

# Council of Councils Operating Procedures for 2014

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# Council Operating Procedures – Brief History

- The Council of Councils approved the 2013 Operating Procedures at the May 14, 2013 Meeting
- The Council is being asked to approve Operating Procedures for use in 2014

# What I will cover today

- Scope of Council Operating Procedures
- Discussion and Vote

# Council Operating Procedures – No Changes Proposed to Scope

## Closed Session

- NIH-Wide Council Operating Procedures
- Procedures Specific to Common Fund (CF) and Office of Research Infrastructure (ORIP) Applications

## Open Session

- CF and ORIP Concept Clearance

## Authorities Delegated to Staff

## Procedures for Revisions to the Operating Procedures

# **Discussion and Vote**

# Initiative to Enhance Reproducibility and Transparency of Research Findings

# Background

- Reproducibility and transparency of research findings have been noted as an issue in multiple publications.
  - This is a problem in all areas of research, not just specific types of studies.
  - This has also been observed in both clinical and preclinical research, though the focus here is on reproducibility of preclinical 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.

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

Florian Prinz, Thomas Schlange and Khusru Asadullah

## Statistical Design Considerations in Animal Studies Published Recently in *Cancer Research*

Kenneth R. Hess

## 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.

# 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.

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

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

David Moher\*<sup>1,2</sup>, Iveta Simera<sup>3</sup>, Kenneth F Schulz<sup>4</sup>, John Hoey<sup>5</sup> and Douglas G Altman<sup>3</sup>

## Reforming Science: Methodological and Cultural Reforms

# 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.

## Translating animal research into clinical benefit

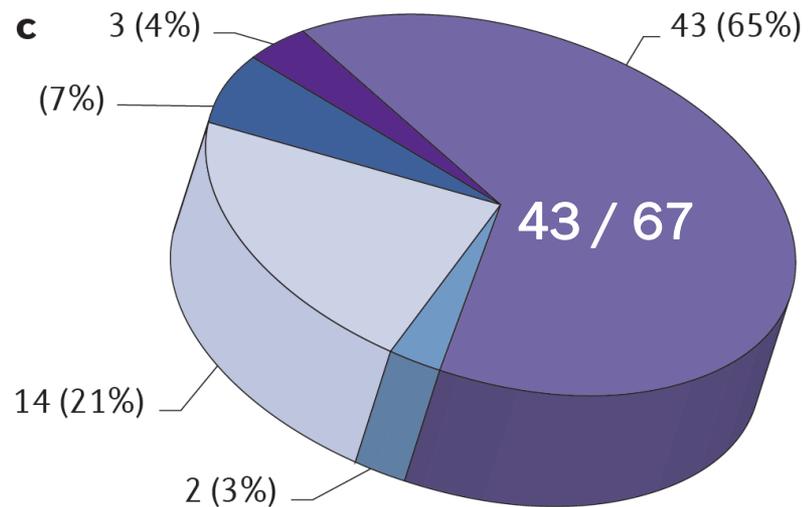
Poor methodological standards in animal studies mean that positive results may not translate to the clinical domain

# Almost 2/3 of 67 in-house projects could not replicate data published by others

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

Prinz, Schlange and Asadullah

Bayer HealthCare



- Inconsistencies
- Not applicable
- Literature data are in line with in-house data
- Main data set was reproducible
- Some results were reproducible

*Nature Reviews Drug Discovery*  
2011; 10:712-713

# Insufficient reporting of methodological approaches is evident for pre-clinical studies

**Table 3. Prevalence of selected quality characteristics in other experimental models**

	<b>Number of publications</b>	<b>Randomisation (%)</b>	<b>Blinded assessment of outcome (%)</b>	<b>Sample-size calculation (%)</b>
Transgenic stroke studies	157	n/a	3	0
Stroke pathophysiology studies	166	5	18	0
Parkinson's disease	118	12	15	0
Multiple sclerosis	183	2	11	0

