The Yale Open Data Access (YODA) Project: Lessons Learned in Data Sharing

Grand Rounds: A Shared Forum of the NIH HCS Collaboratory and PCORnet
June 30, 2017

Joseph S. Ross, MD, MHS
Section of General Internal Medicine, School of Medicine
Center for Outcomes Research and Evaluation, Yale-New Haven Hospital
Open Data, Open Science – Why?

Underreporting Research Is Scientific Misconduct

Iain Chalmers, FRCOG

Substantial numbers of clinical trials are never reported in print, and among those that are, many are not reported in sufficient detail to enable judgments to be made about the validity of their results. Failure to publish an adequate account of a well-designed clinical trial is a form of scientific misconduct that can lead those caring for patients to make inappropriate treatment decisions. Investigators, research ethics committees, funding bodies, and scientific editors all have responsibilities to reduce underreporting of clinical trials. An extended use of prospective registration of trials at inception, as well as benefiting clinical research in other ways, could help people to play their respective roles in reducing underreporting of clinical trials.

Trial Publication after Registration in ClinicalTrials.Gov: A Cross-Sectional Analysis

- Trials registered at CT.gov in 2000 onwards, completed as of June 2007 (≥ 2 years for all)
- 46% of trials published

<table>
<thead>
<tr>
<th>Trial Funder</th>
<th>Publication, %</th>
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</thead>
<tbody>
<tr>
<td>Industry</td>
<td>40</td>
</tr>
<tr>
<td>Non-government / Non-industry</td>
<td>56</td>
</tr>
<tr>
<td>Government (US and non-US)</td>
<td>47</td>
</tr>
</tbody>
</table>

Industry FDA Pivotal Trials

Within 2 years of approval:

• 86% of pivotal trials for new drug approvals published (2005-2011)

• 89% of pivotal trials for high-risk cardiovascular medical device approvals published (2011-2013)

Source: Smithy et al., JAMA IM 2014;174:1518-20; Phillips et. al., JAMA IM 2016;In press.
Trial Publication after Registration in ClinicalTrials.Gov: A Cross-Sectional Analysis

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<tr>
<td>US NIH</td>
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<td>56</td>
</tr>
<tr>
<td>non-US Government</td>
<td>57</td>
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</tbody>
</table>

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

46% published w/in 2 years, 68% overall

Source: Ross et al., BMJ 2012;344:d7292.
Publication and reporting of clinical trial results: cross sectional analysis across academic medical centers

Ruijun Chen,1 Nihar R Desai,2,3 Joseph S Ross,3,4,5,6 Weiwei Zhang,3 Katherine H Chau,1 Brian Wayda,7 Karthik Murugiah,8 Daniel Y Lu,9 Amit Mittal,1 Harlan M Krumholz2,3,5,6

ABSTRACT

OBJECTIVE
To determine rates of publication and reporting of results within two years for all completed clinical trials registered in ClinicalTrials.gov across leading academic medical centers in the United States.

DESIGN
Cross sectional analysis.

SETTING
Academic medical centers in the United States.

PARTICIPANTS
Academic medical centers with 40 or more completed interventional trials registered on ClinicalTrials.gov.

METHODS
Using the Aggregate Analysis of ClinicalTrials.gov database and manual review, we identified all interventional clinical trials registered on ClinicalTrials.gov with a primary completion date between October 2007 and September 2010 and with a lead investigator affiliated with an academic medical center.

MAIN OUTCOME MEASURES
The proportion of trials that disseminated results, defined as publication or reporting of results on ClinicalTrials.gov, overall and within 24 months of study completion.

RESULTS
We identified 4347 interventional clinical trials across 51 academic medical centers. Among the trials, 1005 (23%) enrolled more than 100 patients, 1216 (28%) were double blind, and 2169 (50%) were phase II through IV. Overall, academic medical centers disseminated results for 2892 (66%) trials, with 1560 (35.9%) achieving this within 24 months of study completion. The proportion of clinical trials with results disseminated within 24 months of study completion ranged from 16.2% (6/37) to 55.3% (57/103) across academic medical centers. The proportion of clinical trials published within 24 months of study completion ranged from 10.8% (4/37) to 40.3% (31/77) across academic medical centers, whereas results reporting on ClinicalTrials.gov ranged from 1.6% (2/122) to 40.7% (72/177).

