Scientific sea-change? Responding to the clarion calls for improved research rigor

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Seminar Series: Promoting and maintaining a culture of research accountability

CTSI Career Development Seminar
January 26, 2018
University of Minnesota Clinical and Translational Science Institute

Quality Central

Sharpening the focus on sound science and quality practices

I'm interested in:

1. **Institution- and scientist-driven responses to research reproducibility concerns.**
2. **Scientist efforts to drive, establish, and evaluate research best practices.**
3. **Developing strategies that can help us stand up for (and demonstrate) the quality of our work.**

Clarion call: a strongly expressed demand or request for action.

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

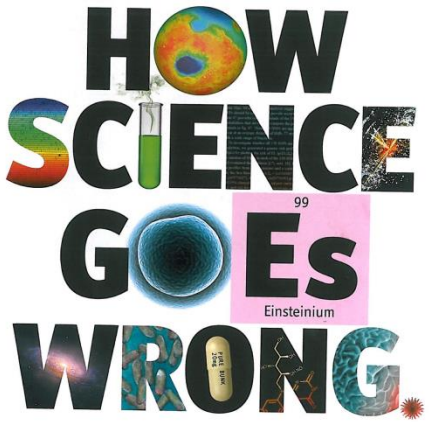
PloS Medicine 2005 doi: 10.1371/journal.pmed.0020124

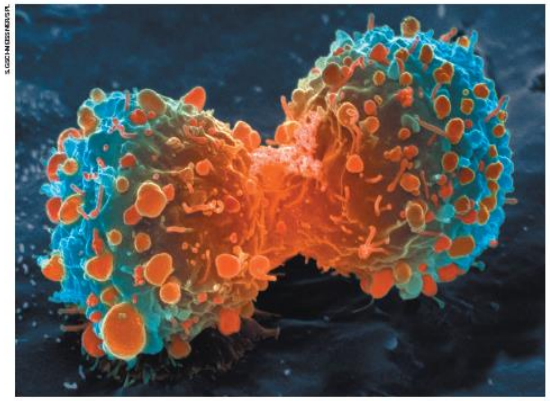
HEALTH

The Human Cost of a Misleading Drug-Safety Study

A reexamination of old data for Paxil found that the antidepressant is more dangerous than the authors let on. How much harm has been done in the 14 years since it was published?

David Dobbs, the Atlantic, 18 Sep 2015





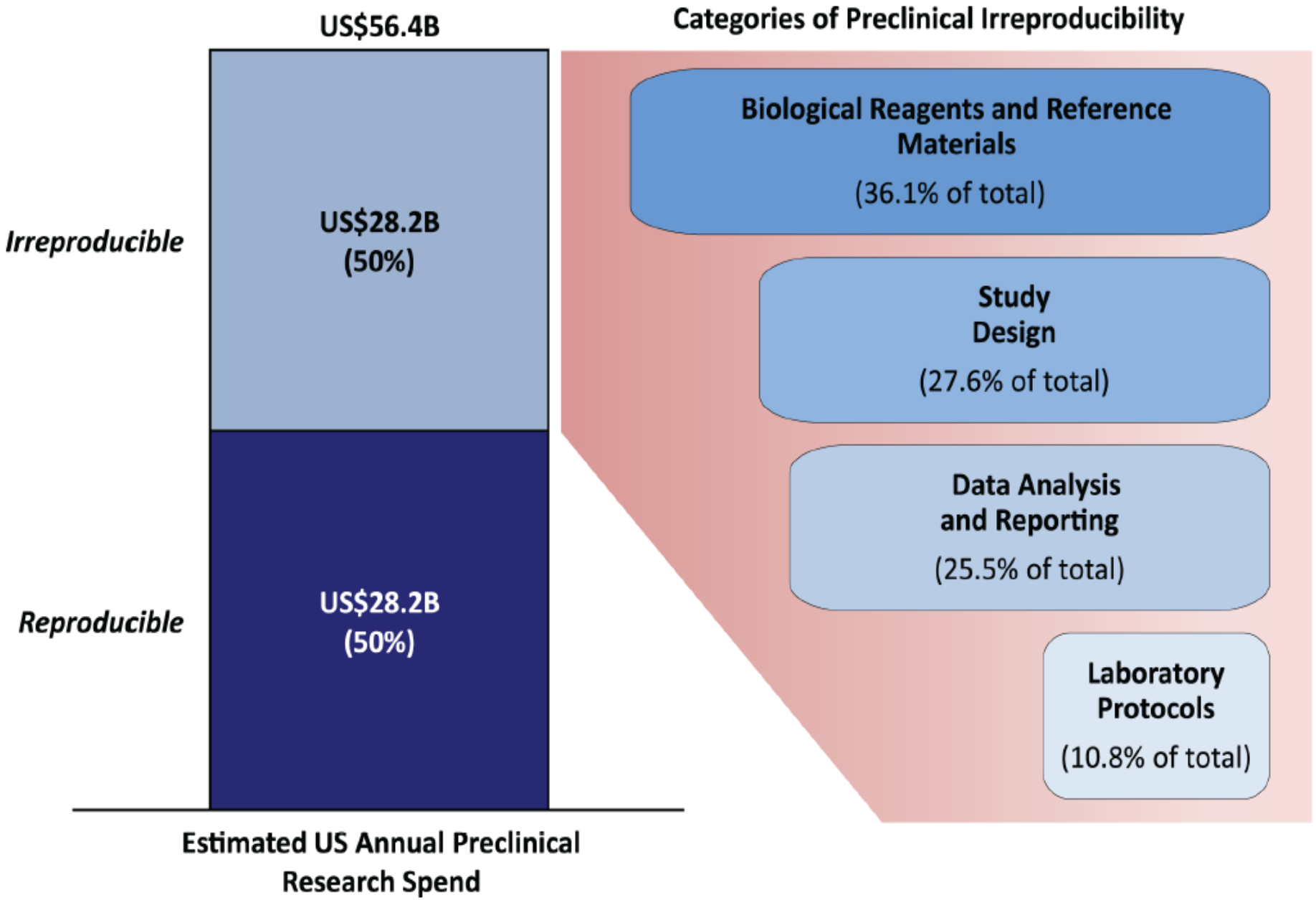
Many landmark findings in preclinical oncology research are not reproducible, in part because of inadequate cell lines and animal models.

