

# Perspectives on Extramural Research

Michael S Lauer, MD

Deputy Director for Extramural Research, National Institutes of Health

Meeting of the Council on Governmental Relations

Friday, October 21, 2016

Washington Marriott Hotel, 1221 22<sup>nd</sup> Street NW, Washington DC

Disclosures: None

# A Personal Story Starts ~5 Years Ago ...



EDITORIAL

## A Threat to Medical Innovation

“The ... current situation ... is putting truly excellent laboratories out of business. In the spirit of ‘never waste a good crisis,’ a serious evaluation of ... NIH ... policies and programs is warranted. They include ... large collective funding efforts [like] ***expensive clinical and epidemiological research.***”

# BMJ

BMJ 2011;344:d7292 doi: 10.1136/bmj.d7292 (Published 3 January 2012)

Page 1 of 10

## RESEARCH

### Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis

 OPEN ACCESS

Joseph S Ross *assistant professor of medicine*<sup>1,2</sup>, Tony Tse *program analyst at ClinicalTrials.gov*<sup>3</sup>, Deborah A Zarin *director of ClinicalTrials.gov*<sup>3</sup>, Hui Xu *postgraduate house staff trainee*<sup>4</sup>, Lei Zhou *postgraduate house staff trainee*<sup>4</sup>, Harlan M Krumholz *Harold H Hines Jr professor of medicine and professor of investigative medicine and of public health*<sup>2,5,6</sup>



# Can't Ignore This Any Longer ...

FRED UPTON, MICHIGAN  
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WASHINGTON, DC 20515-6115

Majority (202) 225-2927  
Minority (202) 225-3641

February 14, 2012

The Honorable Francis S. Collins  
Director  
National Institutes of Health  
9000 Rockville Pike  
Bethesda, Maryland 20892

“This study raises concerns whether NIH is adequately implementing...”

Dear Dr. Collins:

We are writing to express our concern over a recent report documenting the underreporting of results of clinical drug trials. The most recent issue of the British Medical Journal contains a study by researchers from the University of Nottingham that finds that researchers and pharmaceutical companies routinely fail to publish data from clinical drug trials in a timely fashion. This study raises concerns whether NIH is adequately implementing the law



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

## Publication of Trials Funded by the National Heart, Lung, and Blood Institute

David Gordon, M.D., Ph.D., Wendy Taddei-Peters, Ph.D., Alice Mascette, M.D.,  
Melissa Antman, Ph.D., Peter G. Kaufmann, Ph.D., and Michael S. Lauer, M.D.

ABSTRACT

### BACKGROUND

Rapid publication of clinical trials is essential in order for the findings to yield maximal benefits for public health and scientific progress. Factors affecting the speed of publication of the main results of government-funded trials have not been well characterized.

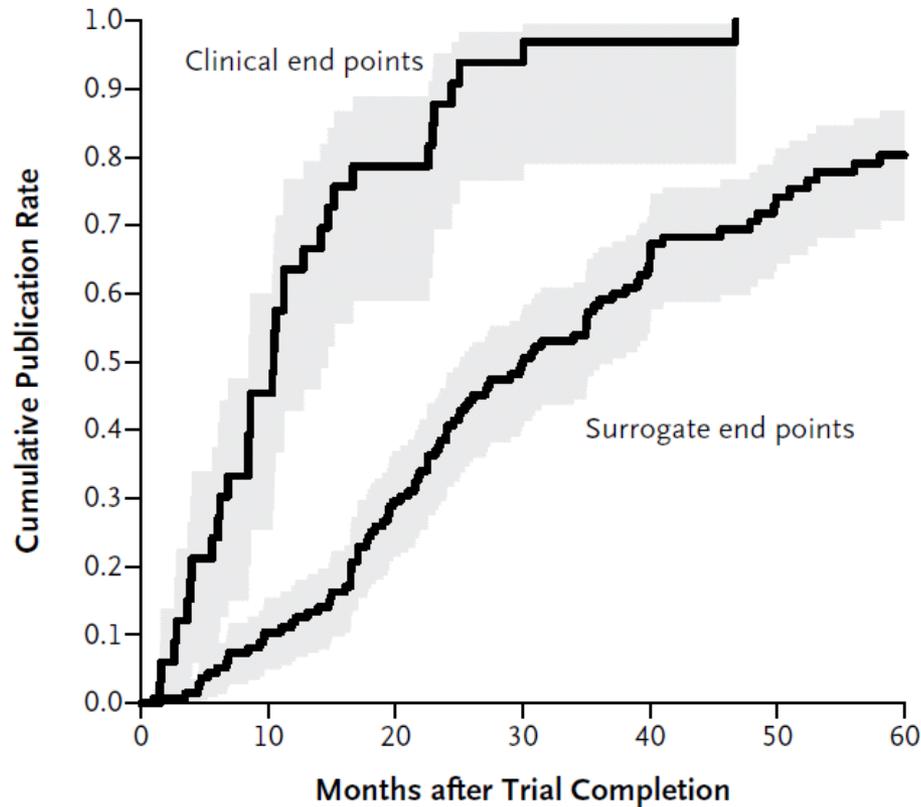
### METHODS

We analyzed 244 extramural randomized clinical trials of cardiovascular interventions that were supported by the National Heart, Lung, and Blood Institute (NHLBI). We selected trials for which data collection had been completed between January 1, 2000, and December 31, 2011. Our primary outcome measure was the time between completion of the trial and publication of the main results in a peer-reviewed journal.