CONCLUSIONS
Despite the ethical mandate and expressed values and mission of academic institutions, there is poor performance and noticeable variation in the dissemination of clinical trial results across leading academic medical centers.

Introduction
Randomized clinical trials are the ideal means for evaluating the efficacy and safety of medical drugs and devices. Timely dissemination of the findings from clinical trials is a prerequisite for ensuring that clinical decisions made by patients and physicians reflect the best scientific evidence, and that future scientific investigation benefits from previous inquiry. Dissemination is principally achieved through publication in peer reviewed biomedical journals as well as through public reporting of results on clinical trial registries.4,5 However, a large body of research found that between 25% and 50% of clinical trials remain unpublished for times years after study completion.4,5 Similar studies have shown that the results of many clinical...
Publication and reporting of clinical trial results: cross sectional analysis across academic medical centers

36% published or reported results w/in 2 years, 66% overall

Source: Ross et al., BMJ 2012;344:d7292.
Publication and reporting of clinical trial results: cross sectional analysis across academic medical centers

51 AMCs, range 16% - 55%

Source: Chen et al., BMJ 2016;352:i637.
• ~50% of clinical trials are never published
• Even when published, limited portion of collected data is reported
  – Particularly safety details
• Patients and physicians frequently make treatment decisions based on a fraction of potentially available clinical data

Why Share Data?

- Promotes data transparency, potential to lead to better informed clinical decisions
- Positions research as a public good
- Respects contributions of participants:
  - maximizing value of collected data, while
  - minimizing duplicative data collection
- Facilitates secondary studies of existing data
- Promotes reproducibility:
  - sample, design, and analysis
Did Medtronic sell an unsafe product?

Article by: JANET MOORE, Star Tribune  |  Updated: November 14, 2011 - 6:04 PM

Under fire, the company looks to a top researcher to answer questions about its big seller Infuse.

Why Share Data?

How to Share Data?
YODA Project
A Model for Dissemination and Independent Analysis of Industry Data

Source: Krumholz and Ross, JAMA 2011;306:1593-4.
Medtronic Partnership

- Initiated in 2011
- Patient-level data for 17 rhBMP-2 clinical trials
- Large effort devoted to 2 independent reviews
- Data access policy established with Steering Cmte, experts, stakeholders, public comment input
- Required registration, public reporting, publication
- Designed to:
  - Ensure high quality evidence reviews,
  - Provide public assurance via independent review, and
  - Facilitate external investigator access to data
A Historic Moment for Open Science: The Yale University Open Data Access Project and Medtronic

The Changing Structure of Industry-Sponsored Clinical Research: Pioneering Data Sharing and Transparency

Closing in on the Truth About Recombinant Human Bone Morphogenetic Protein-2: Evidence Synthesis, Data Sharing, Peer Review, and Reproducible Research

Meta-analysis of Trials of Recombinant Human Bone Morphogenetic Protein-2: What Should Spine Surgeons and Their Patients Do With This Information?
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

Andriy Noshchenko, PhD, Emily M. Lindley, PhD, Evalina L. Burger, MD, Christopher M. J. Cain, MD, and Vikas V. Patel, MA, MD

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

Amber L. Laurie, MS,* Yiyi Chen, PhD,* Roger Chou, MD,1 and Rongwei Fu, PhD,*1
In Stunning Win For Open Science, Johnson & Johnson Decides To Release Its Clinical Trial Data To Researchers
Principles of the YODA Project

• Promote sharing of clinical research data to advance science and improve public health and healthcare
• Promote responsible conduct of research
• Ensure good stewardship of clinical research data by external investigators
• Protect rights of research participants
Johnson & Johnson Partnership

• No independent reviews – focused on providing access to clinical trial data:
  – All pharmaceutical products (including historical)
  – Device and diagnostic products from 2014 onward

• Revised data access policy, established clear procedures, with input from Steering Cmte, experts, stakeholders, and public comment

• Continue to require application, registration, public reporting, publication

• YODA Project website provides info on trial and supporting documentation
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy

