Yale University
Open Data Access Project

A Model for Dissemination and Independent Analysis of Clinical Trial Program Data

Yale University
Center for Outcomes
Research and Evaluation

Funded by a contract with Medtronic, Inc.

Session Objectives

- Why do we need to promote data sharing?
- What is the YODA Project model?
- How was the model recently implemented?
- What are some remaining challenges to sharing data?

Rationale

- **A substantial number of clinical trials are conducted, but never published**

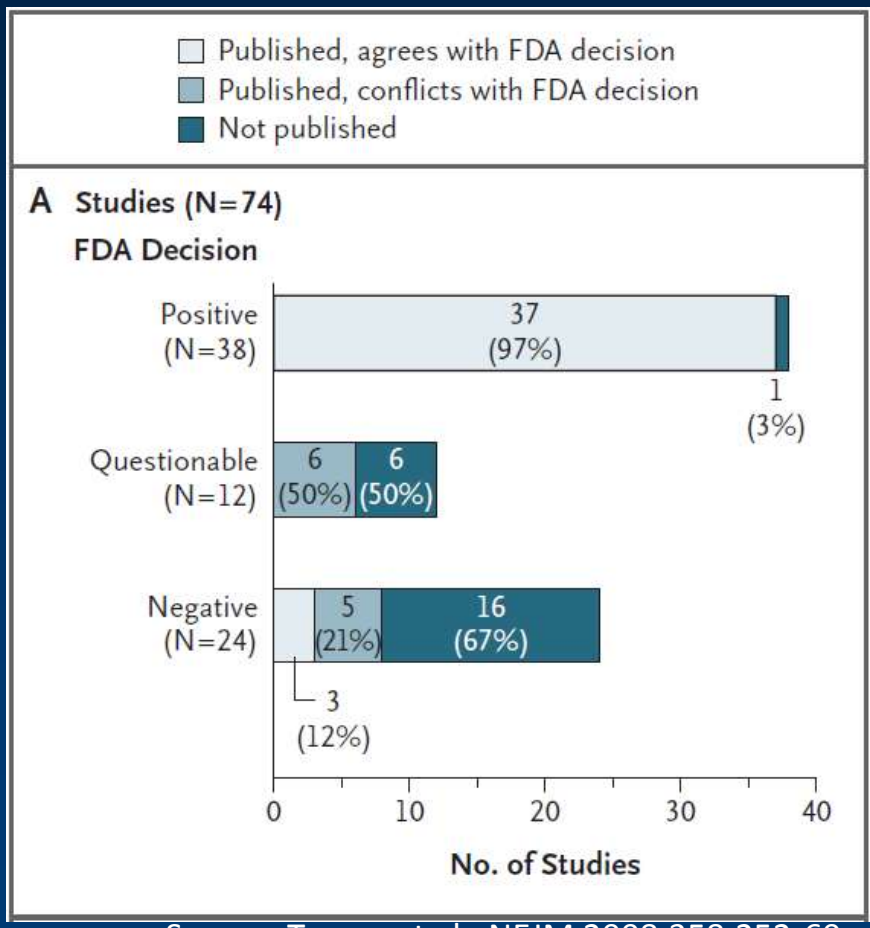
The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Table 1. Overall Publication Status of FDA-Registered Antidepressant Studies.

Publication Status	No. of Studies (%)	No. of Patients in Studies (%)
Published results agree with FDA decision	40 (54)	7,272 (58)
Published results conflict with FDA decision (published as positive)	11 (15)	1,843 (15)
Results not published	23 (31)	3,449 (27)
Total	74 (100)	12,564 (100)



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Source: Turner et al., NEJM 2008;358:252-60.