# Confirmation ... With a Twist

Unadjusted rate ratio, 5.47 (95% CI, 3.74–7.98); P=0.001  
 Adjusted rate ratio, 2.11 (95% CI, 1.26–3.53); P=0.004



### No. at Risk

Surrogate end points	199	158	110	67	40	24	16
Clinical end points	45	22	7	2	1	0	0

## Publication and reporting of clinical trial results: cross sectional analysis across academic medical centers

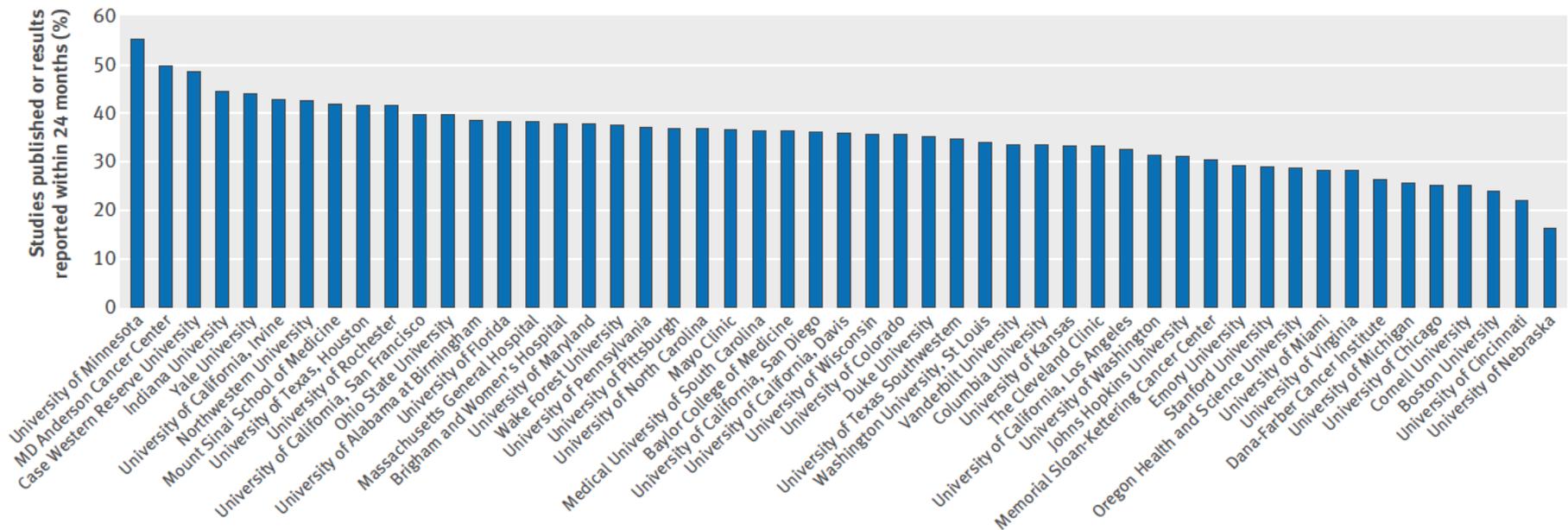


Fig 2 | Rates of dissemination of clinical trial results (publication of results or reporting of results on ClinicalTrials.gov) within 24 months across academic institutions. Of 4347 completed clinical trials, this figure excludes trials without dissemination of results (n=1455) as well as those with publication date and results reporting date <0 (n=216)

# Academic Medical Centers Get An F In Sharing Research Results

Updated February 24, 2016 · 9:43 AM ET

Published February 23, 2016 · 1:59 PM ET

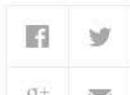
Commentary

HARLAN KRUMHOLZ

# Meaning ...



SHARE



Who will check the study results if they aren't made public?

*Simone Golob/Carbis*

<http://www.npr.org/sections/health-shots/2016/02/23/467712481/academic-medical-centers-get-an-f-in-sharing-research-results>



# Underreporting Research Is Scientific Misconduct

Iain Chalmers, FRCOG

“Substantial numbers of clinical trials are never reported ... Failure to publish is a form of scientific misconduct that can lead to inappropriate treatment decisions. Investigators, ethics committees, **funding bodies**, and scientific editors all have responsibilities to reduce underreporting of clinical trials.”

JAMA 1990;263:1405-8

# A New Policy (26 Years Later) ...

## VIEWPOINT

## Toward a New Era of Trust and Transparency in Clinical Trials

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**Kathy L. Hudson, PhD**

National Institutes of Health, Bethesda, Maryland.

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**Michael S. Lauer, MD**

National Institutes of Health, Bethesda, Maryland.

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**Francis S. Collins, MD, PhD**