PRODUCT INFO

- **Generic Name**: Abiraterone acetate
- **Product Name**: ZYTiga®
- **Therapeutic Area**: Cancers and Other Neoplasms
- **Enrollment**: 1,135

SUPPORTING DOCUMENTATION

- Analysis Datasets
- Annotated Case Report Form (CRF)
- Clinical Study Report
- Collected Datasets
- Data Definition Specification
- Protocol with Amendments
- Statistical Analysis Plan

APPROVED DATA REQUESTS ASSOCIATED WITH THIS TRIAL
- Investigator name, affiliation, co-investigators
- Research proposal, including background, study design, main outcomes, statistical analysis plan
- COI statement
• Once approved, require signed DUA
• Investigators gain access to data maintained on secure platform, via VPN
• Prevents distribution, protects patient privacy
**Number of Data Requests Submitted**

*As of April 1, 2017*
- Public reporting of approved requests, submitted proposals, results of project
- Thus far, 5 completed projects, 3 under peer-review
RESEARCH ARTICLE

Benefits and Harms of Sodium-Glucose Co-Transporter 2 Inhibitors in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

Heidi Storgaard¹, Lise L. Gluud², Cathy Bennett³, Magnus F. Grøndahl¹, Mikkel B. Christensen¹, Filip K. Knop¹,⁵,⁶, Tina Vilsbøll¹,⁵

ORIGINAL RESEARCH

5-Day versus 10-Day Course of Fluoroquinolones in Outpatient Males with a Urinary Tract Infection (UTI)

Geoffrey A. Mospan, PharmD, BCPS, and Kurt A. Wargo, PharmD, FCCP, BCPS (AQ-ID)
Data Requestor Affiliation

*As of April 1, 2017

<table>
<thead>
<tr>
<th>Quarter</th>
<th>2014-Q4</th>
<th>2015-Q1</th>
<th>2015-Q2</th>
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<th>2015-Q4</th>
<th>2016-Q1</th>
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<td>67%</td>
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<td>80%</td>
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*As of April 1, 2017
Number of Data Requests Requiring Revisions during Review

Thus far, one has Required External Review

*As of April 1, 2017

Revisions during YODA Project review

<table>
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<tr>
<th>Quarter</th>
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<th>External Review</th>
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<td>1</td>
</tr>
<tr>
<td>2017-Q1</td>
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<td>0</td>
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</table>

n=8, n=3, n=6, n=5, n=7, n=9, n=9, n=7, n=6
Specific Products Requested
Number of Trials Requested among All Data Requests

*As of April 1, 2017*
Conditions Studied
Number of Trials Requested among All Data Requests

*As of April 1, 2017
Specifics of Approved Data Requests

*As of April 1, 2017*

**Type of Data Requested in Approved Data Requests (n=60)**
- Cumulative: 92%
  - Full CSR only: 8%
  - IPD: 84%

**Number of Trials Requested in Approved Data Requests (n=60)**
- Cumulative: 100%
  - 8+ trials: 35%
  - 5-7 trials: 33%
  - 2-4 trials: 20%
  - 1 trial: 2%

**Type of Products Requested within Requests for Multiple Trials (n=41)**
- Cumulative: 100%
  - Different products, different TA: 17%
  - Different products, same TA: 20%
  - Same product: 63%
Data Request Status

*As of April 1, 2017

<table>
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<tr>
<th>Status</th>
<th>Percentage</th>
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<tr>
<td>Incomplete with results reported</td>
<td>4%</td>
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<tr>
<td>Complete with results reported</td>
<td>3%</td>
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<tr>
<td>Data access granted</td>
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<tr>
<td>Approved with signed DUA</td>
<td>1%</td>
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<tr>
<td>Approved pending signed DUA</td>
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<tr>
<td>Under review</td>
<td>7%</td>
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<tr>
<td>Withdrawn/closed</td>
<td>9%</td>
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2017 - Q1
n=68
Data Request Response Time

* Reflects time to decision of whether to approve or to request additional clarification.

