Open Science: Are we there yet?

Adrian F. Hernandez, MD

Aug 9 2019

The Principles: Raging Agreement

Why share clinical trial data?

- **Scientific advancement**
  - Answer multiple new questions
  - Combine data to increase power
  - Faster speed of discovery
  - Avoid duplication of efforts
- **Research integrity**
  - Validate original analyses
  - Transparency

However, Its been a Journey to Open Science

- ICMJE 2005
- CT.Gov and WHO ICRTP
- FDAAA 2007
- IOM 2015 Report
- EMA Policy 70
- ICMJE Proposal 2016
- FDA and NIH Final Rules 2016
- Sprint Challenge and NEJM meeting 2017
- ICMJE 2017 Requirements
- OHRP HHS 2017 Revised Informed Consent Rule
- NLM/NIH Meeting 2017 on Open Science
- AAMC Meeting 2018 on Academic Incentives
- National Academy of Medicine Meetings (2) 2019
- ……..

3 Questions

What are the incentives?

Have we made progress?

Depending on your views on progress, what would you change?

Case Study #1

Context:

- Its 2011 & a large clinical trial is completed
  - First of its kind
  - Largest ever
  - Published in NEJM
  - Sponsor interest is medium to low or completely cool to continue any additional analyses

- Young faculty member is the CC PI
  - *Friendly* advice from a colleague
    - "You should hold on to everything. That trial will make your career…"

- **Funding:** Multiple future mechanisms

Case Study #2

Context:

Junior investigator develops a concept to improve functional capacity for patients with heart failure- preserved ejection fraction

Potential medical product: Novel intervention targeting neuro-cardio axis

Experimental plan: 3 series of early phase studies:

- Small, short duration intense physiological
- Small, short duration cardiopulmonary Exercise
- 60 participant, longer duration activity test

Funding:

- AMC foundation
- Future plans – K, R01, AHA
- Industry/Intellectual property

Choices

A

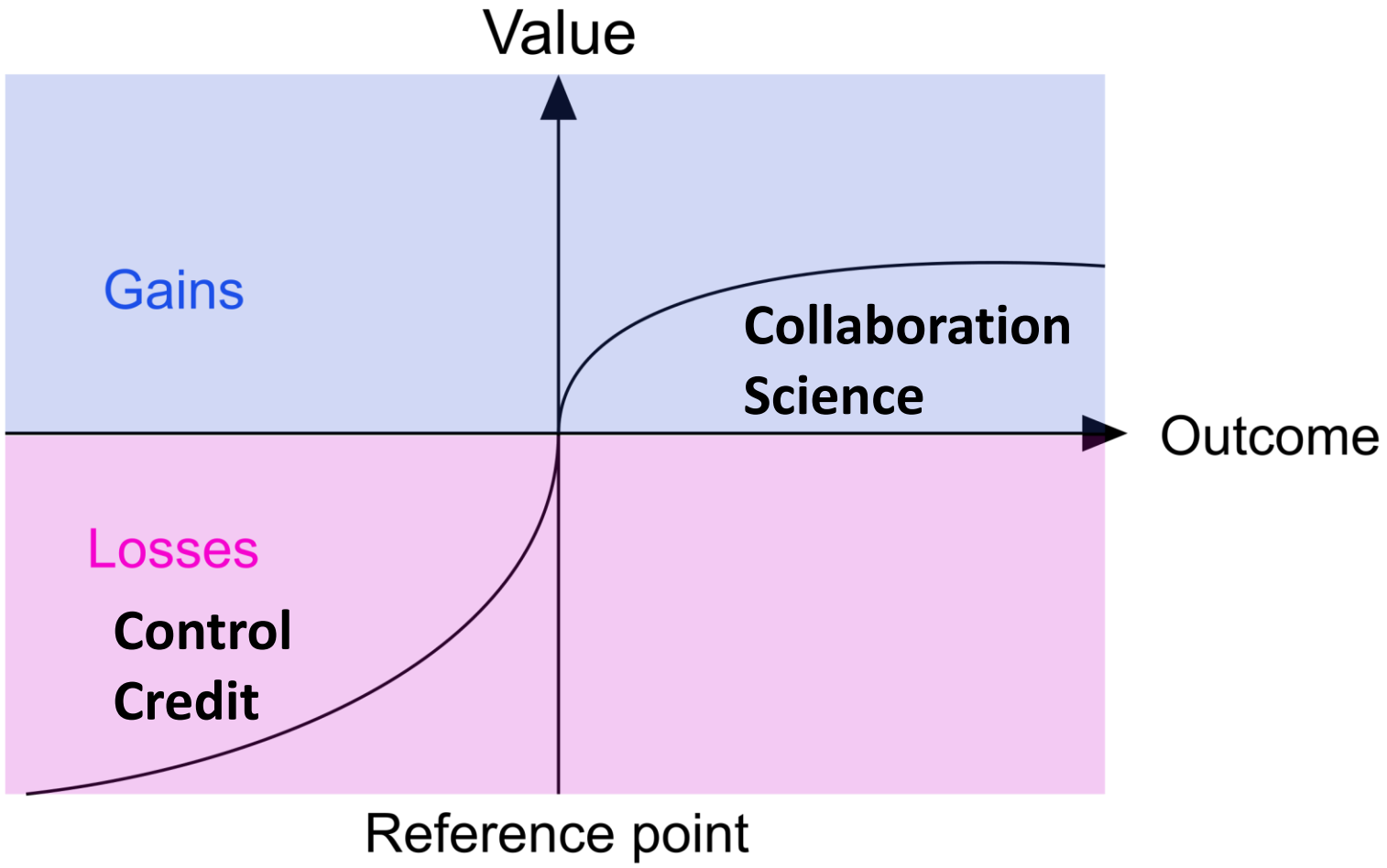
Hoard

B

Share

Is losing > than winning?

