease impact in control and treatment groups for males and females aggregated. The disease impact is measured on a scale from 0 to 100, with the x-axis representing different categories: Aggregated, Male, Female. The bars in blue represent the control group, while the bars in yellow represent the treatment group. The graph shows a higher disease impact in the treatment group compared to the control group, with the female category showing the highest impact.
The effects of the selective poly-ADP ribose polymerase (PARP-1) inhibitor PJ-34 in wild-type (WT) mice of both genders. Treatment with PJ-34 at ischemic onset reduced total infarction in male mice compared with saline-treated controls (* $P<0.001$). A significant increase in ischemic damage was seen in PJ-34-treated females compared with control (* $P<0.001$).

Reproducibility in Cell Culture Studies

- >400 misidentified cell lines have been cataloged, dating back to the 1960s.
- ~70% of researchers surveyed in 2004 had never checked the identity of their cell lines.
- Major repositories report that 14-30% of cell lines submitted are contaminated.
- In a 2013 survey, <50% of cell lines had an unambiguous identifier and source in publications.
- NIGMS currently exploring options for standards for cell line authentication and methods for cell authentication.
Reproducibility in Cell Culture Studies

Possible action areas:

- Add a section to applications analogous to model organism sharing plans on plans for validation of key reagents, including cell lines
- Facilitate the development and dissemination of consensus standards for authentication, handling, controls, and reporting
- Promote development of more efficient and cost-effective tools for characterizing cell lines and reagents
- Promote development of defined, controllable and affordable cell culture media and reagents
## Trans-NIH actions

### Implementation of pilots (cont.)

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PubMed Commons

Today's scientists find it tough to keep up with all of the latest journal articles, innovative methods, and interesting projects of colleagues in their fields. That's understandable, because there are tens of thousands of journals, hundreds of conferences in major fields, dozens of emerging...
Conditional genome engineering in Toxoplasma gondii uncovers alternative invasion mechanisms

*Nature Methods* 2013
## Trans-NIH actions

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<td>Reduce &quot;perverse incentives&quot;</td>
<td>• Explore options with longer period of support</td>
<td>• NIH Pioneer Awards</td>
</tr>
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<td></td>
<td>• Change bio-sketch (coordinated by the Office of Extramural Research)</td>
<td>• NCI’s Outstanding Investigator Award</td>
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<td>• NIGMS’s Maximizing Investigators’ Research Award (in development)</td>
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Changes to the NIH Biosketch

- Pilot underway with OER coordinating efforts
- Roll-out of the modified biosketch for all grant applications received for FY 2016 funding and beyond (applications submitted in mid-2015)
- Also complements SciENcv, the federal-wide system that provides comprehensive CV information for applicants and reduces the administrative burden associated with grant applications
## Trans-NIH actions
Leveraging ongoing activities

<table>
<thead>
<tr>
<th>IC</th>
<th>Activity</th>
<th>Purpose</th>
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<tr>
<td>NIDDK</td>
<td>Mouse Metabolic Phenotyping Centers</td>
<td>Provides scientific community with high quality, standardized phenotyping services</td>
</tr>
<tr>
<td>NIAID</td>
<td>ImmPort and TrialShare</td>
<td>Provides access to clinical trials data</td>
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<tr>
<td>NIA</td>
<td>Interventions Testing Program Studies</td>
<td>Provides multi-site replication of preclinical studies</td>
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<tr>
<td>OD</td>
<td>BD2K initiatives in providing access to data</td>
<td>Will provide access to data sets including “negative findings”</td>
</tr>
<tr>
<td>NLM</td>
<td>Indexing and PubMed Commons</td>
<td>Links retractions, errata, and comments, discussions, and letters-to-the editor</td>
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Stakeholder Engagement

- Workshop in June 2014 with Journal Editors to identify common opportunity areas
  - Endorsement of consensus principles by more than 135 journals
Principles and Guidelines for Reporting Preclinical Research

The signatories represent Journals that publish preclinical biological research — an area of research that encompasses both exploratory studies and hypothesis-testing studies, with many different designs. The reproducibility of these studies is expected to vary. The Journals agree to adhere to the following principles with the aim of facilitating the interpretation and repetition of experiments as they have been conducted in the published study. These measures and principles do not obviate the need for replication and reproduction in subsequent investigations to establish the robustness of published results across multiple biological systems.

1. Rigorous statistical analysis
   A section outlining the Journal’s policies for statistical analysis should be included in the Information for Authors, and the journal should have a mechanism to check the statistical accuracy of submissions.

2. Transparency in reporting
   Journals should have enhanced methods sections (including encouraging efficient examination by review editors). Journal should use a checklist during editorial processing to ensure the review process adheres to the guidelines.

Background

NIH held a joint workshop in June 2014 with the Nature Publishing Group and Science on the issue of reproducibility and rigor of research findings, with Journal editors representing over 30 basic/preclinical science Journals in which NIH-funded investigations have most often published. The workshop focused on the common opportunities in the scientific publishing arena to enhance rigor and further support research that is reproducible, robust, and transparent.

The journal editors at that workshop came to consensus on a set of principles to facilitate these goals, which a number of journals have agreed to endorse. These principles and the journals that have agreed to endorse them are shown below.

Related Links

Endorsements - Principles and Guidelines for Reporting Preclinical Research

Landis, et al Paper on Transparency in Reporting of Preclinical Research

Workshop on Scientific Publishing and the Replicability of Preclinical Research

And more than 125 more!

www.nih.gov/about/reporting-preclinical-research.htm
Stakeholder Engagement

- Workshop in June 2014 with Journal Editors to identify common opportunity areas
  - Endorsement of consensus principles by more than 135 journals
- Workshop in July 2014 with PhRMA to identify areas of common interest with industry
  - PhRMA obtaining feedback from its Biomedical Advisory Committee (BMAC) and working with NIH to determine interest in further collaborations
- Obtaining input on barriers to reproducibility re: research reagents
  - Request for Information open until December 22, 2014
- Meetings with professional societies and institutions
Stakeholder Engagement

Meetings with/Presentations to (select list):

❖ Society for Neuroscience (SfN) – November 16th, 2014, led by NINDS, Francis Collins, Keynote Speaker

❖ National Health Medical Research Council – November 12th, 2014 (virtual presentation to Australia)

❖ Virginia Commonwealth University – September 22nd, 2014

❖ Life Sciences Subcommittee of Committee on Science – May 28th, 2014

❖ Clinical Research Forum and Association for Clinical and Translational Sciences (ACTS) – joint meeting in April 2014

❖ American Society for Pharmacology & Experimental Therapeutics (ASPET) – April 2014

❖ Coalition for the Life Sciences (CLS) – March 2014

❖ Health Research Alliance (HRA) – January 2014
Additional Guidelines and Efforts to Consider

• Reporting guidelines, such as Animal research: Reporting of In Vivo Experiments (ARRIVE), or Consolidated Standards of Reporting Trials (CONSORT)

• Broader coordination efforts related to reproducibility, such as Enhancing the QUAlity and Transparency Of health Research (EQUATOR)
Many thanks...

- Story Landis
- Shai Silberberg
- Harold Varmus
- Janine Clayton
- Jon Lorsch
- Eric Green
- Sally Rockey
- Michael Gottesman
- Della Hann
- Paul Liu
- Mike Rogers
- Jim Deatherage
- Judy Hewitt
- Bill Duval
- Liza Bundesen
- Tara Schwetz

Rashada Alexander