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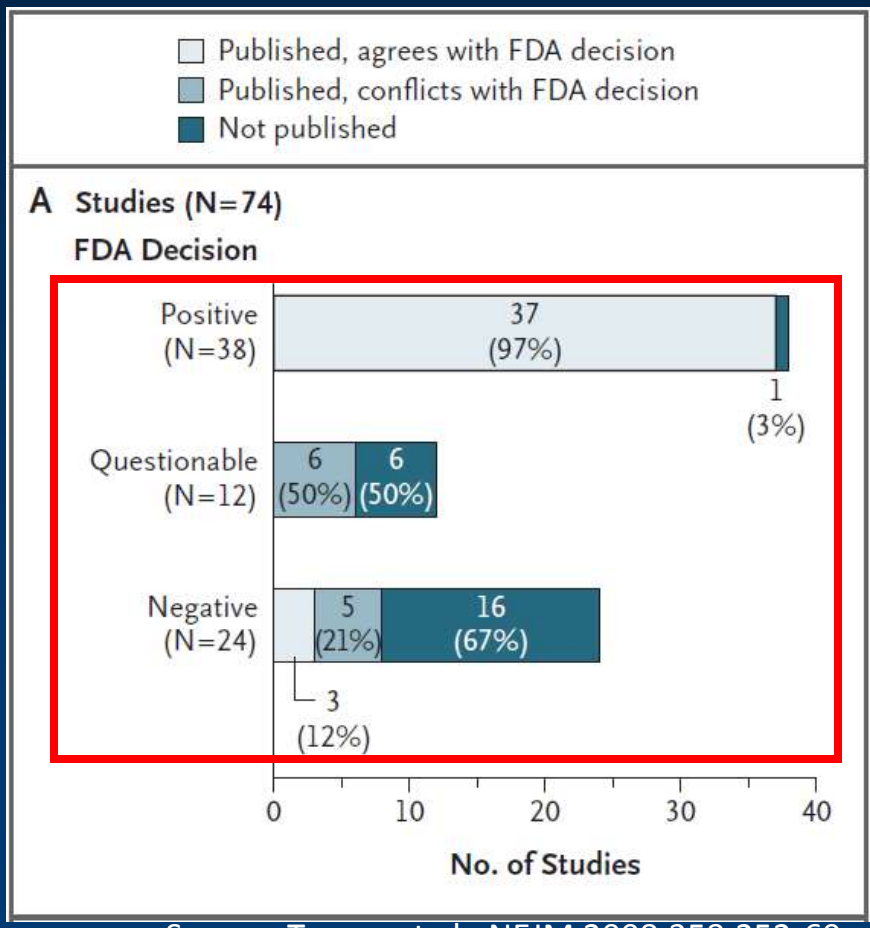

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Source: Turner et al., NEJM 2008;358:252-60.

OPEN ACCESS Freely available online PLoS MEDICINE

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

- 46% of trials published
- Least likely to be published
  - Industry-sponsored studies
  - Single arm trials

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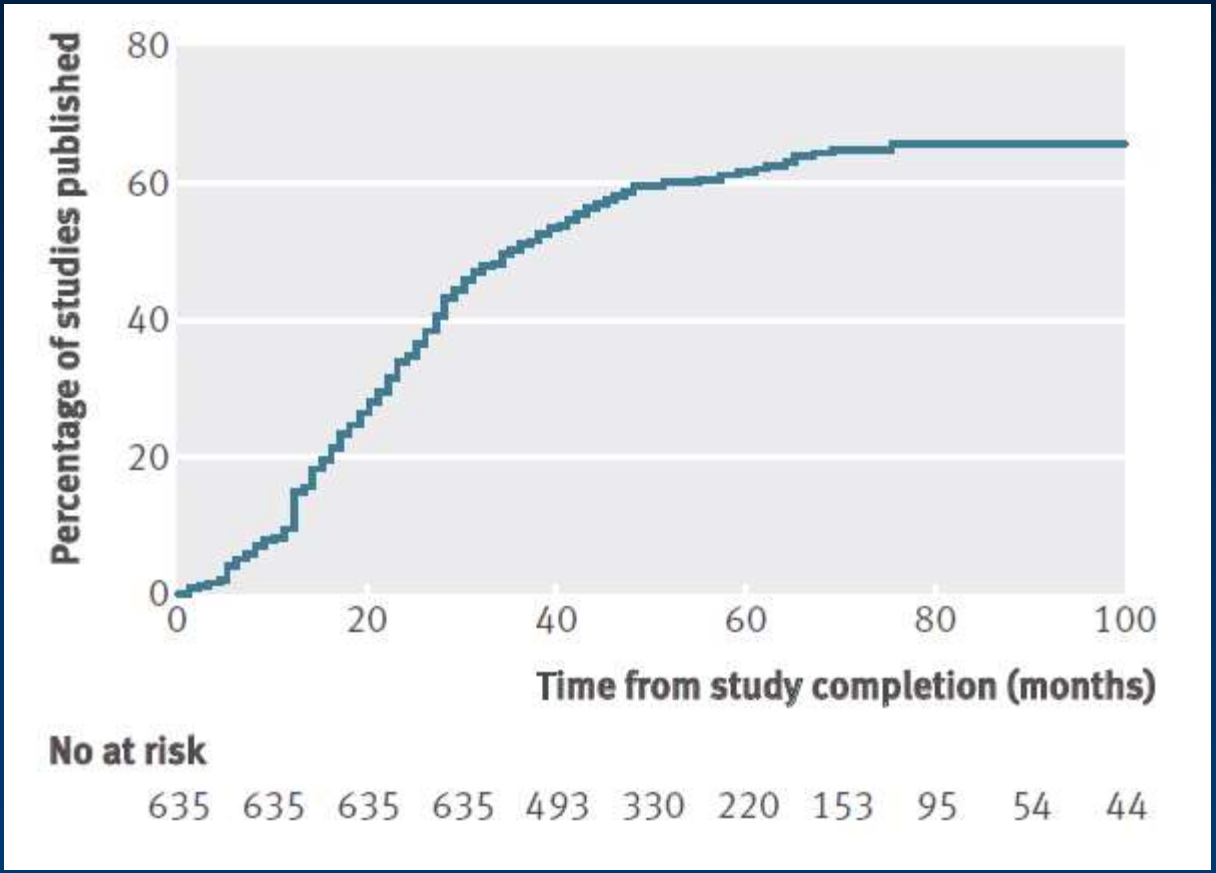
Source: Ross et al., PLoS Medicine 2009;6:e1000144.