# Deficient reporting is widespread

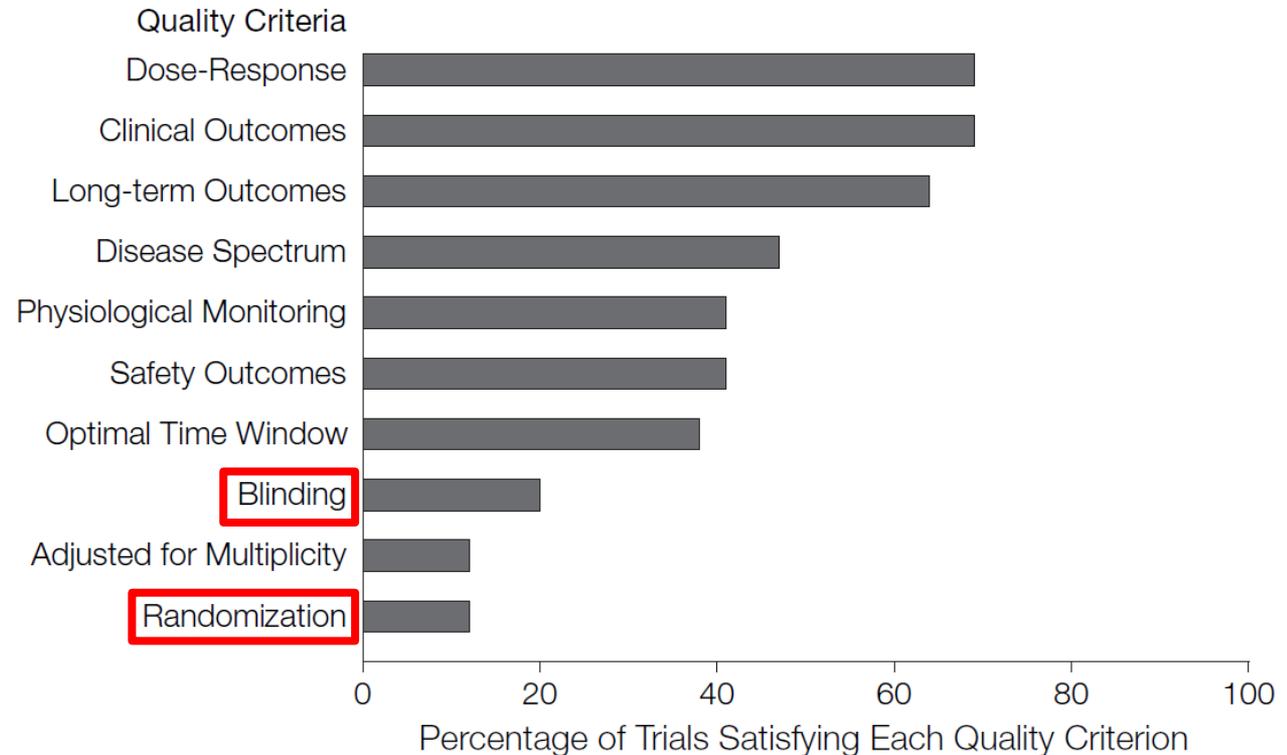
## Journals:

- Cell
- Nature
- Science
- Nature Medicine
- Nature Genetics
- Nature Immunology
- Nature Biotechnology

>500 citations

Translated to human studies

**Figure 1.** Methodological Quality of Animal Trials (n=76)



Hackam and Redelmeier, *JAMA* 2006, 295: 1751-1752

# Challenges to Applicability of Animal Studies to Humans

- Methodological quality of animal experiments.
- Biological differences between species and strains.
- Differences in design between animal experiments and clinical trials.
- Insufficient reporting of details of animals, methods and materials.
- Publication bias.

# Reproducibility - In the Eye of the Beholder

- Biochemist → Get the same answer over, and over... and over.
- Statistician → Even better with p values.
- Animal experimentalist → Yes... but \$\$\$\$.
- Animal welfare → Use only numbers that are absolutely necessary.
- University administrator → Publish or perish, preferably cheaply.

## Background (cont.)

- Topic discussed in workshops by NINDS and NCI in 2012.
  - NINDS held a workshop, “Optimizing the Predictive Value of Preclinical Research”, in June 2012, and workshop summary was published in [Nature in October 2012.](#)
  - NCI held workshops on reproducibility and data standards in September and December of 2012.

## Background (cont.)

- Topic was also discussed by IC Directors in December of 2012.
  - IC leadership was supportive of further focus on reproducibility.
  - Ad-hoc group formed by Francis Collins to develop approaches to redressing these issues.
  - Group's deliberations brought to IC Directors for feedback.
  - IC Director input used to inform plans for Trans-NIH and IC-level next steps.

# Underlying Issues

- Poor training
- Poor evaluation
- Perverse reward incentives

# Principles for Addressing the Underlying Issues

1. Raise community awareness.
2. Enhance formal training.
3. Improve the evaluation of applications.
4. Protect the integrity of science by adoption of more systematic review processes.
5. Increase stability for investigators.

# Recommendation #1

- Encourage ICs to discuss the issue with Advisory Councils and BSCs and/or hold workshops to signal attention to the issue of reproducibility to stakeholder communities.  
*(Maps to Principle #1)*

## **Action:**

- All ICs and OD Offices will discuss reproducibility and transparency of research findings with their stakeholder communities to alert them to the issues, and solicit feedback by the end of the 2013 calendar year.