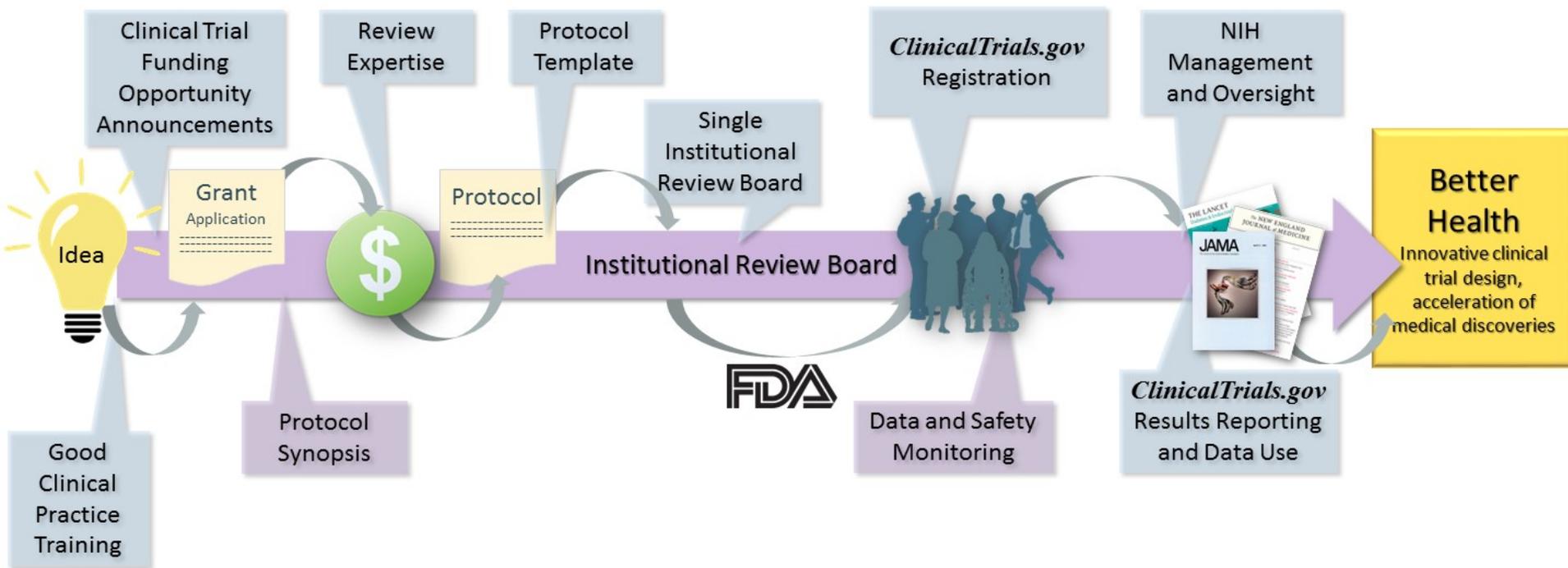
National Institutes of Health, Bethesda, Maryland.

“To realize the benefits of a clinical trial, the data must be broadly shared quickly. The DHHS has released a regulation for registration and summary results reporting...”

JAMA 2016 (online September 16, 2016)

# Improving Clinical Trials Oversight

## Clinical Trial Lifespan: Quality at Every Point





POINT OF VIEW

## Strategies from UW-Madison for rescuing biomedical research in the US

**Abstract** A cross-campus, cross-career stage and cross-disciplinary series of discussions at a large public university has produced a series of recommendations for addressing the problems confronting the biomedical research ecosystem.  
DOI: 10.7554/eLife.01079



 PERSPECTIVE

## Rescuing US biomedical research from its systemic flaws

**Bruce Alberts<sup>a</sup>, Marc W. Kirschner<sup>b</sup>, Shirley Tilghman<sup>c,1</sup>, and Harold Varmus<sup>d</sup>**

<sup>a</sup>Department of Biophysics and Biochemistry, University of California, San Francisco, CA 94158; <sup>b</sup>Department of Systems Biology, Harvard Medical School, Boston, MA 02115; <sup>c</sup>Department of Molecular Biology, Princeton University, Princeton, NJ 08540; and <sup>d</sup>National Cancer Institute, Bethesda, MD 20892

Edited by Inder M. Verma, The Salk Institute for Biological Studies, La Jolla, CA, and approved March 18, 2014 (received for review March 7, 2014)

The long-held but erroneous assumption of never-ending rapid growth in biomedical science has created an unsustainable hypercompetitive system that is discouraging even the most outstanding prospective students from entering our profession—and making it difficult for seasoned investigators to produce their best work. This is a recipe for long-term decline, and the problems cannot be solved with simplistic approaches. Instead, it is time to confront the dangers at hand and rethink some fundamental features of the US biomedical research ecosystem.



FEATURE ARTICLE



POINT OF VIEW

## Strategies from UW-Madison for rescuing biomedical research in the US

**Abstract** A cross-campus, cross-career stage and cross-disciplinary series of discussions at a large public university has produced a series of recommendations for addressing the problems confronting the biomedical research community in the US.