NIH Funded Trials



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Source: Ross et al., BMJ 2012;344:d7292.

Rationale

- A substantial number of clinical trials are conducted, but never published
- **Even among published trials, a limited portion of the collected data is reported**
  - **Particularly relevant for safety information**

Reporting of Safety Results in Published Reports of Randomized Controlled Trials

- **89% of RCTs in high-impact journals described adverse events (11% did not)**
- **However,**
  - **27% no mention of severe adverse events**
  - **47% no mention of patient withdrawals due to adverse events**

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Source: Pitrou et al., Arch Intern Med 2009;169:1756-1761.

Rationale

- A substantial number of clinical trials are conducted, but never published
- Even among published trials, a limited portion of the collected data is reported
  - Particularly relevant for safety information
- **Thus, patients and physicians frequently make treatment decisions with access to only a fraction of clinical research data**

Focus on Industry

- **Issues relevant to clinical trials conducted both publicly and privately, but are particularly important among industry trials**
  - **Industry funds majority of clinical trial research about drugs, devices and other products, both pre-market and post-market**
  - **Industry research is proprietary, no requirement for publication or dissemination**
  - **Public perception: industry has a financial interest in promoting "supportive" research, not publishing rest**

Public Health Need

- Steps must be taken to align the interests of industry and the public, particularly when concerns arise about safety or effectiveness
- The public has a compelling interest in having the entirety of the data available for independent analysis
- Industry has legitimate concerns

Objectives of the YODA Project

- The project's goals are to
  - Promote clinical trial program data access
  - Increase transparency of ALL clinical research
  - Facilitate sharing of (industry) clinical trial research data
  - Accelerate generation of new knowledge

