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

Value

Outcome

Reference point

Gains

Collaboration Science

Losses

Control

Credit
Have we earned or lost trust?
Benefits vs. Risks

RIGOR MORTIS

How sloppy science undermines tomorrow's medicine

RICHARD HARRIS
Good News: In Doctors, we trust

A majority of U.S. adults say medical doctors care about their patients’ interests all or most of the time

% of U.S. adults who say the following about medical doctors

<table>
<thead>
<tr>
<th>Overall view of medical doctors</th>
<th>Mostly positive</th>
<th>Neither</th>
<th>Mostly negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>74</td>
<td>18</td>
<td>8</td>
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</tbody>
</table>

Medical doctors do each of the following...

<table>
<thead>
<tr>
<th>Medical doctors do each of the following...</th>
<th>All or most of the time</th>
<th>Some of the time</th>
<th>Only a little/none of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Care about the best interests of their patients</td>
<td>57</td>
<td>33</td>
<td>9</td>
</tr>
<tr>
<td>Do a good job providing recommendations</td>
<td>49</td>
<td>42</td>
<td>9</td>
</tr>
<tr>
<td>Provide fair and accurate information</td>
<td>48</td>
<td>43</td>
<td>9</td>
</tr>
<tr>
<td>Are transparent about conflicts of interest</td>
<td>15</td>
<td>50</td>
<td>33</td>
</tr>
<tr>
<td>Admit mistakes and take responsibility</td>
<td>12</td>
<td>46</td>
<td>41</td>
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Problem of professional misconduct

<table>
<thead>
<tr>
<th>Problem of professional misconduct</th>
<th>Very big problem</th>
<th>Moderately big problem</th>
<th>Small problem</th>
<th>Not a problem</th>
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Face serious consequences for misconduct

<table>
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<tr>
<th>Face serious consequences for misconduct</th>
<th>All or most of the time</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>20</td>
<td>50</td>
<td>30</td>
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Pew Research Center, August 2019, “Trust and Mistrust in Americans’ Views of Scientific Experts
Bad News: In researchers, we trust some of the time

About four-in-ten Americans say medical researchers do a good job all or most of the time

<table>
<thead>
<tr>
<th>% of U.S. adults who say the following about medical research scientists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall view of medical research scientists</td>
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<tr>
<td>Mostly positive</td>
</tr>
<tr>
<td>68</td>
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Medical research scientists do each of the following ...

<table>
<thead>
<tr>
<th>Do a good job conducting research</th>
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<td>All or most of the time</td>
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<td>43</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Care about the best interests of the public</th>
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<tr>
<td>All or most of the time</td>
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<table>
<thead>
<tr>
<th>Provide fair and accurate information</th>
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<td>All or most of the time</td>
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<td>32</td>
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<tbody>
<tr>
<td>Very big problem</td>
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<td>14</td>
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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, the company’s executive, tried to reassure investors that Novartis did not intentionally deceive the F.D.A. while seeking approval for its $5 million gene therapy.

Novartis CEO Vas Narasimhan on Wednesday defended his company’s decision to wait three months to tell authorities about falsified data 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

IN SCIENTISTS WE TRUST

Confidence in researchers among adults in the United States has been on the rise since 2016, and is on a par with public trust in the military.

- A great deal
- A fair amount

<table>
<thead>
<tr>
<th></th>
<th>2016</th>
<th>2019</th>
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</thead>
<tbody>
<tr>
<td>Scientists</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>The military</td>
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<td>70</td>
</tr>
<tr>
<td>Religious leaders</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>The news media</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>Elected officials</td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>

US adults who have a great deal or fair amount of confidence in a group to act in the best interests of the public (%)
So, what are the incentives?
Easy...