*As of April 1, 2017
### YODA Project Inquiry Summary

<table>
<thead>
<tr>
<th>Category</th>
<th>Count/Percent</th>
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</thead>
<tbody>
<tr>
<td>Total inquiries, No.</td>
<td>104</td>
</tr>
<tr>
<td>Total inquiries answered to date, No. (%)</td>
<td>100 (96.2)</td>
</tr>
<tr>
<td>Inquiry led to full data request, No. (%)</td>
<td>10 (10.0)</td>
</tr>
<tr>
<td>Median number of days for response to inquiry</td>
<td>14</td>
</tr>
<tr>
<td>Total unique trials requested within answered inquiries, No.</td>
<td>162</td>
</tr>
<tr>
<td>Trial data can be made “available” to request, No. (%)</td>
<td>100 (61.7)</td>
</tr>
<tr>
<td>Trial data cannot be made “available” to request,** No. (%)</td>
<td>62 (38.3)</td>
</tr>
<tr>
<td>Regulatory approval not yet received, No. (%)</td>
<td>9 (14.5)</td>
</tr>
<tr>
<td>Trial ongoing or completed &lt;18 months ago, No. (%)</td>
<td>16 (25.8)</td>
</tr>
<tr>
<td>Data cannot be adequately de-identified, No. (%)</td>
<td>–</td>
</tr>
<tr>
<td>Partner of Data Holder has not agreed to share, No. (%)</td>
<td>8 (12.9)</td>
</tr>
<tr>
<td>Trial is out of scope (i.e., Phase 1, OTC, etc.), No. (%)</td>
<td>25 (40.3)</td>
</tr>
<tr>
<td>Data subject to partner agreement; researcher advised to contact partnering Data Holder, No. (%)</td>
<td>2 (3.2)</td>
</tr>
<tr>
<td>Data cannot be converted to electronic format, No. (%)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Trial materials not available in English, No. (%)</td>
<td>4 (6.5)</td>
</tr>
</tbody>
</table>

*As of June 1, 2017*
Trial Inquiries

*As of April 1, 2017

*Trials available

*Trials not available

*For the YODA Project - Forging a unified scientific community
Reasons for Unavailable Trials

*As of April 1, 2017

- Data subject to partner agreement; researcher advised to contact partner (n=2)
- Data cannot be converted to electronic format (n=1)
- Materials are not available in English (n=4)
- Trial is out of scope (i.e., Phase 1, OTC, etc.) (n=20)
- Data Holder partner hasn’t agreed to share (n=8)
- Data cannot be de-identified (n=0)
- Trial completed < 18 mo. ago or ongoing (n=16)

*As of April 1, 2017
Inquiry Response Time

*As of April 1, 2017

Cumulative
n=73

# of Days
Recommendations

1. “Stakeholders should foster a culture in which data sharing is the expected norm, and should commit to responsible strategies aimed at maximizing benefits, minimizing risks, and overcoming challenges of sharing trial data”

2. Clarified specific points in time by which various types of data are reported/shared

3. Data Holder strategies:
   1. Data Use Agreement
   2. Independent panels, including lay public
   3. Transparency
   4. Monitor “outcomes”

4. More work to be done, need to address key infrastructure, technological, sustainability, and workforce challenges ahead

Source: Institute of Medicine report, January 2015.
Clinical trials will require the following as conditions of consideration for publication:

• As of 1 July 2018, manuscripts must contain a data sharing statement
  – whether deidentified IPD will be shared, extent of data;
  – whether additional, related documents will be available (e.g., study protocol, SAP, etc.);
  – when data will be available and for how long;
  – by what access criteria data will be shared

• Trials that begin enrolling participants on or after 1 January 2019 must include a data sharing plan in the trial's registration

This section of the site provides information on study sponsor's criteria for listing studies and other relevant sponsor specific information.

Select the sponsor's logo to view this information.
How YODA Project is Different

• Not our data
• Independent third party without interests, removing perception of influence over access
• YODA Project has full jurisdiction to make decisions regarding data access
• Policies and procedures established via public comment in the best interests of:
  – Scientific profession and investigators
  – Patients and research subjects
  – Data Holders / Partners
Micro Challenges Ahead

• Creating a platform that facilitates research
  – What trials are or can be made available?
  – What meta-data are needed: CRFs, protocol, SAPs?

• Engaging research community to use data

• Resources are not unlimited – fee?

• Patient privacy, secure data analytic platform – how easy can it be?

