HOW RELIABLE ARE THE PUBLISHED RESULTS OF NIH-FUNDED RESEARCH?

- **Multiple reports of failures to replicate data**

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.

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**.

NCI CONVENED A WORKSHOP ON SEPTEMBER 14, WITH ALL CONSTITUENCIES REPRESENTED, TO ASK

- are the alleged phenomena real?

  --a new problem?
  --rising incidence? (cf increased "retractions")

- if real, what is the explanation?

  --different criteria in academia and industry?
  --different and difficult methodologies?
  --actual errors?
  —intentional or sloppiness?

- what encourages errors?

  who is responsible?
  --investigators, trainees, grantee
  institutions, journals, funders?

- what are the remedies? how would they be implemented?

CONSENSUS

UNANIMOUS AGREEMENT THAT THERE IS A PROBLEM:

MANY PUBLISHED RESULTS ARE MISLEADING OR WRONG

COMMON CHARACTERISTICS OF NON-REPLICABLE DAT

- Inadequate numbers of samples or subjects
- Failure to validate reagents
- Substandard number of experiments
- Data "selection," manipulation, subjective bi
  failure to "blind" observers

ETC

POSSIBLE EXPLANATIONS FOR SLOPPY WORK

THE EVALUATION PROCESS

LABORATORY PRACTICE

REVIEWERS/EDITORS AT JOURNALS

PUBLICATION METRICS (IMPACT FACTORS, "CNS DISEASE", ETC)

APPOINTMENT AND PROMOTION COMMITTEES

STUDY SECTIONS

NATURE OF BIOSKETCH

GROUP DYNAMICS IN LABORATORIES

NEED TO PUBLISH

ASPIRATIONS TO NOVELTY

INADEQUATE ETHICS TRAINING OR TEACHING OF SCIENTIFIC METHOD

REMEDIES DISCUSSED AT NCI WORKSHOP

--First, do no harm!

--Mentorship and training to improve practice and ethical standard

--More publication of "negative results" or failure to confirm, with means to award credit

--Post-publication commentary (cf PMC initiative)

--Change biosketch to focus on major accomplishments and to reward contributions to team efforts

--Greater access to underlying data

--Checklists for journal articles and grant applications

--Subsidized validations? (Who would pay? Who would choose?)

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EXAMPLES OF ACTIONS

AT NINDS

Actions taken by NINDS:
Workshop
"Optimizing the Predictive Value of Preclinical Research"

- ✓ *Guidance crafters*
- ✓ *Journal editors*
- ✓ *Reviewers*
- ✓ *End users*

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 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 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]

Actions taken by NINDS:
Notice in the Guide

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

NOT-NS-11-023

Release Date: August 10, 2011

Issued by: National Institute of Neurological Disorders and Stroke (NINDS)

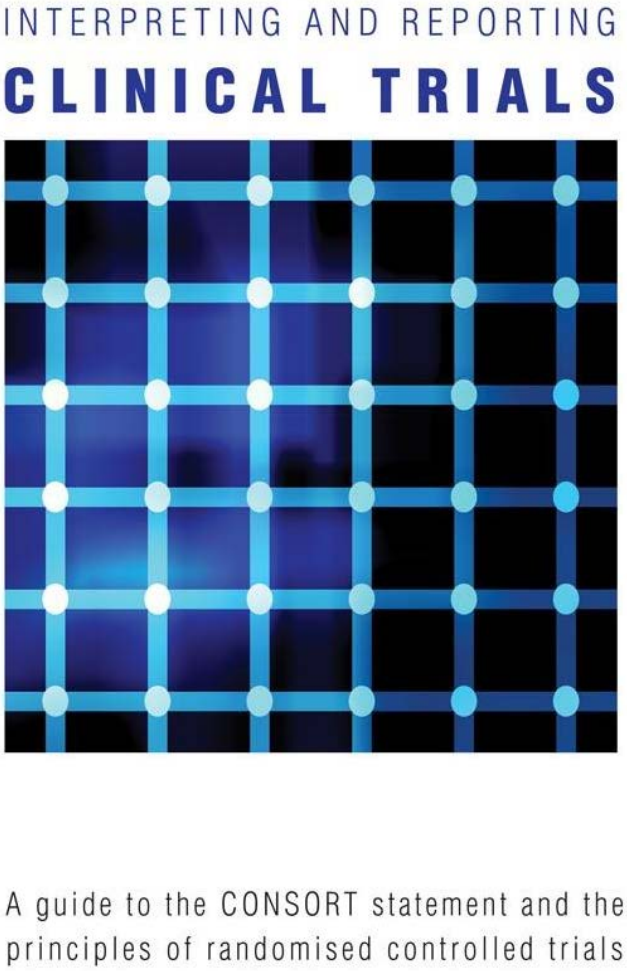
Purpose:

> …..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.

The CONSORT statement provides guidelines for reporting clinical trials

"Randomized trials can yield biased results if they lack methodological rigour.

To assess a trial accurately, readers of a published report need complete, clear, and **transparent** information on its methodology and findings."



POSSIBLE NEXT STEPS FOR THE NIH?

- Trans-NIH committee on the topic (Story Landis, NINDS, chair)
- More workshops to gather information and propose solutions
- Experiments to evaluate existing checklists (e.g. REMARK criteria for biomarker studies published in *Clinical Cancer Research)* or new ones
- A "failure analysis initiative" for individual cases
- Educational campaigns to change the culture via mentoring, ethics training, better evaluation processes (e.g. altered biosketch) statement of norms for "team science", etc.
- Trials of new publication practices: post-publication commentaries; links to unpublished data sets; means to encourage (or mandate) publication and dissemination of, and credit for, "negative" results
- Statements of concern about non-reproducibility with various constituencies (investigators, institutions, journals, industry)

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AN EXAMPLE: HOW CHECKLISTS MIGHT WORK…

- List standards, such as:
  Validate all reagents
  Meet statistical criteria
  Conform to other "best practices"

- Acknowledge differences appropriate for basic, pre-clinical, and clinical work

- Learn from "Omics" report from the IOM

- Develop NIH panels, employed at various stages of scientific process, to create or vet lists

- Encourage use by research groups, institutions, journ (reviewers and editors), and/or NIH study sectio

AN NCI EXAMPLE:

"REMARK" GUIDELINES

Lisa McShane, DCTD