# Recommendation #2

- Integrate modules and/or courses on experimental design into existing required training courses and award terms and conditions. (*Maps to Principle #2*)

## Action:

- OIR will create and pilot a new module on research integrity as it relates to experimental biases and study design to ethics training course required for NIH intramural fellows.
- Once this module is tested, OER will make it available on the web and encourage adoption (or equivalent) by extramural training programs for fellows and trainees.

# Recommendation #3

- Consider options for an evaluation process of the “scientific premise” of a grant application. (*Maps to Principle #3*)

## **Action:**

- Select ICs will perform pilot evaluations of scientific premise of grant applications.

# Recommendation #4

- Collaborate further with scientific journals and the scientific community on efforts to improve rigor. (*Maps to Principle #4*)

## Action:

- NIH will continue outreach to Journals to partner with them to determine value of recently adopted reporting guidelines.
- NIH will evaluate the PubMed Commons Community Response Effort, which is a pilot program testing options for scientists to post online comments on original research articles.

# Recommendation #5

- Adapt NIH bio-sketch to allow investigators to place their work into a functional context. (*Maps to Principle #5*)
- Action:
  - Select ICs will perform pilot evaluations of changes to bio-sketch to include elements that aid in framing the PIs work and describing the applicant's contribution to the publications cited.
  - Select ICs will also pilot additional experiments to reduce “perverse incentives”.
  - Efforts by NCI to reduce “perverse incentives” will be evaluated.
    - NCI recently developed an Outstanding Investigator Award to address perverse incentives by providing substantial, longer-term support to experienced investigators

# Additional Suggestions for Consideration – Suggestion A

- Consider the use of guidelines and/or checklists to systematically evaluate grant applications.

*(Maps to Principle #3)*

## **Action:**

- Select ICs will pilot the use of a checklist to enhance systematic review of applications.

# Additional Suggestions for Consideration – Suggestion B

- Consider the advisability and approach to supporting replication/reproducibility studies or centers. (*Maps to Principle #4*)

## Action:

- Select ICs will pilot additional use of supporting replication studies.
- Evaluate ongoing efforts by NINDS.
  - Pilot work has been done by NINDS in supporting replication studies.
- Evaluate ongoing efforts by NIA.
  - NIA is currently supporting the Interventions Testing Program, where preclinical studies are conducted with multi-site duplication, rigorous methodology and statistical analysis.

# Pilot Implementation Considerations

- Discussions with IC Directors elucidated important issues to consider as the pilots are designed, implemented, and evaluated.
  - One size does not fit all (i.e., difficulties and differences in implementation across fields and research areas (e.g., clinical vs. basic research, community science)).
  - Effects on experienced vs. early-career researchers.
  - Costs of housing and managing additional data.
  - Potential of added burden to review process.
  - Difficulty of publishing negative results
- Pilots will provide information and data on how these issues might affect larger-scale implementation.

# IC Participation in Reproducibility Pilots

- Pilot #1: Evaluation process of the “scientific premise” of a grant application
  - 6 ICs will do pilots or have ongoing efforts in this area.
- Pilot #2: Checklist to systematically evaluate grant applications
  - 12 ICs will do pilots (separately or in collaboration with other ICs) or have published checklists or other guidance.
- Pilot #3: Changes to bio-sketch
  - 6 ICs will do pilots or have ongoing efforts in this area.
  - SciENCv implementation (led by OER) may also provide an opportunity for ICs to evaluate bio-sketch changes.

# IC Participation in Reproducibility Pilots (Cont.)

- Pilot #4: Approaches to reduce “perverse incentives”
  - 2 ICs have or are piloting awards to enhance support for investigators.
- Pilot #5: Supporting replication studies
  - 7 ICs will pilot (separately or in collaboration with other ICs) or already have programs to support replication studies.

# Ongoing IC Projects

- Several ICs have existing or ongoing projects separate from and/or complementary to the proposed pilots.
  - **NIA:** Supports the Interventions Testing Program, where preclinical studies are conducted with multi-site duplication, rigorous methodology and statistical analysis.
  - **NHGRI:** Expectations of validation studies are an inherent part of the review of functional genomics studies and bioinformatics tool development.
  - **NIDDK:** Supports Mouse Metabolic Phenotyping Centers, which provide the scientific community with standardized, high-quality phenotyping services.
  - **NINDS:** Established a Scientific Rigor Working Group to forge action plans for rigor-focused efforts.