• Maintaining public input, transparency

• Scope and intensity of review

• Data Use Agreements
Macro Challenges Ahead

• Large pharmaceutical companies far ahead
  – What about mid-size, small biotech?
  – What about medical device companies?
  – What about academics?

• Linking data sharing platforms

• Dream of automated meta-analyses – will we ever get there?
VITAL DIRECTIONS FROM THE NATIONAL ACADEMY OF MEDICINE

Data Acquisition, Curation, and Use for a Continuously Learning Health System

Health-related data and research data are vital resources for clinical care, informed clinical choice, quality improvement, drug and device safety, effectiveness assessments, and scientific discovery. Such data are the raw materials that can be used to produce information to support personal choices about health care, system choices about optimizing medical and public health strategies, and policy choices about current and future laws and regulations. Data provide the necessary ingredients for medical breakthroughs.

Sharing, curation, and use of data for a continuously learning health system hold great potential to better engage people in their health and health care. Initially introduced by the Institute of Medicine, a learning health system is described by the Office of the National Coordinator for Health Information Technology (ONC) as an ecosystem in which all stakeholders can contribute, share, and analyze data and where continuous learning cycles encourage the creation of new knowledge that can be used by a variety of health information systems. In part, the difficulty to fully leverage relevant data, encouraging individuals’ access to their data by clarifying individuals’ rights to their data. This will require the creation of the tools and infrastructure needed for patients to own their data to work for them—and may also require regulatory changes. A final vital direction is developing seamless means to synthesize data from disparate sources. Priority considerations in promoting these vital directions therefore include those that follow.

- Foster a culture of data sharing. For data sharing to become more common, the culture of healthcare, public health, and medical science will need to evolve such that refusing to share is understood as counter to the best interests of individuals and society. There should be a broad appreciation for an individual’s right to access and share his or her own health data. In research, there should be expectations that good science and good scientific citizenship require that participant-level data be available for evaluation and reuse. Incentives should be aligned to reflect that culture. It will be important to create support and rewards for sharing data and penalties for not sharing data. Financial incentives should reward health systems that facilitate data sharing, companies with data-sharing programs, and vendors with interoperability features. Academic promotion could consider data sharing and downstream use of the shared data. Metrics on ease of data accessibility at the health system, hospital, or office level should be publicly reported.

Recent Progress on Health Data Access and Use

In recent years, policy makers, organizations, and individuals have advanced efforts to promote the culture and infrastructure needed to support the secure accessibility of health and health care data. For example, the companies that are part of the Pharmaceutical Research and Manufacturers of America have committed to sharing their data. The International Committee of Medical Journal Editors released a proposal stating the belief that there is “an ethical obligation to responsibly share data generated by intervention trials.” The promulgation of common standards, implementation of appropriate legislation and regulations, growth of public activism regarding health information, and technological advancements have speeded changes in expectations and capabilities. Funders are increasingly making support contingent on data sharing. Agencies such as the National Institutes of Health and the Patient Centered Outcomes Research Institute and private foundations including the Wellcome Trust and the Bill & Melinda Gates Foundation have mandated forms of data sharing as a condition of funding. On the clinical side, companies that provide 30% of the country’s electronic health records and several large health systems have signed the ONC interoperability pledge and committed to consumer access, no blocking/enhancing transparency, and standards.

Summary Recommendations for Vital Directions

To enable data to fuel a learning health system, progress is important across several domains. Change is needed in the culture and incentive structures of the health system to move away from a status quo with little opportunity for data sharing. Barriers to digital health data sharing create inefficiencies and errors that cost lives and resources. Strategically important in this respect is encouraging individuals’ access to their data by clarifying individuals’ rights to their data. This will require the creation of the tools and infrastructure needed for patients to own their data to work for them—and may also require regulatory changes. A final vital direction is developing seamless means to synthesize data from disparate sources. Priority considerations in promoting these vital directions therefore include those that follow.

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- Create the operational functionality for data sharing. The first step in this respect is for government to
Objectives Remain Clear

• Facilitate greater access to clinical trial data, increasing transparency and accelerating generation of new knowledge, while promoting responsible conduct of research

• Better inform patients, clinicians, and industry so that decisions can be based on the most comprehensive and contemporary evidence available relevant to benefits and harms of therapies