Objectives of the YODA Project

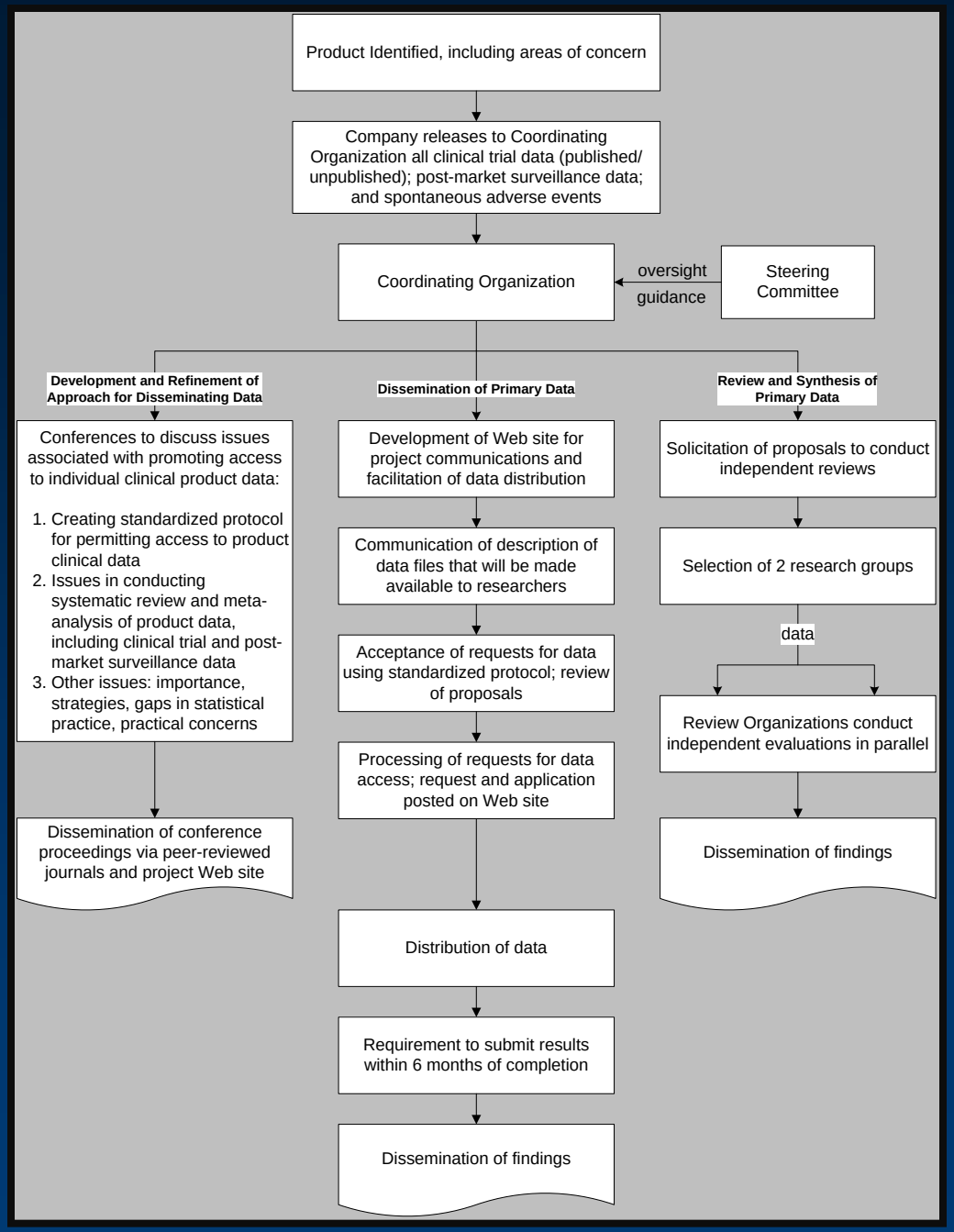
- **Patients, providers, and industry will be better informed**
  - **Access to independent assessment and dissemination of data relevant to the benefits and harms of industry products**
- **Physicians and patients can base their decisions on the most comprehensive and contemporary evidence available**

YODA Project Mission

- Promote open science
- Promote transparency
- Ensure good stewardship of clinical trial data
- Serve the needs of society
- Respect the legitimate concerns of industry

A Model for Dissemination and Independent Analysis of Industry Data

Designed to facilitate release of data, ensure high quality evidence reviews, and provide public with scrutiny of an independent review.



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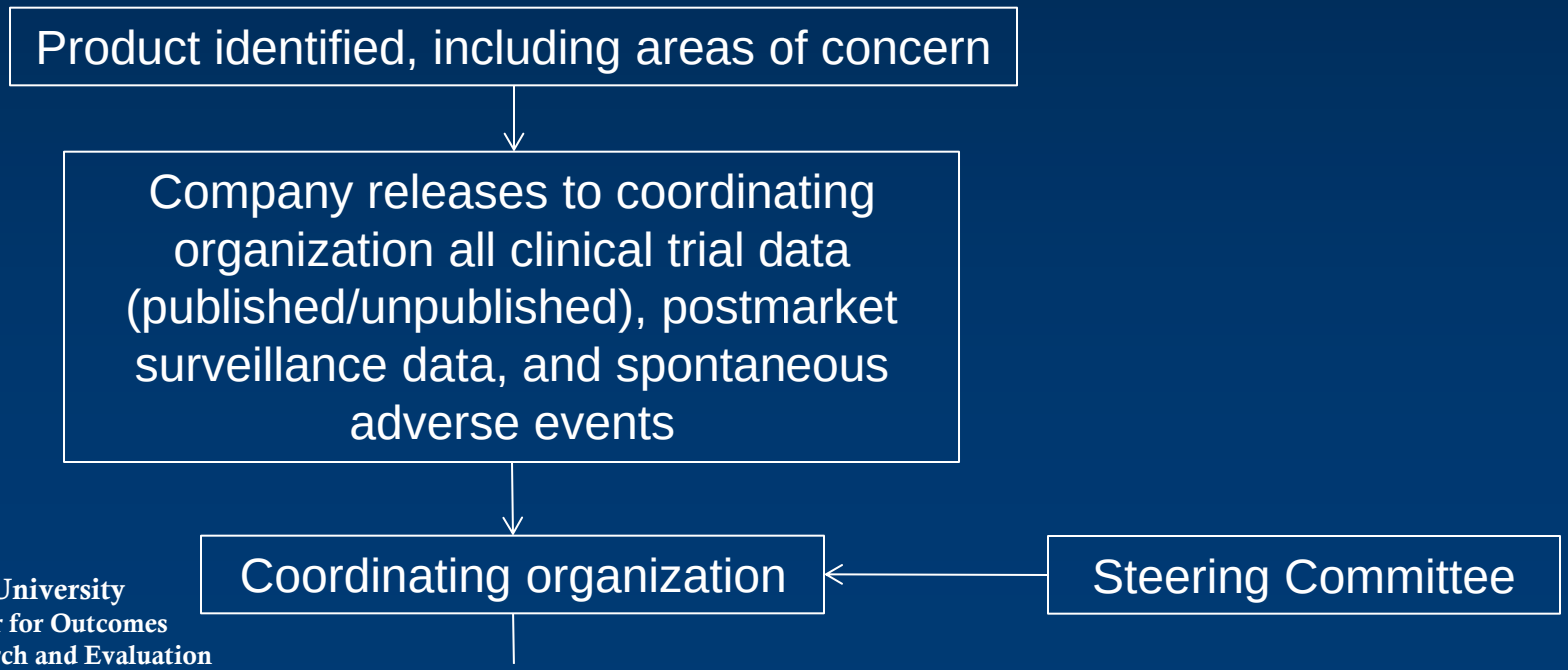
Source: Krumholz and Ross, JAMA 2011;306:1593-4.