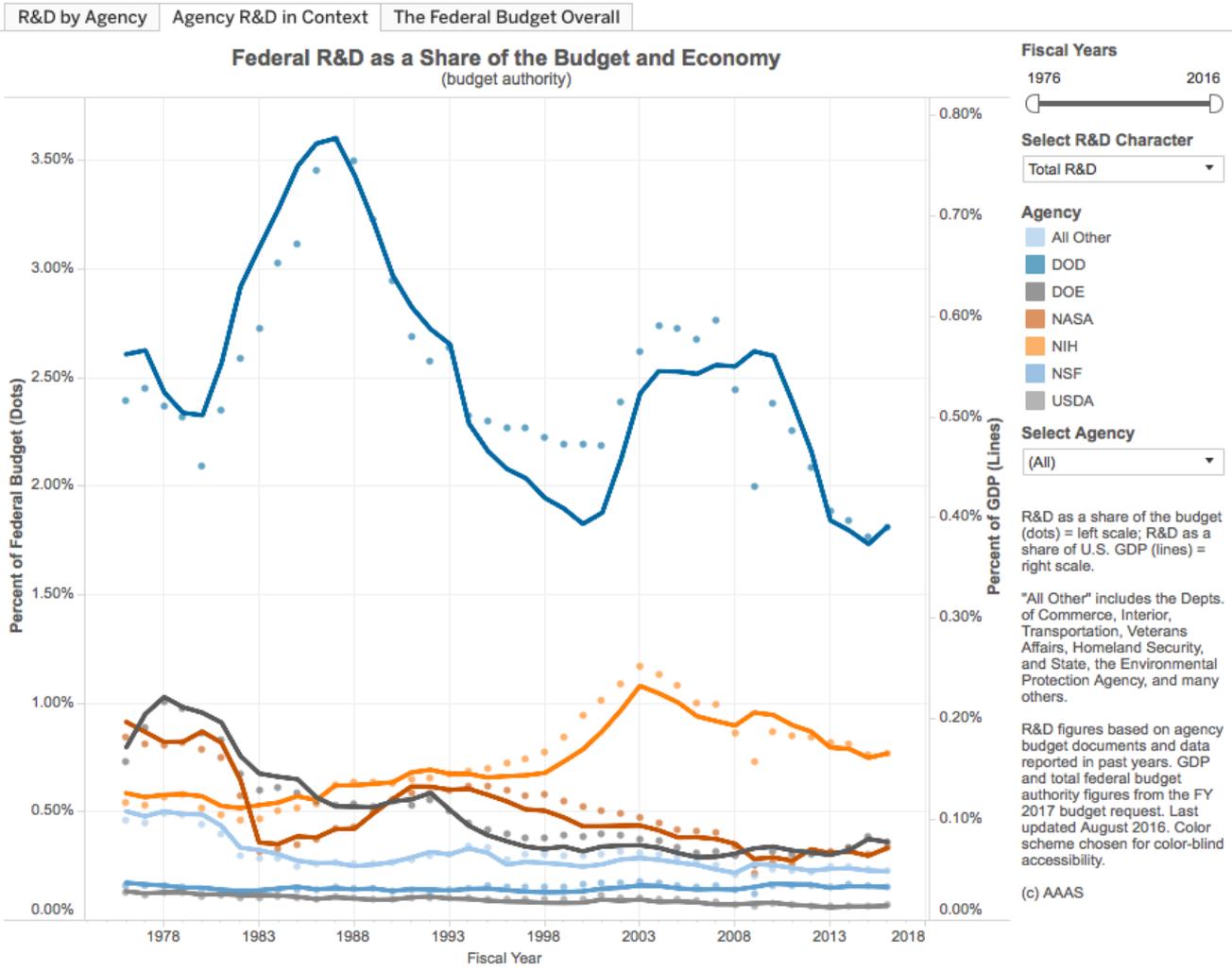
DOI: [10.7554/eLife.09305.001](https://doi.org/10.7554/eLife.09305.001)

“We identified two **core problems**:

- **Too many researchers** vying for **too few dollars**.
- Too many postdocs competing for too few positions.

Most other issues can be viewed as symptoms.”

# Too Few Dollars ...



## Maximizing the return on taxpayers' investments in fundamental biomedical research

Jon R. Lorsch

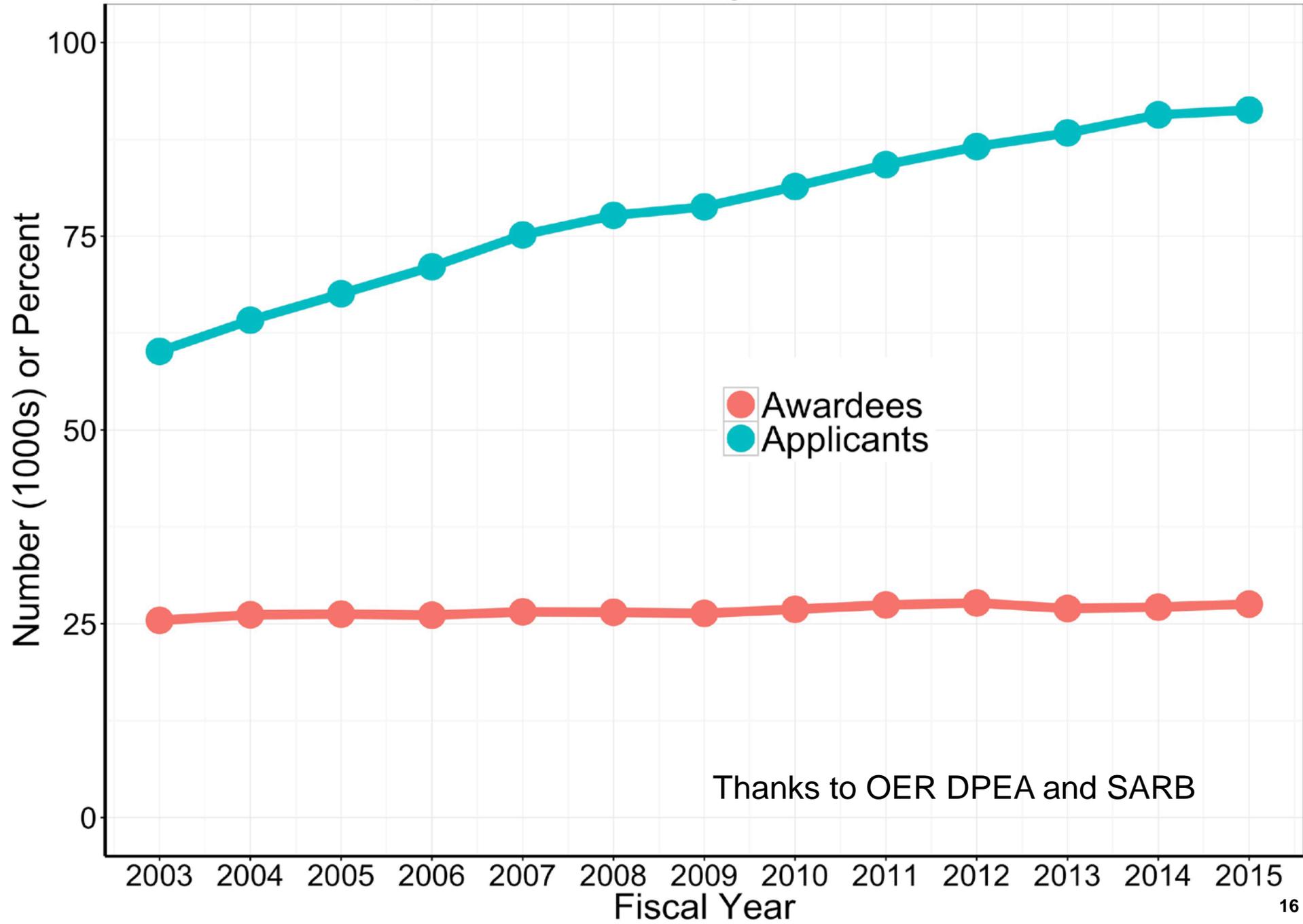
National Institute of General Medical Sciences, National Institutes of Health, Bethesda, MD 20892