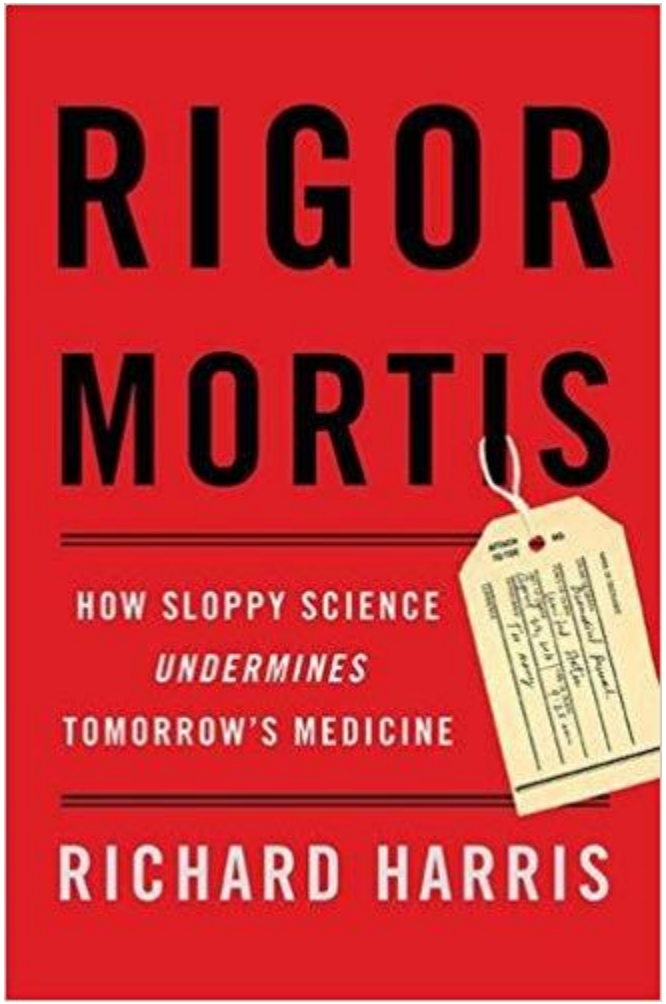
Prospect Theory



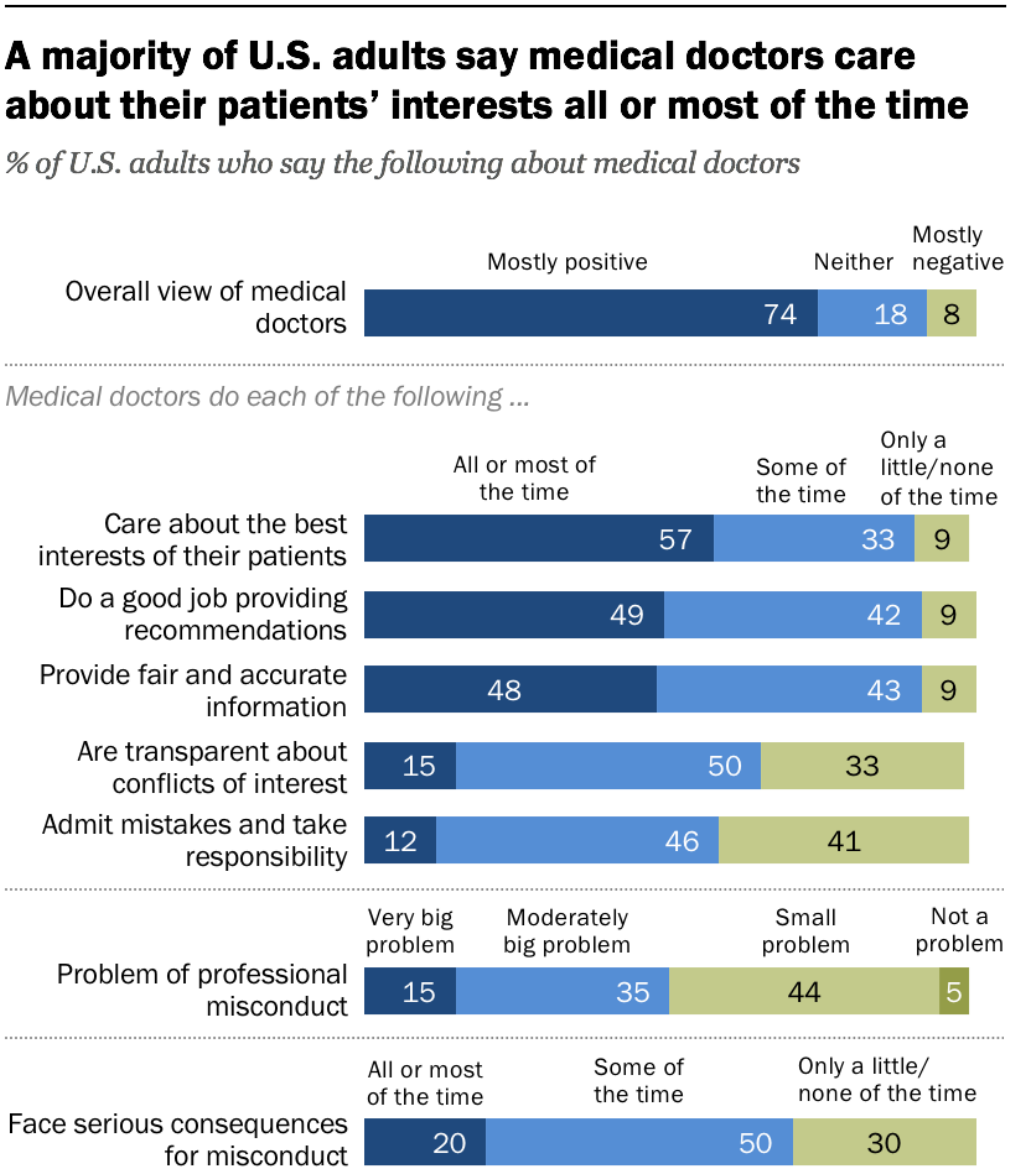
Have we earned or lost trust?