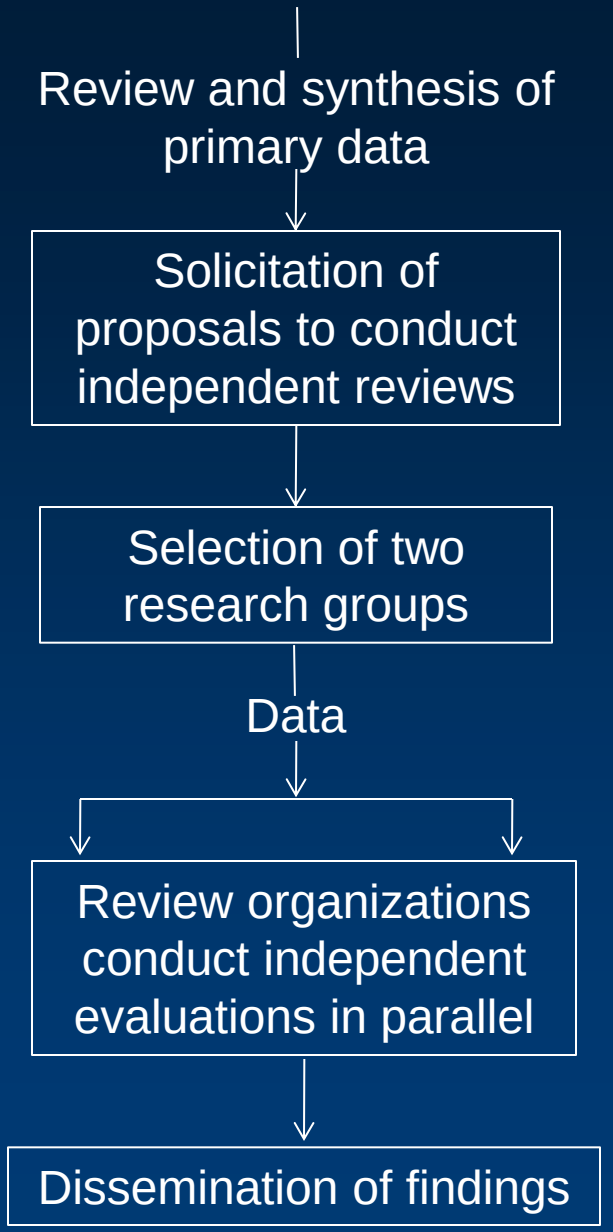
YODA Project Model

- **Begins with company release of data to coordinating organization**
- **Coordinating organization assembles independent steering committee for oversight**