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.

"Fifty-three papers were deemed 'landmark' studies. … Nevertheless, scientific findings were confirmed in only 6 (11%) cases."
Nature **483,** 531–533 (2012) doi:10.1038

Magnitude of the reproducibility crisis and key sources of irreproducibility



Freedman LP, et al: The Economics of Reproducibility in Preclinical Research. PLoS Biol. 2015; 13(6)

Clarion call: a strongly expressed demand or request for action.

Objectives for today:

Describe the strategies implemented by the first responders to the 'reproducibility crisis'

Describe the proposed Institution 'to do ' list for improving research reproducibility

Define strategies for the individual scientist to improve and demonstrate the quality of their research.

Research Accountability

Research Ecosystem and Stakeholders:

Funders
Researchers and Research Institutions
Journals
Industry
Nonprofits/Scientific Societies
Public

The expectations others have of us
The expectations we have for others

What is meant by research rigor?

"strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results" NIH

"theoretical or experimental approaches undertaken in a way that enhances confidence in the veracity of the findings."

Such approaches include redundancy in experimental design, sound statistical analysis, error recognition, avoidance of logical traps and intellectual honesty" Casadevall A. Rigorous Science: a How—To Guide. 8 Nov 2016 http://mbio.asm.org/content/7/6/e01902-16.full

"the use of unbiased and stringent methodologies to *analyze, interpret, and report experimental findings*" FASEB

Reproducibility2020: Progress and Priorities

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Keywords: reproducibility, preclinical research, study design, reagents and reference materials, protocol sharing, scientific publications

bioRxiv preprint first posted online Feb. 16, 2017; doi:http://dx.doi.org/10.1101/109017

Reproducibility affects our ecosystem

Stakeholder	Implications
Funders	• Impeded progress towards mission and goals • Wasted resources spent on funding follow-on research based on a flawed premise • Inefficient use of resources spent on checking, correcting, and refuting irreproducible work
Researchers & Research Institutions	• Adverse effect on reputation and career prospects • Difficulty in obtaining future funding • Failure of research projects that are based on irreproducible findings from the literature • Ethical concerns related to animal and human subject participation in inadequate studies
Journals	• Impact of irreproducibility could negatively affect reputation, readership and journal prestige • Increased administrative costs of managing retractions and errata
Industry	• Expensive failed clinical trials • Resources wasted on failed in-house results reproduction • Decreased trust in providers' products leading to decreased sales
Nonprofits Societies	• Unrealized opportunities to provide value to stakeholders and members in line with mission
Public	• Delayed realization or lost opportunities of health benefits based on preclinical research findings, negatively impacting the discovery of life-saving therapies and cures • Inefficient spending of taxpayers' money • Decline of public trust in science