Required Reading: Outsiders and what they say…

Benefits vs. Risks



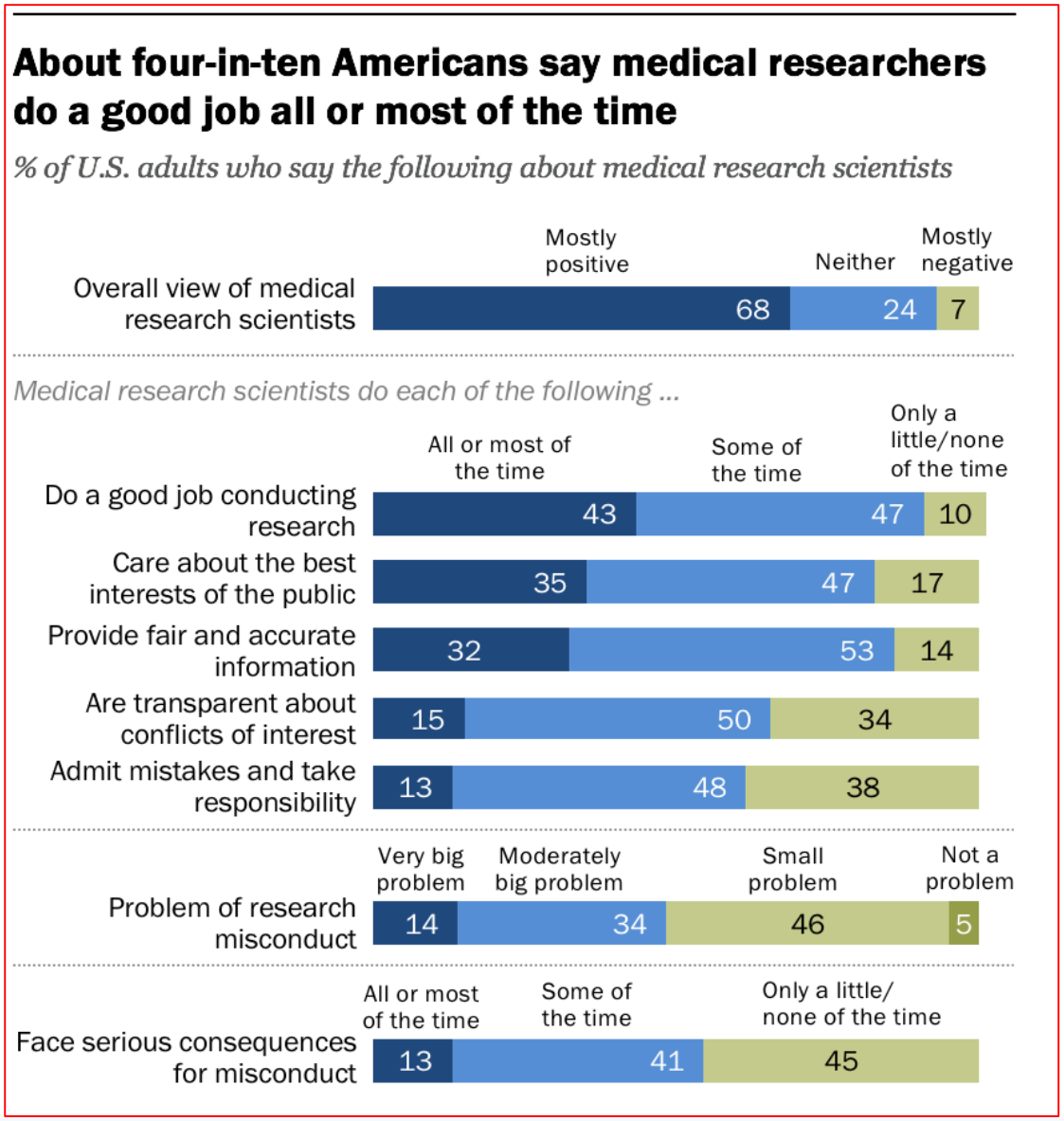
Good News: In Doctors, we trust



Pew Research Center, August 2019, "Trust and Mistrust in Americans' Views of Scientific Experts

Bad News: In researchers, we trust

some of the time



Is this what we want?

But it can always get worse…

The New York Times

Novartis C.E.O. Defends Company's Decision to Withhold False Data From the F.D.A.

Responding to the agency's stern rebuke, Vas Narasimhan, t
company's executive, tried to reassure investors that Novarti
intentionally deceive the F.D.A. while seeking approval for it
million gene therapy.

STAT[1]

Novartis CEO: 'We tried to do the right things' in FDA data scandal

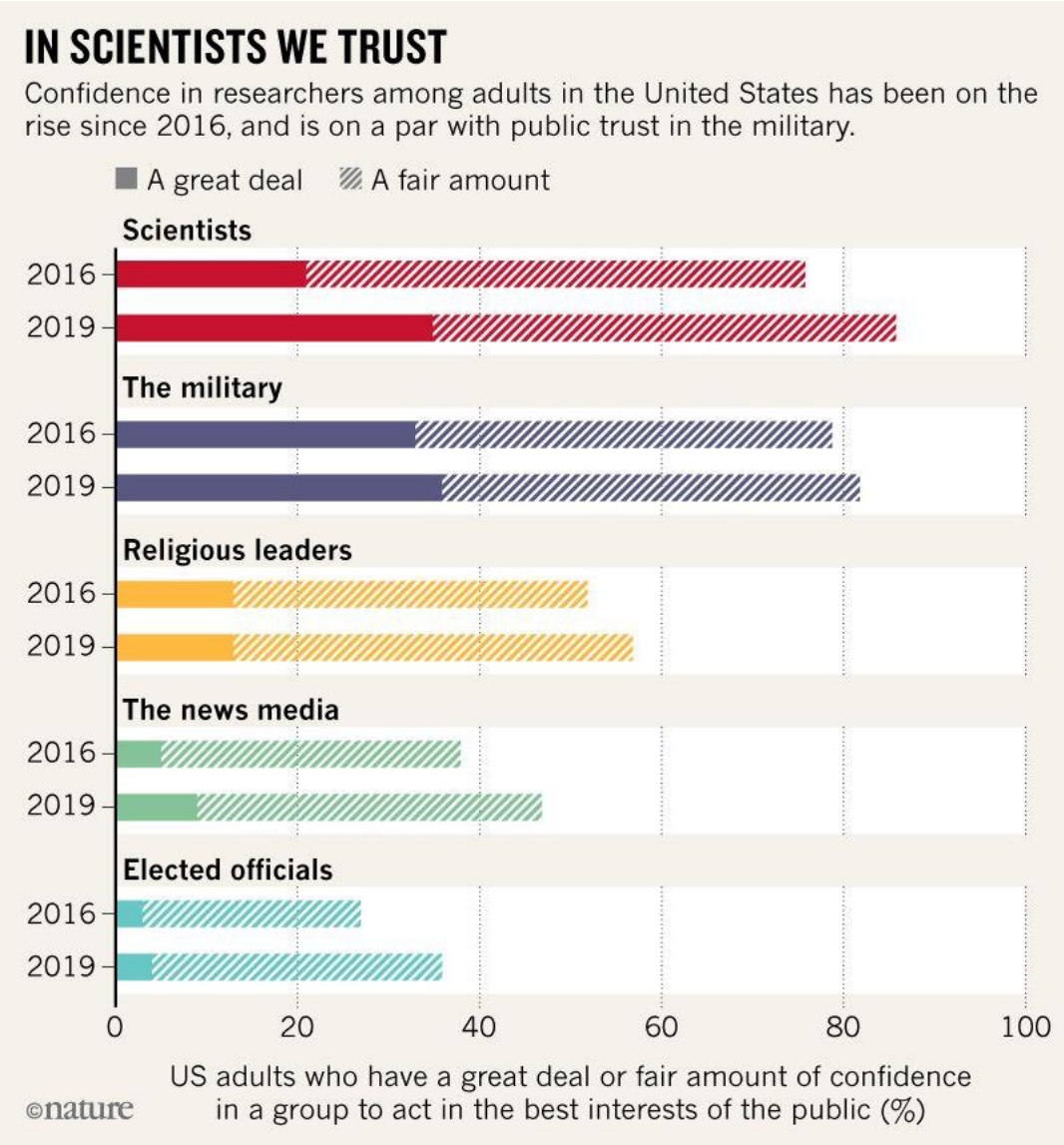
By Damian Garde[2] @damiangarde[3]

August 7, 2019

Dom Smith/STAT

Novartis CEO Vas Narasimhan on Wednesday defended his company's decision to wait three months to tell authorities about falsified data[4] submitted to the Food and Drug Administration, saying the company "tried to do the right things" in the process.