## Changing our funding metric

“A question that at first glance may seem trivial but is, I believe, a significant one is whether our key metric for how... we invest in ... research should be the number of grants we award or ***the number of investigators we support.***”

Lorsch JR. Mol Biol Cell 2015;26:1578-82

# Awardees, Applicants, and Funding Rates for all RPGs over Time



# More Thoughts About Core Problems



TWEET SHARE

## The 7 biggest problems facing science, according to 270 scientists

*by Julia Belluz, Brad Plumer, and Brian Resnick on September 7, 2016*



- **Academia has a huge money problem**
- Too many studies are poorly designed
- Replicating results is crucial — and rare
- **Peer review is broken**
- Science is locked behind paywalls
- Science is poorly communicated
- **Life as a young academic is stressful**

<http://www.vox.com/2016/7/14/12016710/science-challenges-research-funding-peer-review-process>

# More and More and More Proposals for Projects

**"Bitter competition leads to group leaders working desperately to get any money just to avoid closing their labs, submitting more proposals, overwhelming the grant system further. It's all kinds of vicious circles on top of each other."**

**—Maximilian Press, graduate student in genome science, University of Washington**



# Different Approach to Funding Investigators

## Maximizing Investigator's Research Award (R35)

R35 Outstanding Investigator Award

Reissue of [RFA-GM-16-002](#)

- [NOT-OD-16-004](#) - NIH & AHRQ Announce Upcoming Changes to Policies, Instructions and Forms for 2016 Grant Applications (November 18, 2015)

[RFA-GM-17-002](#)

# Programs, not Individual Projects

- Stability of funding
- Flexibility – “follow your nose”
- Distribution of funding
- ***Less time writing grant applications***
- Less time reviewing grant applications

<https://publications.nigms.nih.gov/presentations/MIRA-Reissue-RFA-GM-17-002-Webinar-Revised.pdf>

## NHLBI Emerging Investigator Award (EIA) (R35)

R35 Outstanding Investigator Award

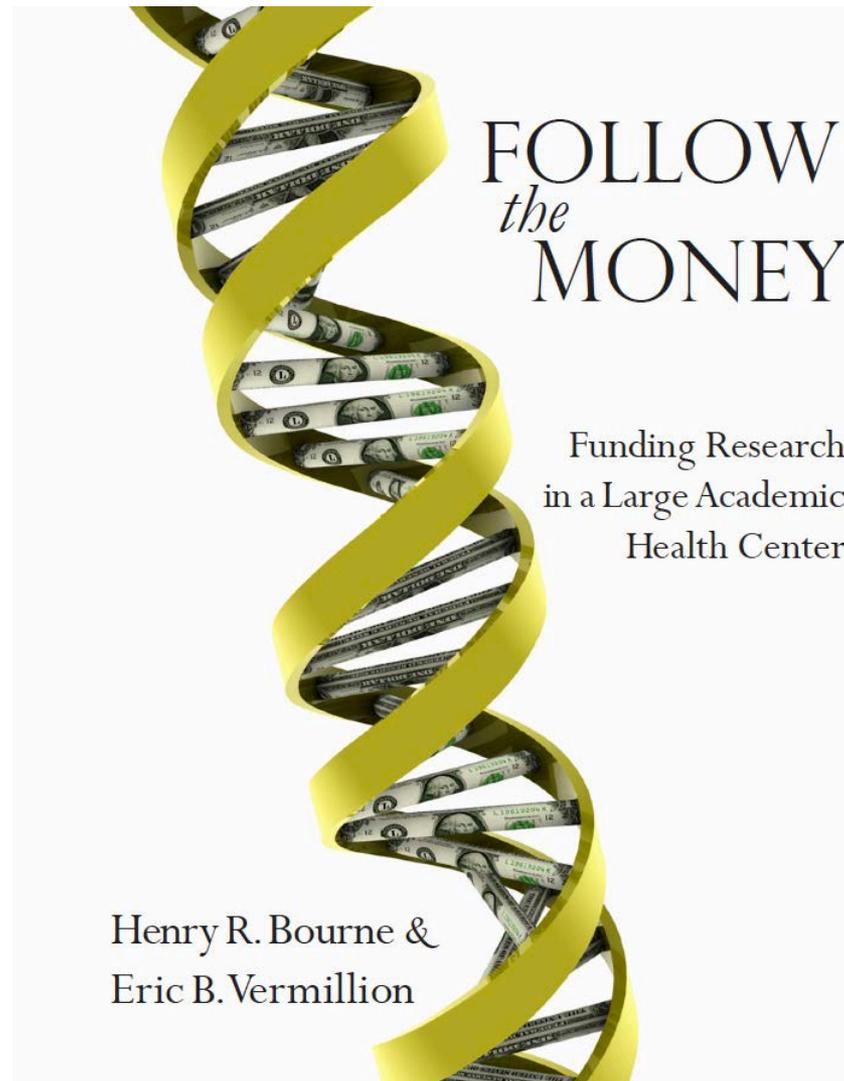
New

- [March 22, 2016](#) - Notice of Correction to Funding Opportunity Description for RFA-HL-16-025. See Notice [NOT-HL-16-302](#).
- [January 6, 2016](#) - Notice of Correction to Award Information for RFA-HL-16-025. See Notice [NOT-HL-15-296](#).
- [December 16, 2015](#) - Notice of Availability of Frequently Asked Questions and Answers for RFA-HL-16-025. See Notice [NOT-HL-15-289](#).
- [NOT-OD-16-004](#) - NIH & AHRQ Announce Upcoming Changes to Policies, Instructions and Forms for 2016 Grant Applications (November 18, 2015)