Reproducibility2020: F1000Research 2017, 6:604

Proposed solutions to enhance reproducibility

Stakeholder	Actions to improve reproducibility in preclinical research
Funders	• Enact policies requiring study design pre-registration, cell line authentication and reagent validation, laboratory protocol transparency, and open access to publications. Provide relevant funding commitments where necessary • Include specific line items in grant review to score reproducibility factors • Provide resources for study design training , statistics and quality assurance consultation or support for grantees and grant applicants • Fund the development of open access and transparency tools, and additional research to better characterize reproducibility • Fund the development of new technologies and methods that enhance reproducibility • Encourage grantees to develop communities of practice for protocol sharing and testing, and dedicate resources to facilitate and incentivize these communities • Fund innovative training programs including online modules • Strengthen peer review

NEW GRANT GUIDELINES

what you need to know

WHY UPDATE THE GUIDELINES?

The updates focus on four areas deemed important for enhancing rigor and transparency:

1. **PREMISE** — The scientific premise forming the basis of the proposed research
2. **DESIGN** — Rigorous experimental design for robust and unbiased results
3. **VARIABLES** — Consideration of relevant biological variables
4. **AUTHENTICATION** — Authentication of key biological and/or chemical resources

Send inquiries to reproducibility@nih.gov

See also NIH Notice NOT-OD-16-011
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-011.html

WHAT ARE THE UPDATES?

1 UPDATES TO RESEARCH STRATEGY GUIDANCE

The research strategy is where you discuss the significance, innovation, and approach of your research plan. Let's look at an R01, for example:

The new **research strategy** guidelines require that you:

- State the strengths and weakness of published research or preliminary data crucial to the support of your application
- Describe how your experimental design and methods will achieve robust and unbiased results
- Explain how biological variables, such as sex, are factored into research design and provide justification if only one sex is used

2 NEW ATTACHMENT FOR AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES

From now on, you must briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.

These include, but are not limited to:

CELL LINES ↔ SPECIALTY CHEMICALS

ANTIBODIES ↔ 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.

- ☒ **DO NOT** put experimental methods or preliminary data in this section
- ☑ **DO** focus on authentication and validation of key resources

3 NEW REVIEWER GUIDELINES

Here are the additional criteria the reviewers will be asked to use:

- Is there a **strong scientific premise** for the project?
- Have the investigators presented adequate plans to address **relevant biological variables**, such as sex, for studies in vertebrate animals or human subjects?
- Have the investigators presented strategies to ensure a **robust and unbiased approach**, as appropriate for the work proposed?

Reviewers will also be asked to comment on that new attachment (see Update 2)!

Rigor and Reproducibility in NIH Applications: Resource Chart

NIH Grants Policy Website: http://grants.nih.gov/reproducibility/index.htm

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

AREA OF FOCUS	WHAT DOES IT MEAN?	WHERE SHOULD IT BE INCLUDED IN THE APPLICATION?
Scientific Premise	The **scientific premise** for an application is the research that is used to form the basis for the proposed research question(s). Describe the general strengths and weaknesses of the prior research being cited as crucial to support the application. Consider discussing the rigor of previous experimental designs, as well as the incorporation of relevant biological variables and authentication of key resources. *See related FAQs, blog post	Research Strategy ➢ Significance
Scientific Rigor (Design)	**Scientific rigor** is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. Emphasize how the experimental design and methods proposed will achieve robust and unbiased results. *See related FAQs, blog post, examples from pilots	Research Strategy ➢ Approach
Biological Variables	**Biological variables**, such as sex, age, weight, and underlying health conditions, are often critical factors affecting health or disease. In particular, sex is a biological variable that is frequently ignored in animal study designs and analyses, leading to an incomplete understanding of potential sex-based differences in basic biological function, disease processes and treatment response. Explain how relevant biological variables, such as the ones noted above, are 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. *See related FAQs, blog posts, article	Research Strategy ➢ Approach
Authentication	**Key biological and/or chemical resources** include, but are not limited to, cell lines, specialty chemicals, antibodies and other biologics. Briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies. These resources may or may not be generated with NIH funds and: • may differ from laboratory to laboratory or over time; • may have qualities and/or qualifications that could influence the research data; • are integral to the proposed research. The authentication plan should state in one page or less how you will authenticate key resources, including the frequency, as needed for your research. Note: Do not include authentication data in your plan. *See related FAQs, blog post	Other Research Plan Section ➢ Include as an attachment ➢ Do not include in the Research Strategy.