And at least, better than politicians

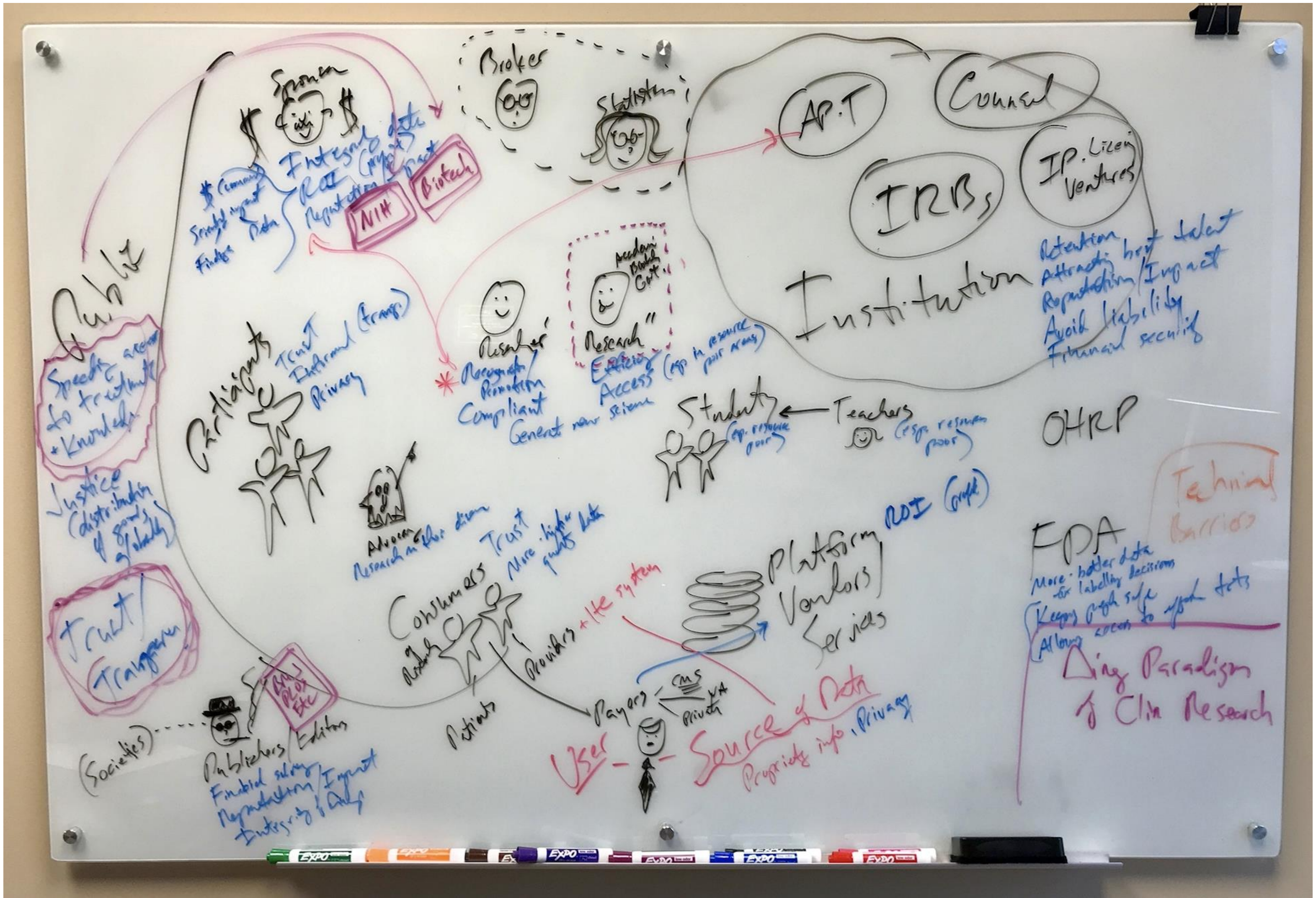


So, what are the incentives?

Easy...

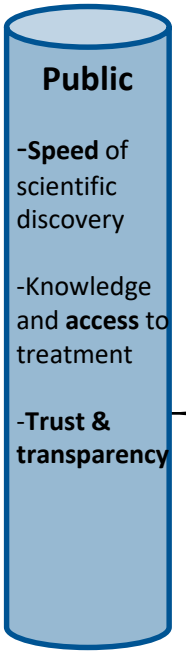
Just ask Kevin Weinfurt to think about something

Incentomap

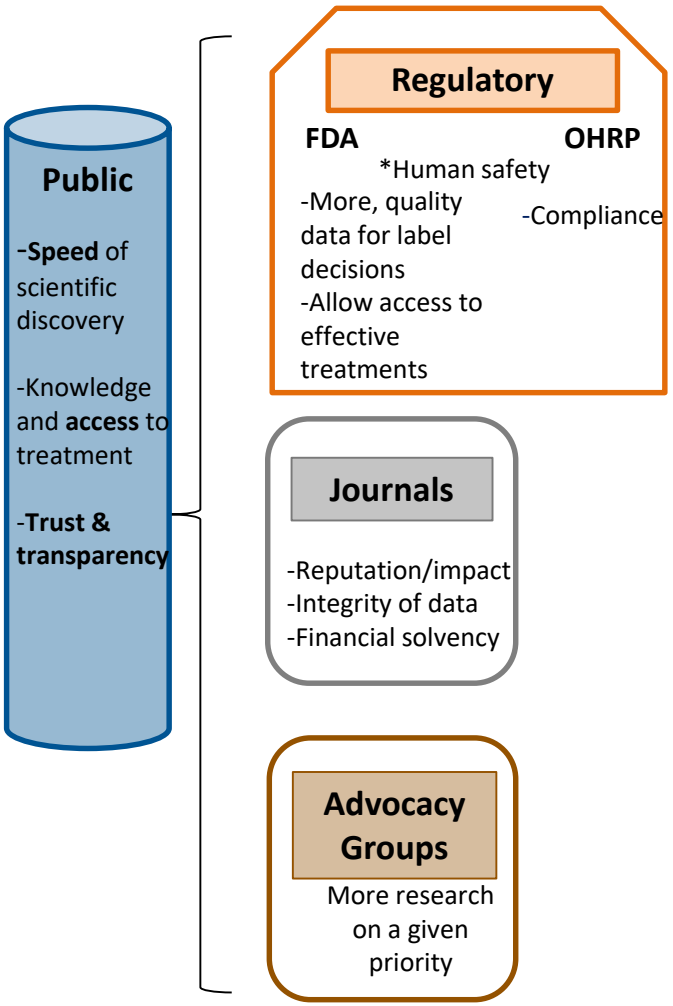


Broker
Sponsor
Statistician
AP·T
Council
IRBs
IP, Licensing, Ventures
Institution
Public
Participants
Trust
Privacy
NIH
Biotech
Researcher
Research
Students
Teachers
OHRP
FDA
Technical Barriers
Platform
Vendors
Services
ROI (graph)
Consumers
Patients
Payors
CMS
VA
Private
User
Source of Data
Privacy
Publishers/Editors
(Societies)
Trust/Transparency
Justice