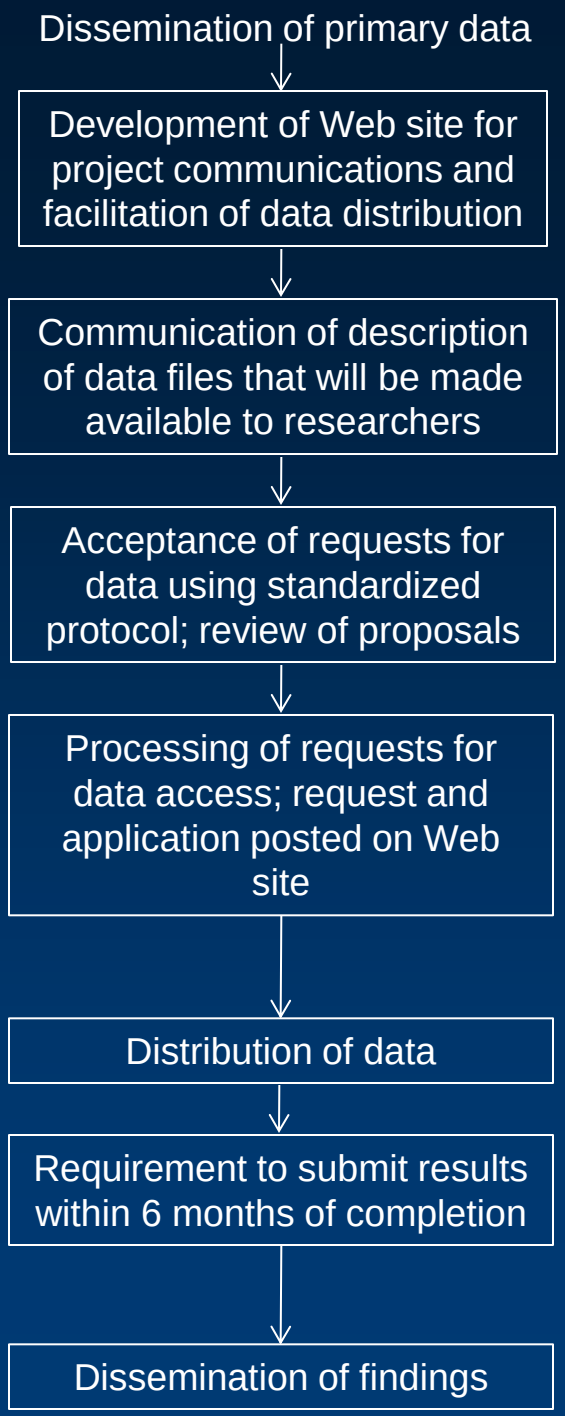
Formal Independent Analysis

- **Coordinating organization contracts with two research groups that independently systematically review and synthesize clinical trial data**
  - **Industry and non-industry research**
  - **Uses individual-level data, in addition to trial summary-level data**
- **Advantages:**
  - **Distance btw company & reviewers**
  - **Reproducibility and validity**



Data Dissemination

- **Coordinating organization makes industry's individual-level data available to other external researchers**
  - **Via a Web site, requiring a registration process, commitment to results reporting**
- **Advantages:**
  - **Complete transparency**



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rhBMP-2 (Infuse)

- **June 2011 issue of the Spine Journal devoted to critical reviews of rhBMP-2 studies**
  - **Complications**
  - **Financial COI**
  - **Marketing practices**

ELSEVIER

The Spine Journal 11 (2011) 471–491

THE SPINE JOURNAL

Review Article

A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned

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Received 18 February 2011; revised 5 April 2011; accepted 27 April 2011

- **Systematic review reassessing safety profile using**
  - **FDA summaries**
  - **Administrative databases**
  - **Subsequent peer-reviewed publications**

Original industry-sponsored rhBMP-2 clinical studies and reported adverse event rates because of rhBMP-2