****This chart is based on general instructions for research grant and mentored career development applications. It should only be used as a guide. For all applications, please read the applicable Funding Opportunity Announcement (FOA) & Application Guide for specific instructions.**

NIH: Your One Page Guide to Rigor and Reproducibility

Stakeholder	Actions to improve reproducibility in preclinical research
Journals	• Adopt more stringent reporting and transparency guidelines • Provide cost-effective open access publication options • Require cell line authentication and promote antibody validation guidelines, as they become available. • Allow archiving of submitted manuscripts before publication • Publish reproduction studies and negative results • Consider pre-registered review models that enable rigorous peer review of study design Encourage greater use of pre-print platforms • Work with researchers to establish data and metadata standards for reporting (e.g., next-generation sequencing) • Require authors to link to version-controlled protocols • Conduct surveys of researchers to better understand reproducibility issues and obtain feedback on journal guidelines and policies • Report on reproducibility issues

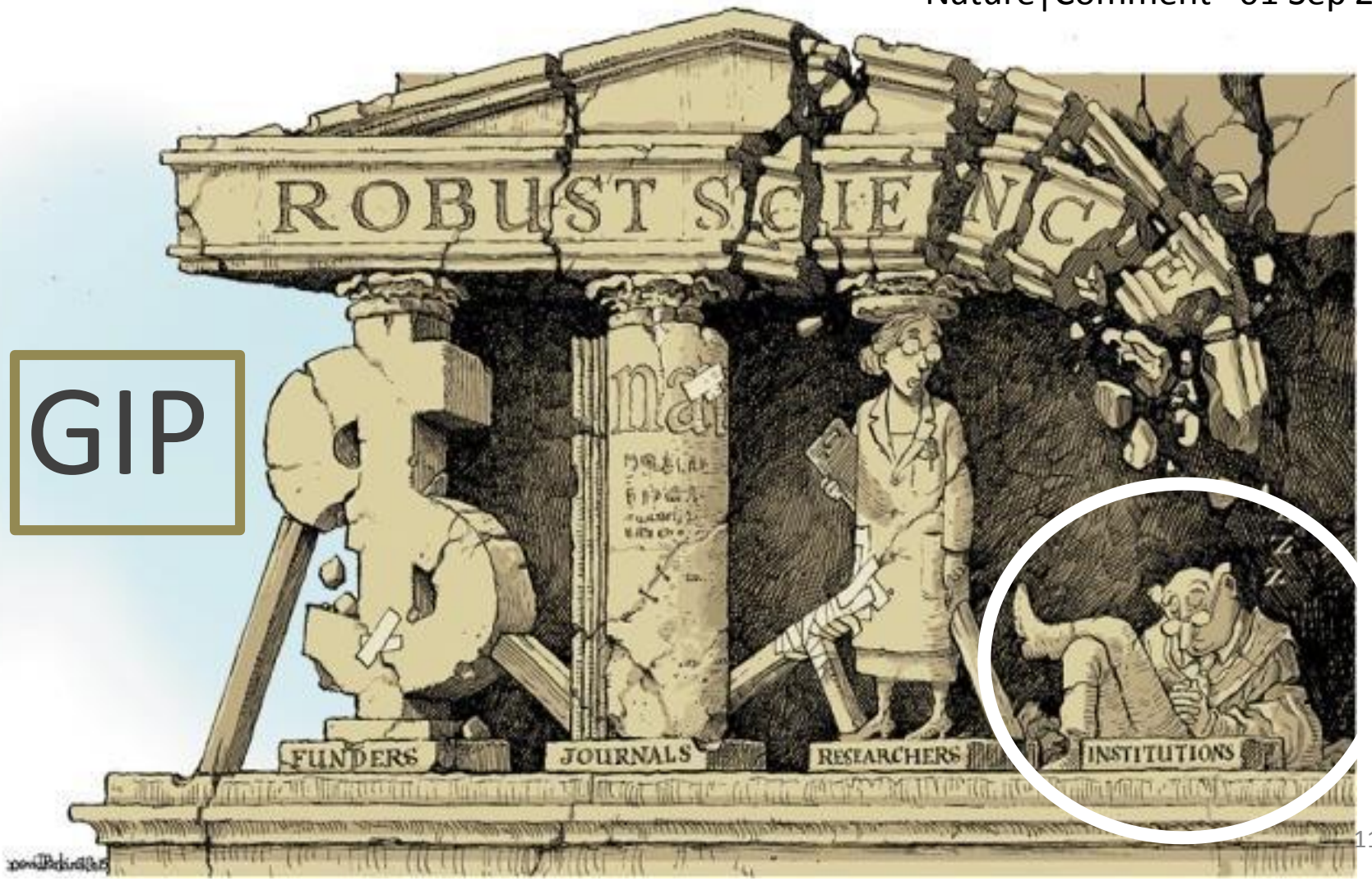
Stakeholder	Actions to improve reproducibility in preclinical research
Industry	• Transparently communicate the results of in-house replication attempts • Enhance protocol transparency, discussion, and version control, especially for reagents and kits • Provide validation data and technical support for reagents and kits • Participate in the establishment of materials standards Nonprofits/Scientific Societies
Nonprofits/ Societies	• Convene multidisciplinary groups to establish relevant standards, including materials standards for commonly used reagents, and data standards for commonly-used experimental methods • Provide professional development for researchers to improve research proficiencies, particularly in the areas of as study design, data analysis, reagent validation, and reporting transparency • Convene meetings focused on reproducibility to facilitate sharing of best practices and develop new policies and procedure