Just ask Kevin Weinfurt to think about something
Stakeholders in Data Sharing and their Relevant Values

Public
- Speed of scientific discovery
- Knowledge and access to treatment
- Trust & transparency

- FDA
- OHRP
- Regulatory
- *Human safety
- More, quality data for label decisions
- Allow access to effective treatments
- Compliance

- Institutions
- IRBs
- APT Council
- Attraction/retention of best talent
- Reputation/impact
- Avoid liability
- Financial security

- Federal (NIH)
- Commercial (Pharma)
- Data integrity
- Reputation/impact
- ROI: scientific impact vs. $$$

- Advocacy Groups
- Sponsors
- Data integrity
- Reputable
- ROI: $$$

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- Journal
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- Integrity of data
- Financial solvency
- More high quality data
- Trust & privacy

- Consumers
- Payers
- Patients
- Providers
- Health Systems
- Data User
- Data Source
- Data integrity
- Privacy
- Proprietary information

- Researchers
- Primary
- Secondary
- Recognition
- Promotion
- Compliance with external policies
- Efficiency of new analyses
- Data access

- Generation of new science

- Students
- Advance learning through use of real data sets
- Teachers
- More research on a given priority

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Commercial (Pharma)
- Data integrity
- Reputation/impact
- ROI: $$$

Participants
- Trust/
- Transparency
- Privacy
- Positive impact

Platforms
- Vendors

ROI: $$$

Consumers
- Payer
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**Sponsors**
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**Institutions**
- IP, licensing, ventures
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**Consumers**
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  - Data integrity
- Data User

**Students**
- Advance learning through use of real data sets
Congrats!
You have a magic wand!
What incentives would need to be changed?
Current and future vectors of influence

Public

- Transparency & Trust
- Scientific discovery
- Access to more effective treatments

Regulatory
FDA
OHRP
Federal regulation

Sponsors
Federal (NIH)
Commercial (Pharma)

Researchers

YODA, SOAR, Vivli

Institutions
Council

IP, licensing, ventures
APT

Cost and availability

Promotion decisions

Participants

Cost
Profit

Platforms
Vendors

Advocacy Groups

Journals

Publication eligibility

Access to funding

Primary
Secondary

Consumers

Patient Providers
Health Systems
Payers

Federal regulation

Access to data, collaboration, integrity

Current and future vectors of influence
A Reaction: Holy Complicated
What’s been successful?
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.
“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
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).

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

- **Public access**: data available to the public.
- **Downloadable data**: data that can be downloaded.
- **Secure interface**: data accessed through a secure interface.
- **Independent Review Panel**: panel evaluates COIs and scientific relevance.
- **Analysis plan, including SAP required**: analysis plan and statistical analysis plan (SAP) are required.
- **IRB approval required**: institutional review board (IRB) approval is necessary.
- **Access restricted based on credentials of requestors**: access is based on the credentials of the requestors.
- **Access/ can veto requests**: contributors determine access or can veto requests.
- **Restricted access to certain data elements**: restricted access to specific data elements.
- **Contributors determine access**: contributors can determine access.

- **Project data sphere (PDS)**
- **ClinicalStudyDataRequest.com**
- **YODA**
- **AHA Precision Medicine Initiative**
- **Duke Data Service (DukeDS)**
- **Vivli**
- **SOAR**

**Open Access**

**Restricted Access**
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 Krumholz1,2,6

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 as 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 Sandesh 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 901 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?

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

- 3068
- 383 Phase 3/4
Use of Open Access Platforms for Clinical Trial Data

Concerns over bias in clinical trial reporting have stimulated calls for more open data sharing. 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
Overview and experience of the YODA Project with clinical trial data sharing after 5 years

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

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
<table>
<thead>
<tr>
<th>First Author</th>
<th>Publication Title</th>
<th>Journal</th>
<th>Year</th>
<th>Publication ID</th>
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<tr>
<td>Singh, S</td>
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<td><em>Inflamm Bowel Dis</em></td>
<td>2018</td>
<td>doi:10.1093/ibd/iiz135</td>
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<td>Zou, X</td>
<td>The role of PANSS symptoms and adverse events in explaining the effects of paliperidone on social functioning: a causal mediation analysis approach.</td>
<td><em>NPI Schizophrenia</em></td>
<td>2018</td>
<td>doi:10.1088/2050-6121/6/5/0054-8</td>
<td></td>
</tr>
</tbody>
</table>
• **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**
<table>
<thead>
<tr>
<th>Institution</th>
<th>Has Policy for Sharing Clinical Trial Data</th>
<th>Requires Sharing</th>
<th>Offers support for sharing</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCSF</td>
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<td>No</td>
<td>Yes</td>
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<tr>
<td>Johns Hopkins</td>
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<td>Pennsylvania</td>
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<tr>
<td>Pittsburgh</td>
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<td>Duke</td>
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<tr>
<td>Vanderbilt</td>
<td>No</td>
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Should academic institutions have an open science policy?
• 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
**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
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.