Authors	rhBMP-2 Placement	rhBMP-2, n	rhBMP-2 Adverse events (%)	Authors comment regarding rhBMP-2–related observed adverse events in study patients
Boden et al. [2]	Anterior interbody (LT-cage, lumbar, rhBMP-2)	11	0	"There were no adverse events related to the rhBMP-2 treatment"
Boden et al. [3]	Posterolateral (lumbar, ± instrumentation)	20	0	"There were no adverse effects directly related to the rhBMP-2…"
Burkus et al. [5]	Anterior interbody (LT-cage, lumbar, INFUSE)	143*	0	"There were no unanticipated device-related adverse events…"
Burkus et al. [6]	Anterior interbody (bone dowel, lumbar, INFUSE)	[24]‡	0	"There were no unanticipated adverse events related to the use of INFUSE Bone Graft." (2002)
Burkus et al. [39]		79	0	None reported (2005)
Burkus et al. [40]	Anterior interbody (LT-cage, lumbar, INFUSE)	277	0	None reported
Baskin et al. [7]	Anterior interbody (cervical, INFUSE)	18	0	"There were no device-related adverse events"
Haid et al. [8]	Posterior interbody fusion (lumbar, INFUSE)	34	0	"No unanticipated device-related adverse events occurred"
Boakye et al. [41]	Anterior interbody (cervical, INFUSE)	24	0	"Analysis of our results demonstrated the safety and efficacy of this combination of cervical spine fusion therapy…. a 100% fusion rate and nonsignificant morbidity"
Dimar et al. (2009)	Posterolateral (lumbar, INFUSE, pedicle screws)	53	0	None reported
Glassman et al. [42]	Posterolateral (lumbar, AMPLIFY, and pedicle screws)	[148]†	0	None reported
Dimar et al. [10]	F			at was specifically : of rhBMP-2 matrix in the entified"
Dawson et al. [11]	F			
Total	A	780	0	se event rate

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Home > Business

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.

hide

Medtronic Inc. has received FDA approval for its "InFuse" device, a genetically engineered bone-growth product used in spinal fusion surgery. Article ran Wed July 3, 2002, Star Tribune, page D1. Handout photo.

Photo: , Handout
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Editorials | 18 June 2013

A Historic Moment for Open Science: The Yale University Open Data Access Project and Medtronic FREE

Harlan M. Krumholz, MD, SM; Joseph S. Ross, MD, MHS; Cary P. Gross, MD; Ezekiel J. Emanuel, MD, PhD; Beth Hodshon, JD, MPH, RN; Jessica D. Ritchie, MPH; Jeffrey B. Low, AB; and Richard Lehman, MD

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Study, as referred to by Medtronic	Number of Patients, rhBMP-2	Number of Patients, Control
INFUSE/LT-CAGE Pilot RCT	11	3
INFUSE/LT-CAGE Open Pivotal RCT	143	136
INFUSE/LT-CAGE Lap Pivotal Single-Arm	134	0
INFUSE/Bone Dowel Pilot RCT	24	22
INFUSE/Bone Dowel Pivotal RCT	55	30
INFUSE/INTER FIX PLIF RCT	34	33
INFUSE/CORNERSTONE ACDF Pilot RCT	18	15
INFUSE/Mastergraft Pilot RCT	25	21
INFUSE/INTER FIX ALIF Pilot RCT	25	20
MAVERICK Disc Pivotal RCT	172	405*
INFUSE/Telamon PEEK Instrumented PLIF Pilot, Single-Arm	30	0
rhBMP-2/BCP US Pilot RCT	22 (11 + 11)	5
rhBMP-2/BCP Canada Pivotal RCT	98	99
AMPLIFY Pivotal RCT	239	224
rhBMP-2/CRM 2-level Pilot, Single-Arm	29	0
rhBMP-2/BCP Mexico Pilot, Single-Arm	15 (8 + 7)	0
INFUSE/CORNERSTONE ACDF Pivotal	2	1
Total	**1076**	**1014**

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Model in Practice: Medtronic

Group	Role
Coordinating Center (Yale)	• Assembled and informed the SC • Designed policies and procedures • Managed subcontractors • Coordinated data dissemination
Medtronic, Inc.	• Provided Yale all data on product • Answered data related questions • Feedback on P&P, reports, manuscripts
Subcontractors (OHSU and University of York)	• Independently analyzed Medtronic data • Prepared a comprehensive report • Prepared a manuscript
Steering Committee	• Participated in data sharing discussions • Provided substantive feedback on all project related issues

Model in Practice: Medtronic

- **Medtronic was not involved in the following**
  - **Selection of SC or subcontractors**
  - **SC meetings**
  - **Methodology used to analyze data**
  - **Journal selection**
  - **Manuscript/Final Report development**
  - **Data release policy and procedures**
  - **Timing of data release**
- **Yale maintained jurisdiction**

Medtronic Project Timeline

Systematic Review and Meta-Analysis of rhBMP-2

2 research groups selected after open competition, both tasked with same objectives

Development of Data Release Policy

First consensus conference, then public comment, final policy

Open Data Access

Dissemination of individual patient level data to external researchers

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Reviews | 18 June 2013

Safety and Effectiveness of Recombinant Human Bone Morphogenetic Protein-2 for Spinal Fusion: A Meta-analysis of Individual-Participant Data FREE