Describe the proposed Institution ‘to do’ list for improving research reproducibility

Robust research: Institutions must do their part for reproducibility

C. Glenn Begley, Alastair M. Buchan & Ulrich Dirnagl

Nature|Comment 01 Sep 2015



GIP

GIP

- Use of established standards
- Routine discussion and critique of research methods
- Incident, error, occurrence flagging, reviewing
- Training and standards
- Records and Quality Management
- Appropriate incentive and evaluation systems
- Enforcement
- Monitoring
- Audit

"We propose that research institutions that receive public funding should apply the same kind of oversight and support to ensure research integrity as is routinely applied for animal husbandry, biosafety and clinical work."

Stakeholder	Actions to improve reproducibility in preclinical research
Institutions	• Participate in multi-stakeholder groups that develop reproducibility policies and guidelines • Develop institutional policies and an organizational culture that values and rewards reproduction studies, study design pre-registration, protocol sharing, and open access • Explore new approaches to mentorship and accountability to ensure that emerging researchers (i.e., graduate students and postdocs) receive necessary training and supervision from experienced Pis • Explicitly consider reproducibility issues during peer review of grants and manuscripts • Make online accessible training modules available that address all major components and evolving approaches of the research process

Stakeholder	Actions to improve reproducibility in preclinical research
Institutions	• Develop programs to teach good experimental practices to ensure a baseline background for all trainees, and to provide continuing education in newest techniques and guidelines. •Explore central support of systematic research rigor initiatives (e.g. quality management systems) to ensure consistency across programs [including core laboratories]. • Explore new incentive structures for career advancement that move away from the traditional impact factor and funding paradigms to reward greater data and methods transparency, adherence to best practices and standards, and reproducibility of published work • Explore ways of including research accountability discussions and expectations in recruitment procedures. • Facilitate data sharing, curating, resource sharing

Sea change


Use of established standards
Routine discussion and critique of research methods
Incident, error, occurrence flagging, reviewing
Training and standards
Records and Quality Management
Appropriate incentive and evaluation systems
Enforcement
Monitoring
Audit

Institutional Research Accountability Initiatives

***Stanford University Metrics Program**

***[Research on Research]**

EU call for IMI (Innovative medicines initiative) Projects: Data quality in preclinical research and development

The Berlin Institute of Health Center for Transforming Biomedical Research

QUEST – Quality | Ethics | Open Science | Translation

Research Rigor and Reproducibility Workshops and Symposia, Webinars, Training Programs

Strategies for the individual scientist to improve and demonstrate the quality of their research.