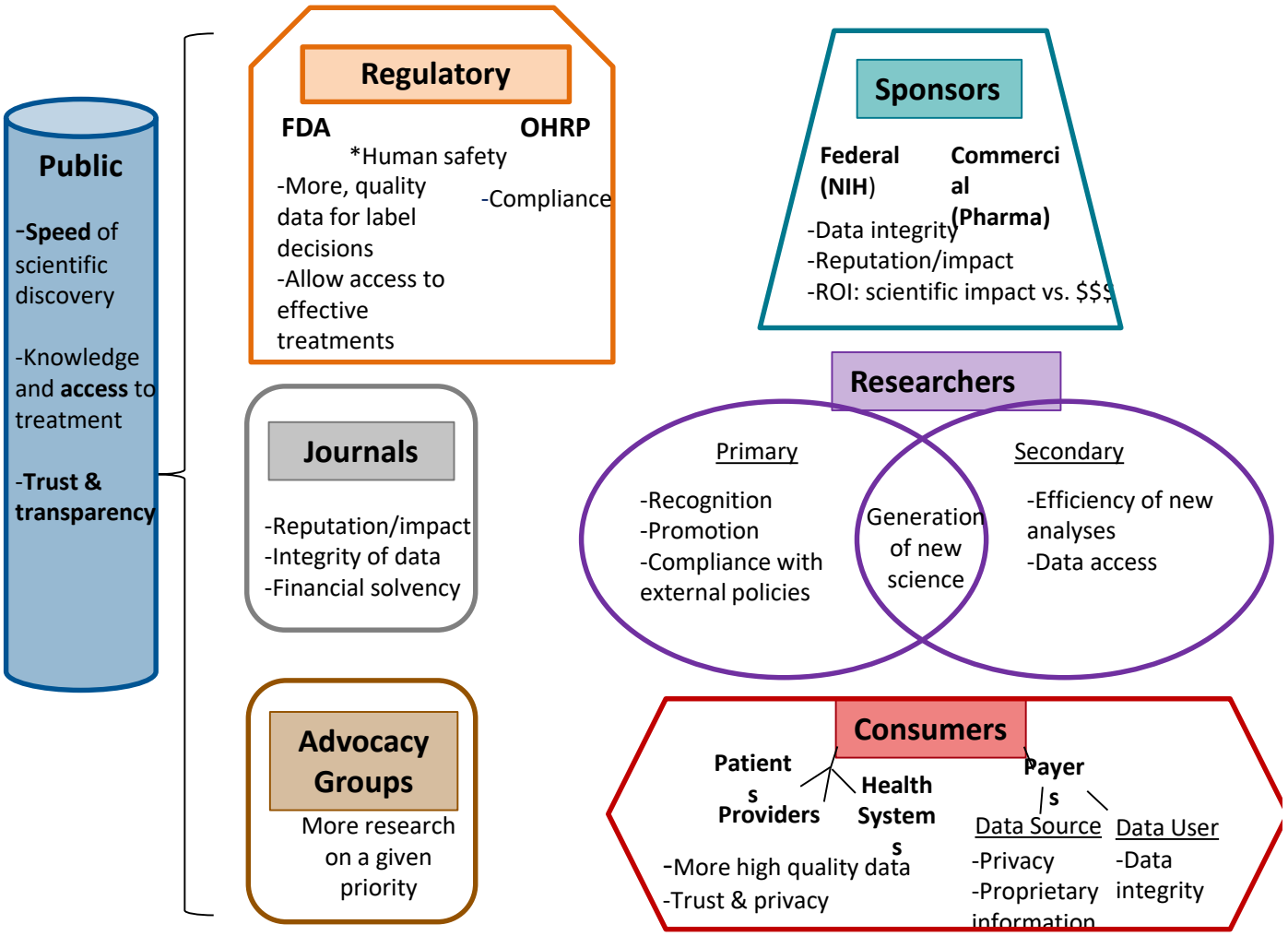
Stakeholders in Data Sharing and their Relevant Values



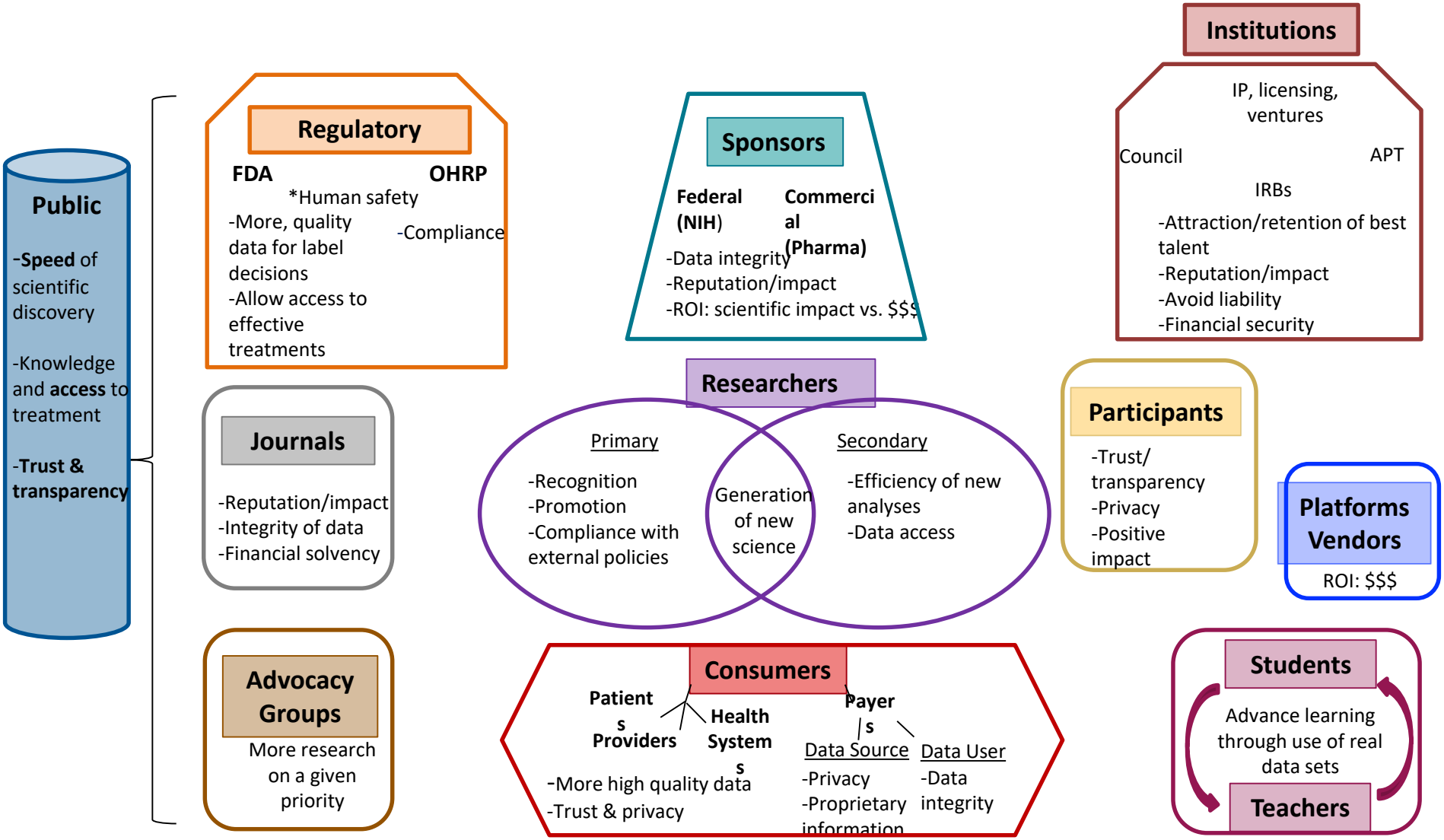
Stakeholders in Data Sharing and their Relevant Values