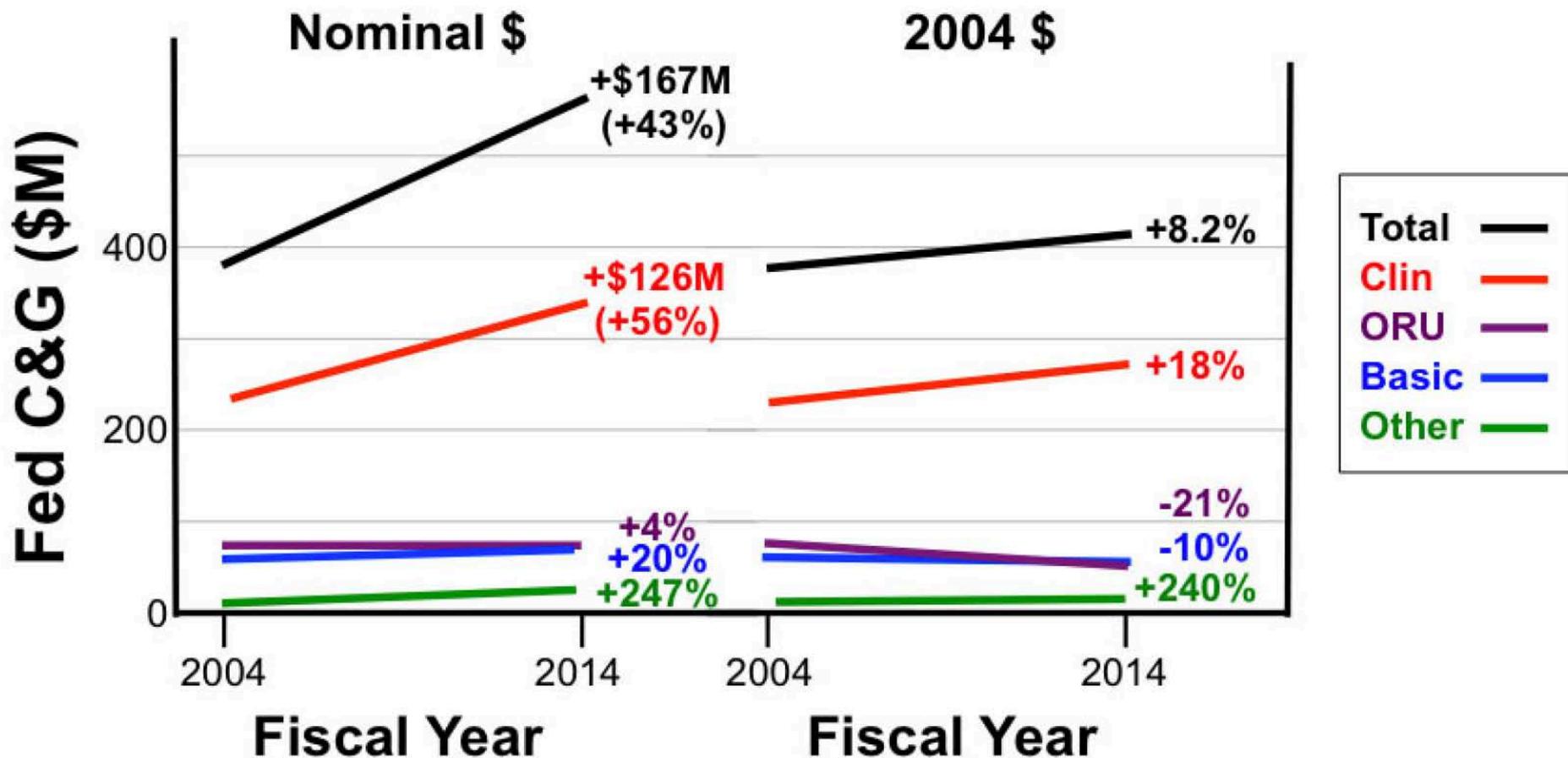
## RFA-HL-16-025



# Perspective from the Other Side ...



# Research Funding “Success”



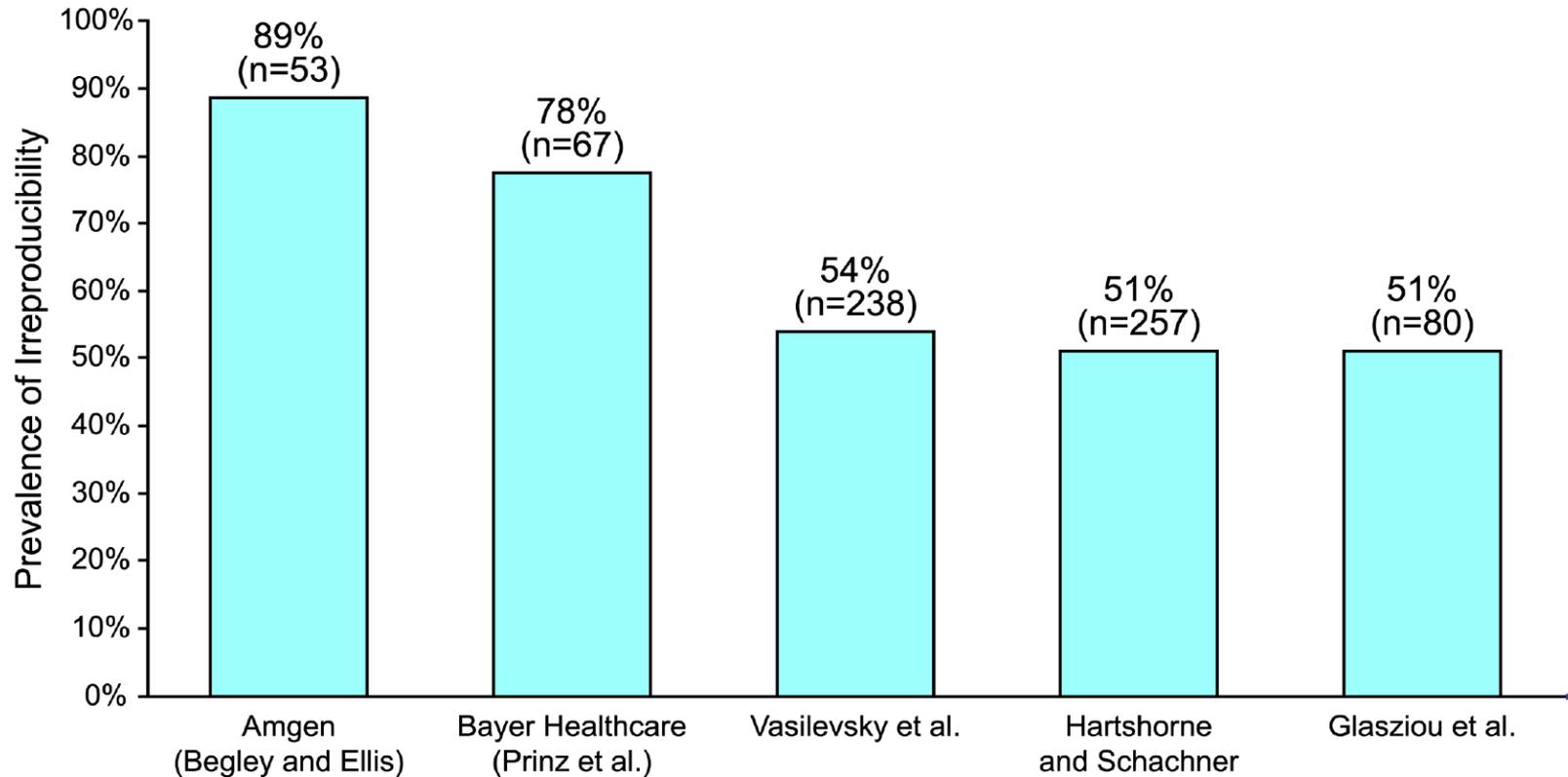
“Soft money paid 38% of researchers’ salary, but many researchers receive very large fractions of their salary from grants. Downturns in funding ... less like to promote innovative discovery. Heavy reliance on soft money may weaken UCSF’s willingness to apply its own standards to judge quality...”

## Pretend the Problems Don't Exist?

“Despite evidence that available resources are limited, UCSF behaves as if quality and quantity are synonyms, and exhibits little interest in plans that do not require expansion. Should UCSF shape new directions for its research and clinical juggernauts, or hang on and enjoy both rides while they last?”

- Academia has a huge money problem
- **Too many studies are poorly designed**
- **Replicating results is crucial — and rare**
- Peer review is broken
- **Science is locked behind paywalls**
- **Science is poorly communicated**
- Life as a young academic is stressful

<http://www.vox.com/2016/7/14/12016710/science-challenges-research-funding-peer-review-process>



**Fig 1. Studies reporting the prevalence of irreproducibility.** Source: Begley and Ellis [6], Prinz et al. [7], Vasilevsky [8], Hartshorne and Schachner [5], and Glasziou et al. [9].