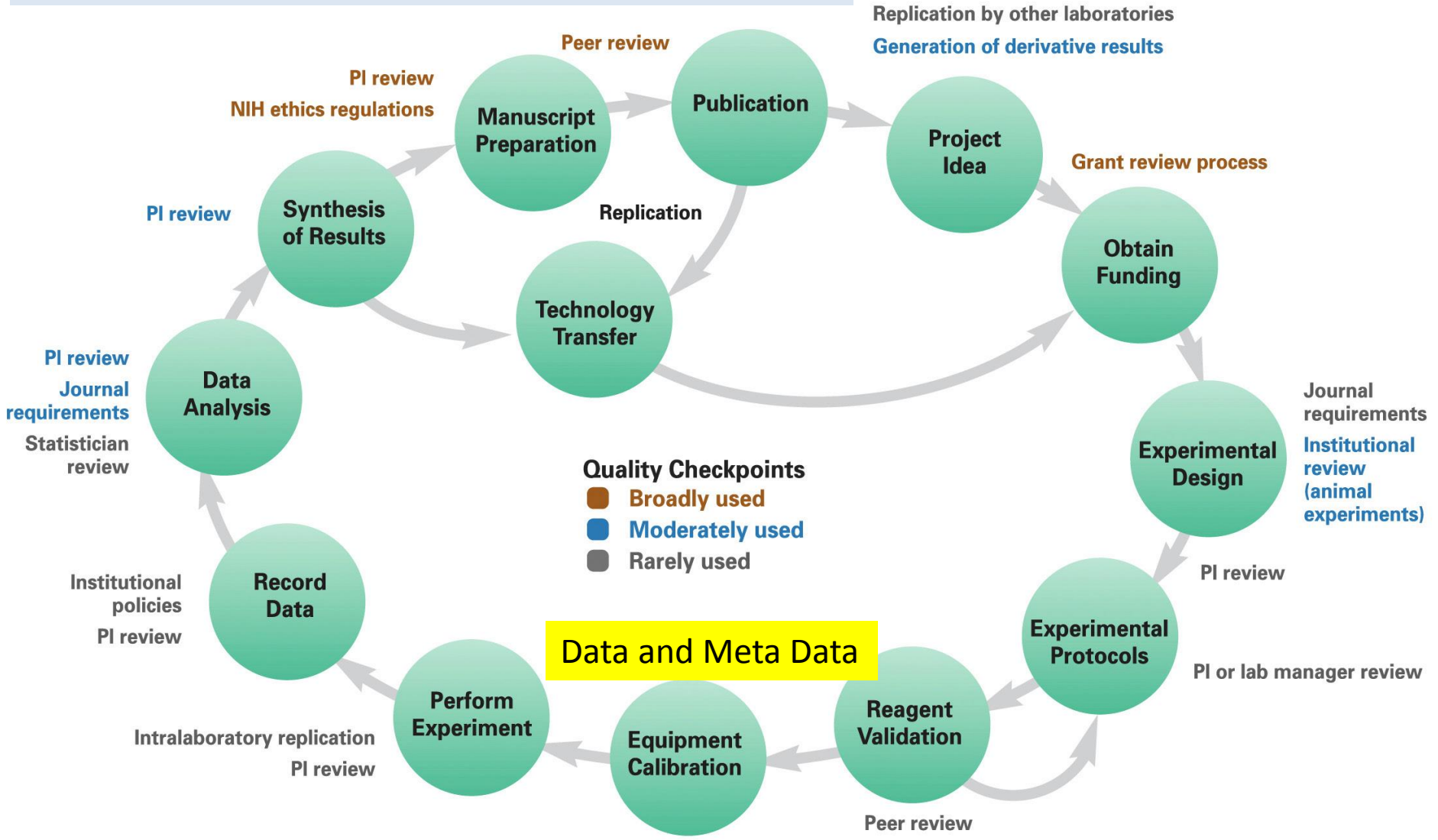
Reduce uncertainty

Two aspects of quality in research

Sound Scientific Principles

Good Quality Practices: management, execution and documentation

Research Life Cycle: Quality Check Points



Green circles indicate common steps in the life science research process. Adjacent color-coded text describes current/traditional quality checkpoints.