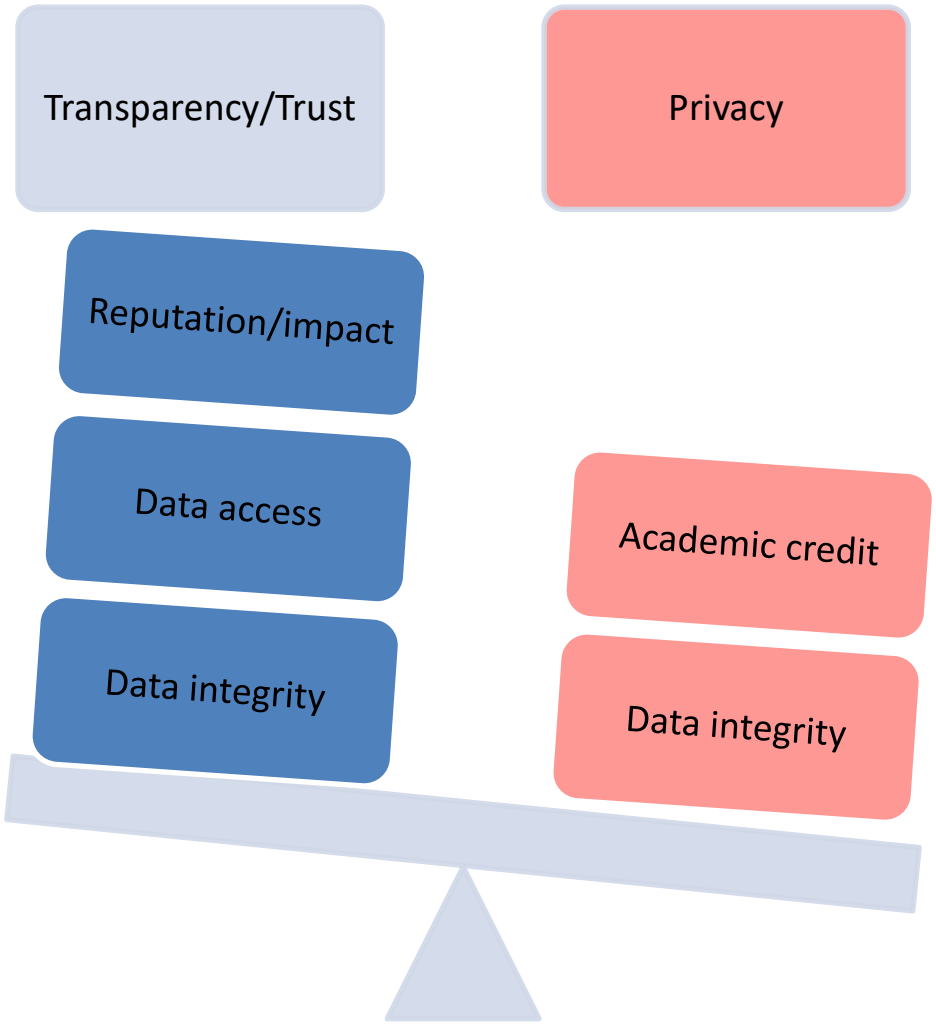
Stakeholders in Data Sharing and their Relevant Values



Stakeholders in Data Sharing and their Relevant Values



Opposing Values



Benefits

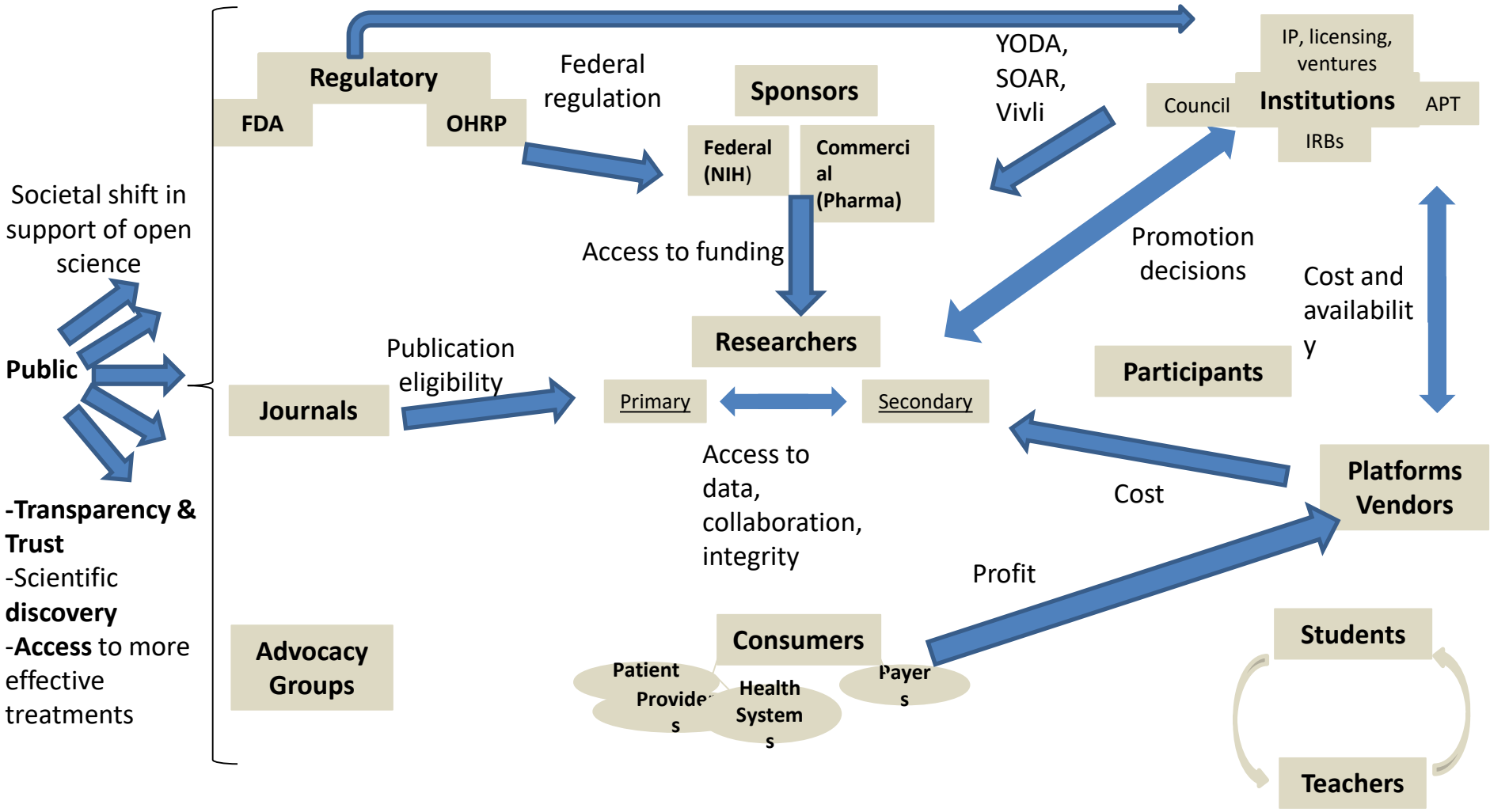
Barriers

Congrats!

You have a magic wand!

What incentives would need to be changed?

Current and future vectors of influence



A Reaction: Holy Complicated

What's been successful?

Landscape of Open Science

Various stakeholders have made progress towards sharing clinical trial data…

- **Scientific organizations**
  - IOM (National Academy of Science)
- **Regulatory agencies**
  - FDA, HHS
- **Sponsors- federal, commercial, private**
  - NIH, pharma, Wellcome trust
- **Journals**
  - ICMJE, BMJ, PLOS

Pharma made a leap of faith

- In May 2013, GSK launched a system to provide greater access to anonymized patient level data from our clinical trials.

EMA Policy

"As of October 2016, the European Medicines Agency (EMA) publishes clinical data submitted by pharmaceutical companies to support their regulatory applications for human medicines under the centralised procedure. This is based on EMA's flagship policy on the publication of clinical data."