doi:10.1371/journal.pbio.1002165.g001

*Open access, freely available online*

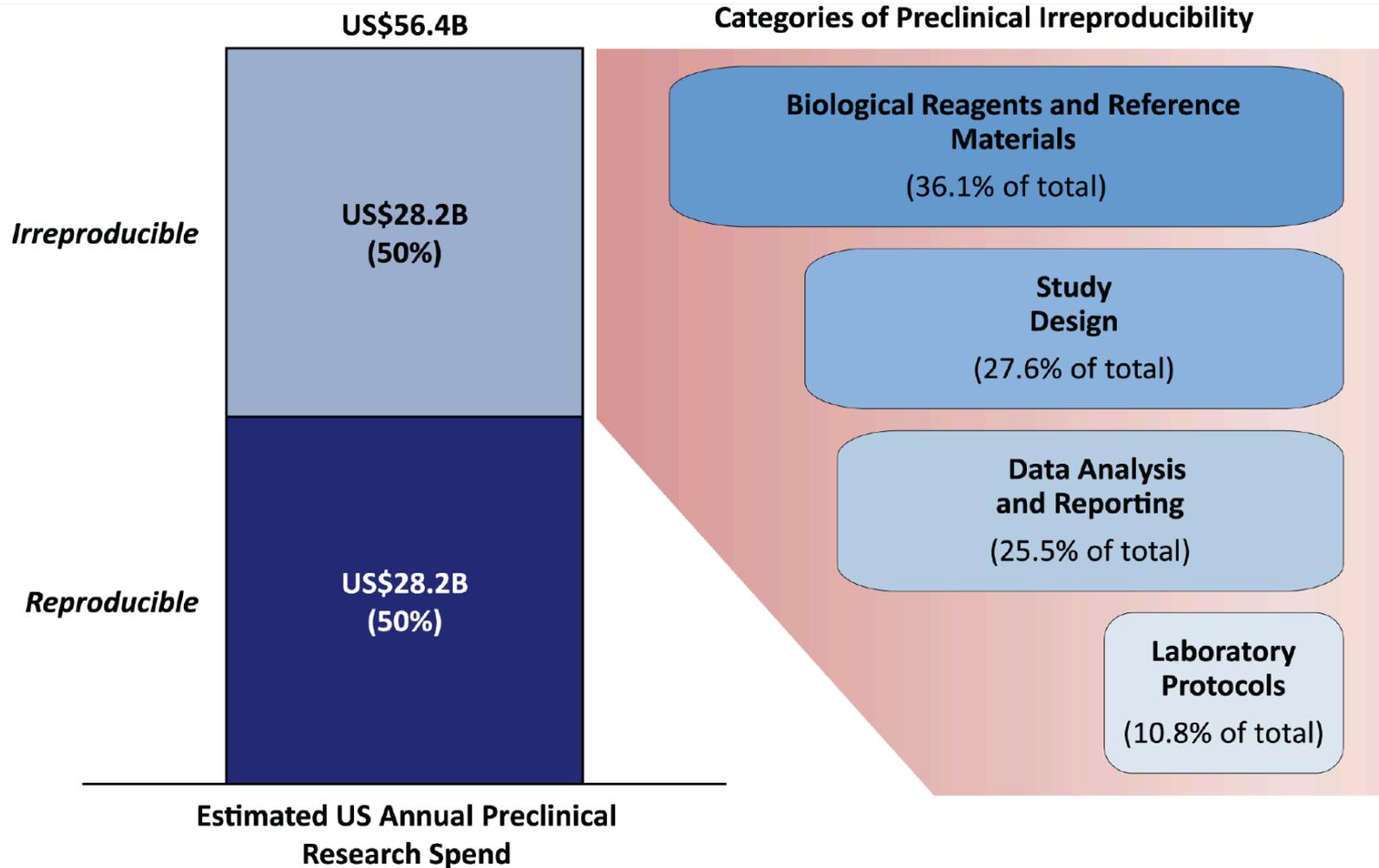
Essay

## Why Most Published Research Findings Are False

John P. A. Ioannidis

- Small – samples, effect size
- Many comparisons, many approaches
- Financial conflicts, “hot” items

Ioannidis JP. PLoS Medicine 2005;2:e124



**Fig 2. Estimated US preclinical research spend and categories of errors that contribute to irreproducibility.** Note that the percentage value of error for each category is the midpoint of the high and low prevalence estimates for that category divided (weighted) by the sum of all midpoint error rates (see [S1 Dataset](#)). Source: Chakma et al. [18] and the American Association for the Advancement of Science (AAAS) [19].



Experiments that use only a small number of animals are common, but might not give meaningful results.

## MEDICAL RESEARCH

# UK funders demand strong statistics for animal studies

*Move addresses concerns that some experiments are not using enough animals.*

## Returning to a Previous Theme...

“Boosting the number of animals in specific experiments need not mean more animals are used overall because multiple small experiments can often be replaced by fewer, larger ones. ‘One potential implication is we need to ask for money to do larger studies,’ says Marcus Muafo (University of Bristol).”

Cressey D. Nature 2015;520:271-2

## PERSPECTIVE

doi:10.1038/nature11556

# A call for transparent reporting to optimize the predictive value of preclinical research

Story C. Landis<sup>1</sup>, Susan G. Amara<sup>2</sup>, Khusru Asadullah<sup>3</sup>, Chris P. Austin<sup>4</sup>, Robi Blumenstein<sup>5</sup>, Eileen W. Bradley<sup>6</sup>, Ronald G. Crystal<sup>7</sup>, Robert B. Darnell<sup>8</sup>, Robert J. Ferrante<sup>9</sup>, Howard Fillit<sup>10</sup>, Robert Finkelstein<sup>1</sup>, Marc Fisher<sup>11</sup>, Howard E. Gendelman<sup>12</sup>, Robert M. Golub<sup>13</sup>, John L. Goudreau<sup>14</sup>, Robert A. Gross<sup>15</sup>, Amelie K. Gubitzi<sup>1</sup>, Sharon E. Hesterlee<sup>16</sup>, David W. Howells<sup>17</sup>, John Huguenard<sup>18</sup>, Katrina Kelner<sup>19</sup>, Walter Koroshetz<sup>1</sup>, Dimitri Krainc<sup>20</sup>, Stanley E. Lazic<sup>21</sup>, Michael S. Levine<sup>22</sup>, Malcolm R. Macleod<sup>23</sup>, John M. McCall<sup>24</sup>, Richard T. Moxley III<sup>25</sup>, Kalyani Narasimhan<sup>26</sup>, Linda J. Noble<sup>27</sup>, Steve Perrin<sup>28</sup>, John D. Porter<sup>1</sup>, Oswald Steward<sup>29</sup>, Ellis Unger<sup>30</sup>, Ursula Utz<sup>1</sup> & Shai D. Silberberg<sup>1</sup>

- Randomization and blinding
- Sample size and data handling

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

## Open Mike

*Helping connect you with the NIH perspective, and helping connect us with yours*

### Updates on Addressing Rigor in Your NIH Applications

Posted on **January 11, 2016** by **Mike Lauer**

As NIH moves ahead with implementing measures to enhance rigor, transparency and reproducibility in NIH-supported research, I'd like to give a brief update on these efforts, and highlight some important timeline changes for implementation in applications for institutional training grants (T), institutional career development awards (K12), and individual fellowships (F). .... [Continue reading](#) →



Dr. Michael Lauer is NIH's Deputy Director for Extramural Research, serving as the principal scientific leader and advisor to the NIH Director on the NIH extramural research program.