Stakeholder	Actions to improve reproducibility in preclinical research
Scientists	• Implement lab policies that improve reproducibility, such as reagent validation and documentation, routine cell line authentication, and independent reproduction of results by another researcher in the lab • Establish strong research, project and data management procedures throughout the research life cycle across all projects • Organize online communities of practice to facilitate discussion and sharing of information within the field • Implement research quality management systems or best practices to ensure consistency and continuous improvement in research processes. • Establish and monitor quality check-points throughout the research life cycle • Use the appropriate standards and guidelines to conduct your work • Define and communicate your commitment to research rigor

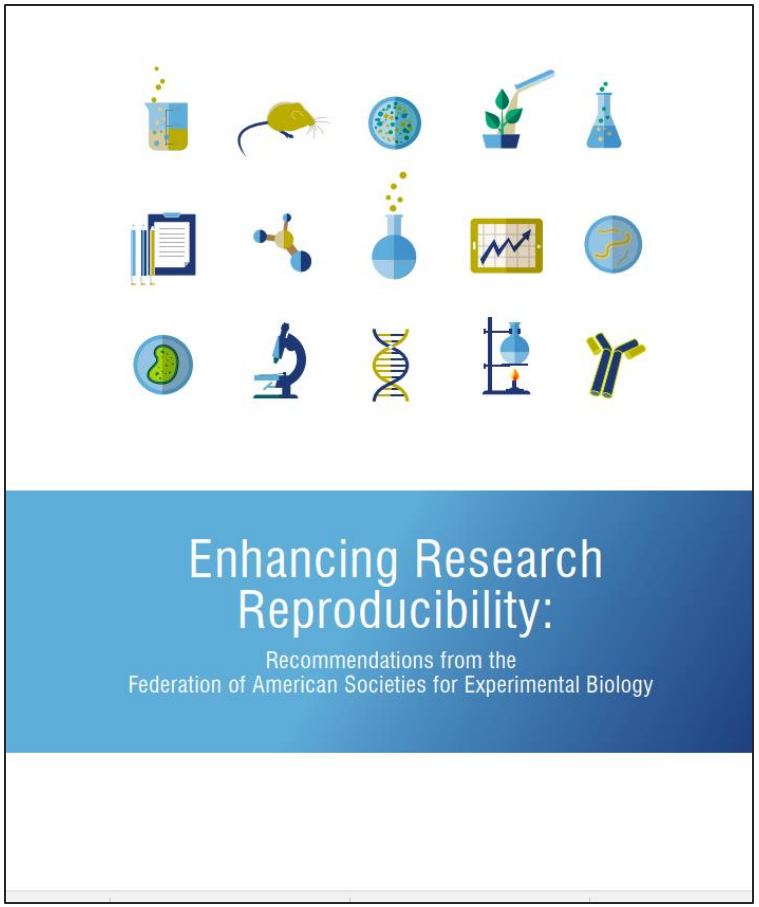
Stakeholder	Actions to improve reproducibility in preclinical research
Scientists	• Develop new technologies and methods that improve reproducibility and assist in validation and authentication processes • Explore new technologies including lab/bench automation and robotics to ensure greater precision, traceable data and minimize errors • Perform results reproduction studies and publish the results • Find the opportunities to publish ‘negative’ data • Generate credible evidence of research accountability (e.g. good documentation practices)

What will we need to respond?