European Medicines Agency Policy 0070

ICMJE requirements*

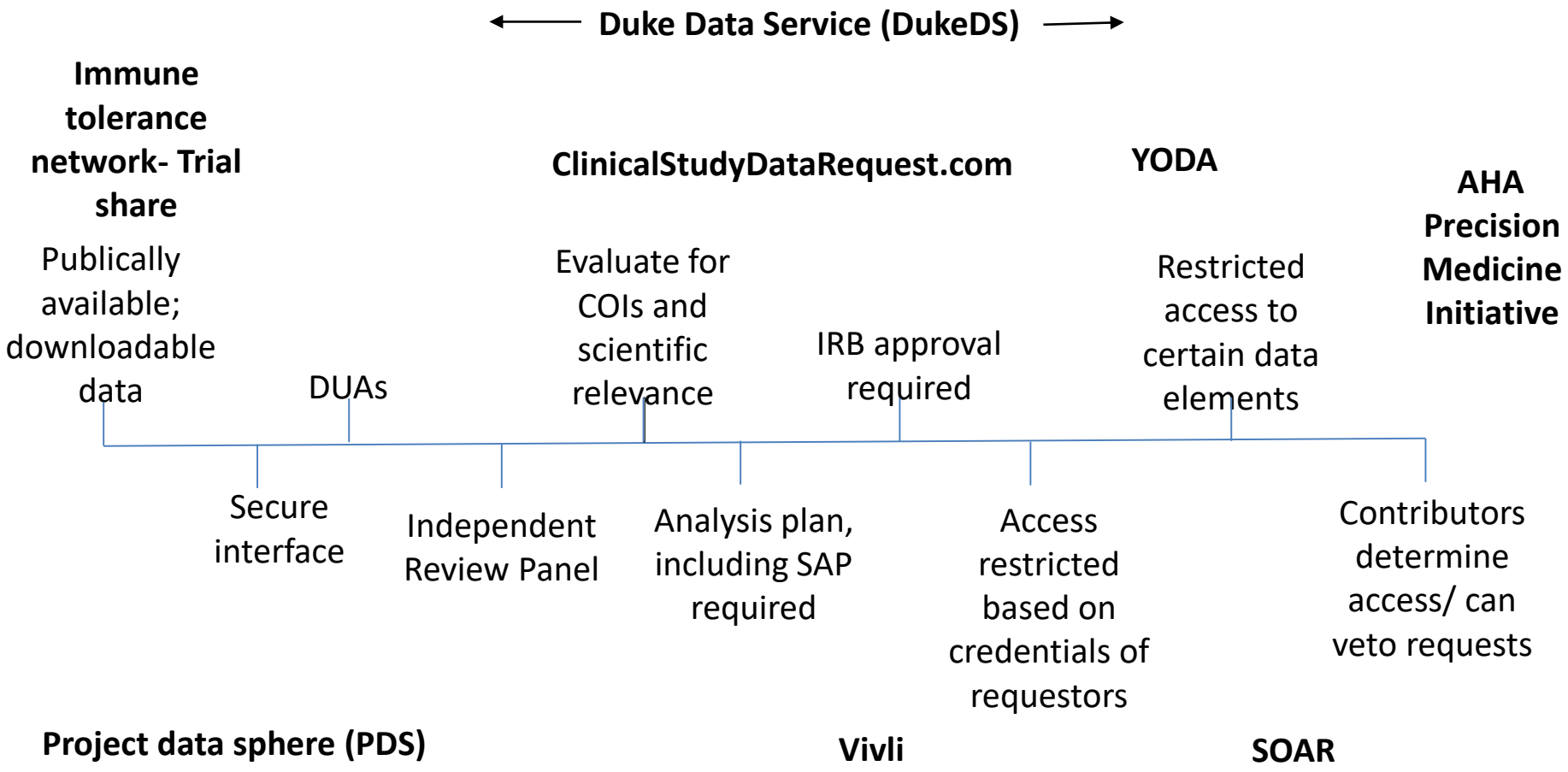
- The ICMJE expects that the Data Sharing Statement and the Data Sharing Plan will include the items listed below. Examples of possible responses are available in the editorial by ICMJE and on the ICMJE website.
  - Whether individual de-identified IPD (including data dictionaries) will be shared
  - What data will be shared
  - Whether additional, related documents will be available
  - When the data will become available and for how long
  - What access criteria will be used to decide if data will be shared (e.g., with whom, for what types of analyses, and by what mechanism).

*Taichman DB, et al. Data sharing statements for clinical trials: a requirement of the International Committee of Medical Journal Editors. Ann Intern Med. 2017;167:63–5.

Many platforms!

- Clinical Study Data Request: multi-sponsor request site (13 companies), managed by the Wellcome Trust
- YODA: Yale Open data Access for two sponsors (Janssen/Medtronic)
- Project Data Sphere (CEO roundtable on cancer)
- INSPIIRE : Integrated System for Pfizer Investigator Initiated Research
- SOAR: Bristol Myers Squibb and Duke Data Strategic Initiative (DCRI)
- Celgene's Clinical Trial Data Sharing
- NIH BioLiNCC
- Vivli.org

Spectrum of Data Sharing Models



Open Science and Success

Open access Research

BMJ Open

Accurate estimation of cardiovascular risk in a non-diabetic adult: detecting and correcting the error in the reported Framingham Risk Score for the Systolic Blood Pressure Intervention Trial population

Frederick Warner,[1,2] Sanket S Dhruva,[3,4] Joseph S Ross,[1,3,5,6] Pranammya Dey,[1,7] Karthik Murugiah,[1,2] Harlan M Krumholz[1,2,6]

nature
International journal of science

Data contest sparks controversy

Hundreds of researchers pick through clinical-trial results from a major blood-pressure study, to the dismay of some who collected the information.

BY HEIDI LEDFORD

When a prestigious medical journal challenged scientists to analyse data from a pivotal blood-pressure study in search of new findings, hundreds of researchers around the world signed up.

The contest, sponsored by the *New England Journal of Medicine*, offered scientists a rare opportunity to access detailed trial data that otherwise might have remained proprietary for another year — if not indefinitely. But the competition, whose winners were announced on

publicly available as soon as possible. Doing so, they argue, opens up the possibility of a wide range of additional analysis, and speeds up analyses that can yield important clinical insights. "Clinical-trial data are quite valuable, but usually they're kept locked away," says Sandosh Padmanabhan, a participant in the competition who researches cardiovascular genomics at the University of Glasgow, UK. "Everybody who does clinical trials needs to open up their data for everybody to use."

The Systolic Blood Pressure Intervention Trial (SPRINT) studied 9,361 people with

the data available for its competition in November 2016.

Wright worries that hundreds of researchers are now picking through the data while the SPRINT investigators are still busy closing down the trial. "Others who had nothing to do with the trial are able to publish a lot faster than we are," he says. "The return on investment is dramatically reduced for the investigators in SPRINT, no question."

The team that won the data competition was led by Noa Dagan, chief data officer at Clalit Research Institute in Tel Aviv, Israel. The

Are we there yet?

Progress?

NIH U.S. National Library of Medicine
ClinicalTrials.gov

- **Completed**
- **167,511**
- **11,702 Phase 3/4 interventional**

ClinicalStudy DataRequest.com

- **3068**
- **383 Phase 3/4**

An ounce of humility

RESEARCH LETTER

JAMA The Journal of the American Medical Association

Use of Open Access Platforms for Clinical Trial Data

Concerns over bias in clinical trial reporting have stimulated calls for more open data sharing.[1] In response, multiple pharmaceutical companies have created mechanisms for investigators to access patient-level clinical trials data. However, if and how these shared clinical trial data are being used is unknown.

- >3255 trials available
- 3 platforma
- 15% of trials requested
- 4.4% validation
- 1 publication

Navar AM et al JAMA 2016

Open Science Maturing?

SCIENTIFIC DATA

OPEN

Overview and experience of the YODA Project with clinical trial data sharing after 5 years

Joseph S. Ross[1,2,3,4], Joanne Waldstreicher[5], Stephen Bamford[6], Jesse A. Berlin[5], Karla Childers[5], Nihar R. Desai[4,7], Ginger Gamble[4], Cary P. Gross[1,2,4,8], Richard Kuntz[9], Richard Lehman[10], Peter Lins[5], Sandra A. Morris[5], Jessica D. Ritchie[4] & Harlan M. Krumholz[2,3,4,7]

Received: 28 March 2018
Accepted: 24 October 2018
Published: 27 November 2018

The Yale University Open Data Access (YODA) Project has facilitated access to clinical trial data since 2013. The purpose of this article is to provide an overview of the Project, describe key decisions that were made when establishing data sharing policies, and suggest how our experience and the

Yoda Publications

First Author	Publication Title	Journal	Year	Publication ID	Cited by:
Fu, R	Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis.	*Ann Intern Med*	2013	doi:10.7326/0003-4819-158-12-201306180-00006	299
Simmonds, MC	Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: a meta-analysis of individual-participant data.	*Ann Intern Med*	2013	doi:10.7326/0003-4819-158-12-201306180-00005	233
Laurie, AL	Meta-analysis of the Impact of Patient Characteristics on Estimates of Effectiveness and Harms of Recombinant Human Bone Morphogenetic Protein-2 in Lumbar Spinal Fusion.	*Spine*	2016	doi:10.1097/BRS.0000000000001580	3
Noshchenko, A	What Is the Clinical Relevance of Radiographic Nonunion After Single-Level Lumbar Interbody Arthrodesis in Degenerative Disc Disease? A Meta-Analysis of the YODA Project Database.	*Spine*	2016	doi:10.1097/BRS.0000000000001113	5
Mospan, GA	5-Day versus 10-Day Course of Fluoroquinolones in Outpatient Males with a Urinary Tract Infection (UTI).	*J Am Board Fam Med*	2016	doi:10.3122/jabfm.2016.06.160065	4
Storgaard, H	Benefits and Harms of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis.	*PLoS One*	2016	doi:10.1371/journal.pone.0166125	37
Gay, HC	Feasibility, Process, and Outcomes of Cardiovascular Clinical Trial Data Sharing: A Reproduction Analysis of the SMART-AF Trial.	*JAMA Cardiol*	2017	doi:10.1001/jamacardio.2017.3808	6
Corbett, M	Certolizumab pegol and secukinumab for treating active psoriatic arthritis following inadequate response to disease-modifying antirheumatic drugs: a systematic review and economic evaluation.	*Health Technol Assess*	2017	doi:10.3310/hta21560	4
Mbuagbaw, L	Review of available evidence on the use of bedaquiline for the treatment of multidrug-resistant tuberculosis: Data analysis report; Appendix to A 2016 review of available evidence on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis.	World Health Organization	2017	Report No. WHO/HTM/TB/2017.01	2
Wang, R	Comparative Efficacy of Tumor Necrosis Factor-alpha Inhibitors in Ankylosing Spondylitis: A Systematic Review and Bayesian Network Metaanalysis.	*J Rheumatol*	2018	doi:10.3899/jrheum.170224	1
Schneider-Thoma J	Second-generation antipsychotic drugs and short-term mortality: a systematic review and meta-analysis of placebo-controlled randomised controlled trials.	*Lancet Psychiatry*	2018	doi: 10.1016/S2215-0366(18)30177-9	1
Singh, S	Impact of Obesity on Short- and Intermediate-Term Outcomes in Inflammatory Bowel Diseases: Pooled Analysis of Placebo Arms of Infliximab Clinical Trials.	*Inflamm Bowel Dis*	2018	doi:10.1093/ibd/izy135	
Singh, S	No Benefit of Concomitant 5-Aminosalicylates in Patients With Ulcerative Colitis Escalated to Biologic Therapy: Pooled Analysis of Individual Participant Data From Clinical Trials.	*Am J Gastroenterol*	2018	doi:10.1038/s41395-018-0144-2	
Singh, S	Obesity and Response to Infliximab in Patients with Inflammatory Bowel Diseases: Pooled Analysis of Individual Participant Data from Clinical Trials.	*Am J Gastroenterol*	2018	doi:10.1038/s41395-018-0104-x	
Zou, X	The role of PANSS symptoms and adverse events in explaining the effects of paliperidone on social functioning: a causal mediation analysis approach.	*NPJ Schizophrenia*	2018	doi:10.1038/s41537-018-0054-8	
Spertus, J	Risk of weight gain for specific antipsychotic drugs: a meta-analysis.	*NPJ Schizophrenia*	2018	doi:10.1038/s41537-018-0053-9	

Academic Institutions

- **Academic institutions supportive of platforms**
  - Yale- YODA (Johnson & Johnson, Medtronic Inc.)
  - DCRI- SOAR (BMS)
  - UCSF/Harvard- Vivli

Despite these efforts, no academic institution has an Open Science policy

Data Sharing Policies Among Top Research Institutions

Institution	Has Policy for Sharing Clinical Trial Data	Requires Sharing	Offers support for sharing
UCSF	No	No	Yes
Johns Hopkins	No	No	Yes
Pennsylvania	No	No	Yes
Stanford	No	No	Yes
Washington University	No	No	Yes
Yale	No	No	Yes
Pittsburgh	No	Supportive	Yes
Duke	No	No	Yes
Columbia	No	No	Yes
Michigan	No	No	Yes
UCSD	No	Supportive	Yes
UCLA	No	Supportive	Yes
U. Washington	No	Supportive	Yes
UNC	No	No	Yes
Northwestern	No	No	Yes
Vanderbilt	No	No	Yes

Should academic institutions have an open science policy?

Rationale

- The scientific method depends on sharing
- As an institution charged with:
  - Caring for patients
  - Generating new knowledge
  - Training new generations of investigators
  - Educating the public
- An Open Science policy is necessary to
  - Maintain research integrity
  - Expand knowledge
  - Promote discovery in human health

Guiding Principles

- **Appropriate access** to research information, with a range of privacy controls depending on the nature of the study
- Proper **oversight** with **minimum barriers** to data access, to prevent against misuse of original data while promoting new discovery
- Maintaining **utility** of data, such that shared data can be used to generate new analyses
- The expectation that results of shared data will similarly be **shared**
- **Acknowledgment** of those who contribute original data

Directly address recognition

Problem: Data sharing is not a traditional measure of academic success

Potential Solutions:

- Incentives:
  - APT- data sharing incorporated into decision process
  - Citation of data sets via unique identifiers (DOIs)
  - Tracking use and products of shared data
  - Recognition tailored to data utility

Case Study #3

- Its 2020 & a large clinical trial is completed
  - First of its kind
  - Largest ever
  - Published in NEJM
  - High interest in the field
- Young faculty member is the CC PI
  - *Friendly* advice from a colleague
    - "You should share everything. That trial will make your career…"
- Rapid promotion due to the multiple citations
- Rapid funding for the next series of studies

Conclusions

Open science remains an important goal to build trust and expand knowledge.

Value is largely unrealized.

We are very far from an ideal state.

Direct incentives need to change for open science to thrive.