Image credit: Mark Airs/Getty Images

More research on research Standards and Guidelines

Faseb: Enhancing Research Reproducibility

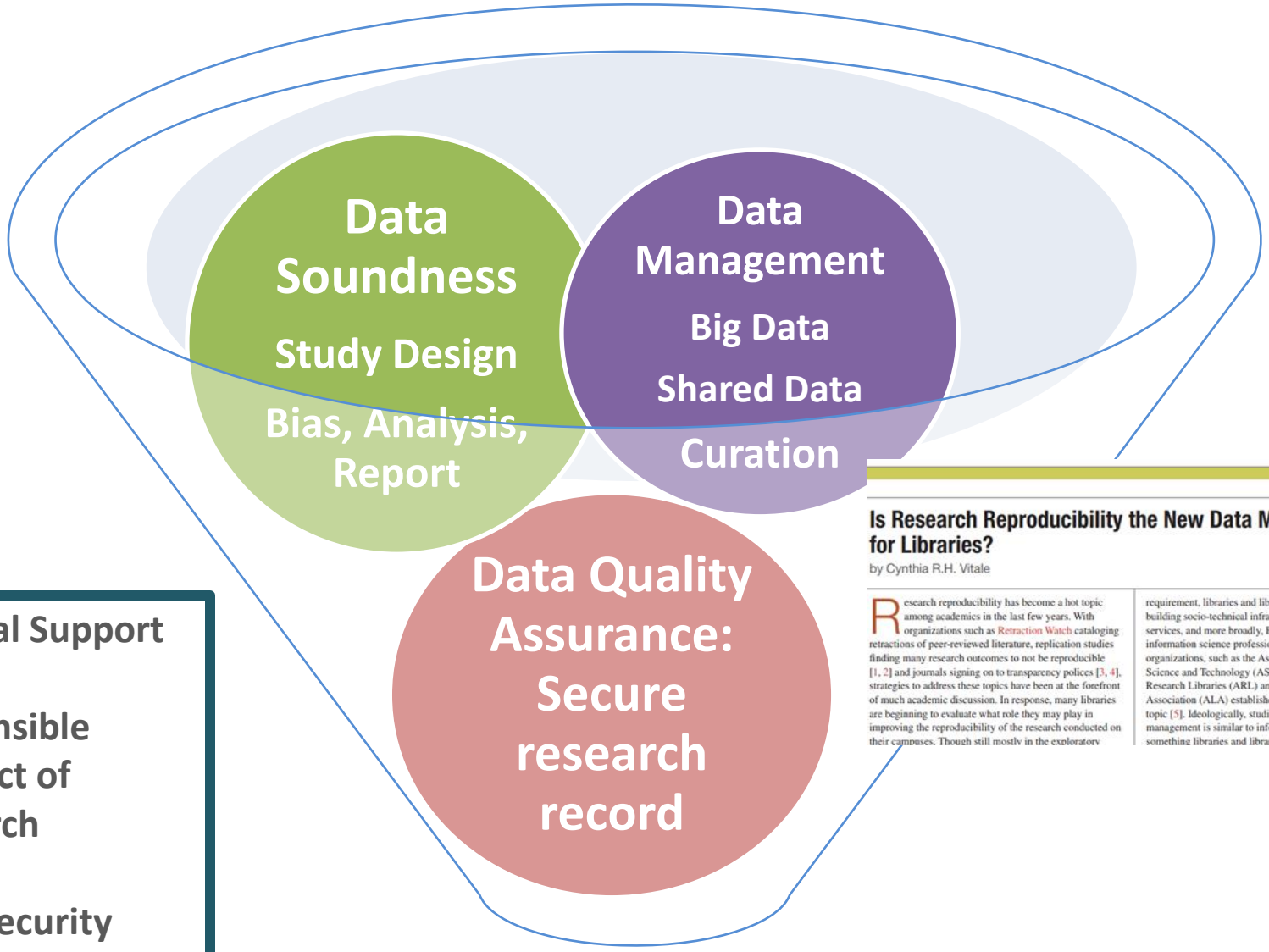


Overarching Recommendations

Recommendations Specific to Research Using Mouse and Other Animal Models

Recommendations Specific to Research Using Antibodies

https://www.faseb.org/Portals/2/PDFs/opa/2016/FASEB_Enhancing%20Research%20Reproducibility.pdf



Is Research Reproducibility the New Data Management for Libraries?

by Cynthia R.H. Vitale

Research reproducibility has become a hot topic among academics in the last few years. With organizations such as Retraction Watch cataloging retractions of peer-reviewed literature, replication studies finding many research outcomes to not be reproducible [1, 2] and journals signing on to transparency polices [3, 4], strategies to address these topics have been at the forefront of much academic discussion. In response, many libraries are beginning to evaluate what role they may play in improving the reproducibility of the research conducted on their campuses. Though still mostly in the exploratory

requirement, libraries and library organizations were building socio-technical infrastructure for data management services, and more broadly, E-Science support, in the information science profession. Major professional organizations, such as the Association for Information Science and Technology (ASIS&T), the Association of Research Libraries (ARL) and the American Library Association (ALA) established initiatives focused on this topic [5]. Ideologically, studies have argued, data management is similar to information management and is something libraries and librarians know much about [6, 7].

Internal Support

Responsible Conduct of Research

Data Security
Data Quality

IT

Research Accountability

An opportunity to lead

Someone will set the new boundaries of preclinical research practice

Scientific sea-change

The research ecosystem is highly intertwined

Scientists depend on one another

Scientists are needed to establish and drive best practices for research accountability

Institutions need to provide scientists with what they need to achieve and demonstrate research accountability.

The world is watching

Scientist specific solutions to research accountability concerns

February 13, 2018

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Image credit: Mark Airs/Getty Images

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