Mark C. Simmonds, PhD, MA; Jennifer V.E. Brown, MSc, BA; Morag K. Heirs, MSc, MA; Julian P.T. Higgins, PhD, BA; Richard J. Mannion, PhD; Mark A. Rodgers, MSc, BSc; and Lesley A. Stewart, PhD, MSc, BSc

Reviews | 18 June 2013

Effectiveness and Harms of Recombinant Human Bone Morphogenetic Protein-2 in Spine Fusion: A Systematic Review and Meta-analysis FREE

Rongwei Fu, PhD; Shelley Selph, MD; Marian McDonagh, PharmD; Kimberly Peterson, MS; Arpita Tiwari, MHS; Roger Chou, MD; and Mark Helfand, MD, MS

Source: Simmonds et al. Ann Intern Med 2013;158:877-889 and Fu et al. 2013;158:890-902.

Two Independent Reviews

Group 1	Decision	Group 2
Same	**Timeframe**	Same
17 Trials, plus 1	**Data Source**	17 Trials
Combined surgical approaches	**Meta-Approach**	Stratified by surgical approach
2-stage model	**Analysis**	2-stage model
Higher short-term fusion rates, no effect on long-term functional outcomes	**Efficacy Outcomes**	No effect on short-term fusion rates or long-term functional outcomes
No difference in risk of adverse events, but risk of cancer higher (RR~2)	**Safety Outcomes**	No difference in risk of adverse events, but risk of cancer higher (RR~3.5)
Full report, peer reviewed publication; coordinated	**Dissemination**	Full report, peer reviewed publication; coordinated

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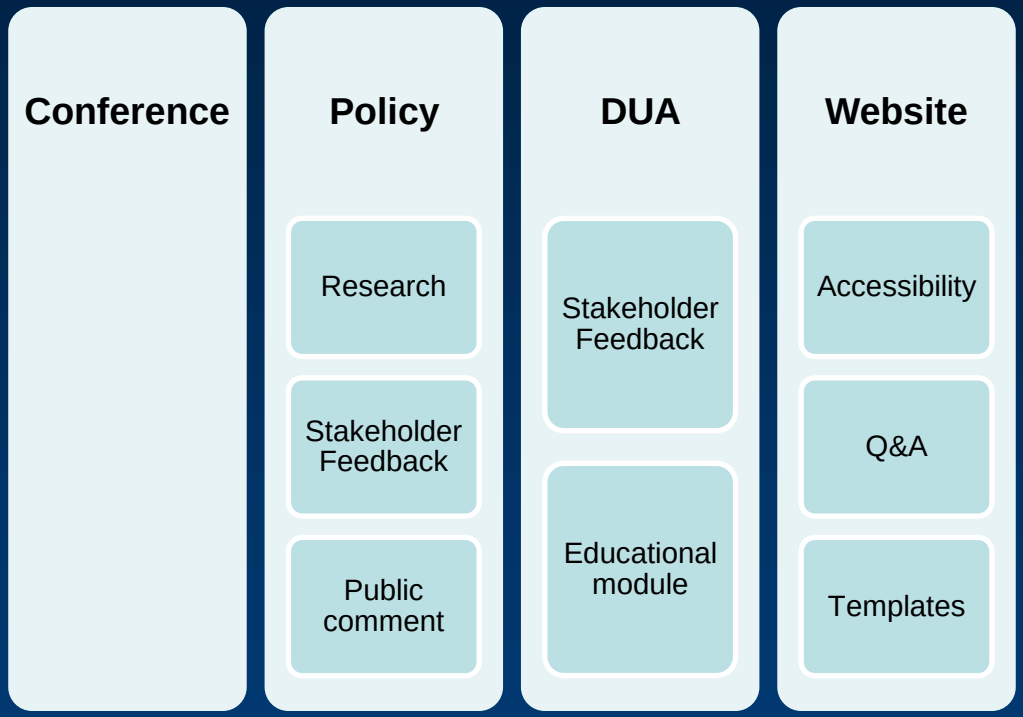
Source: Simmonds et al. Ann Intern Med 2013;158:877-889 and Fu et al. 2013;158:890-902.

Data Release: Policy and Procedure



Data Release: Policy and Procedure

- Data Sharing Conference
  - Attended by stakeholders
  - Issues raised and debated
- Policy Development
  - Research: How are others sharing?
  - Stakeholder feedback
  - 30 day comment period
  - Iterative process
  - YODA maintained jurisdiction over contents

Data Release: Policy and Procedure

- DUA
  - Stakeholder feedback
  - Underscores importance of data sharing process
  - Educational module required
- Website
  - Explored sophisticated, expensive website options
  - Number of applicants – still a mystery
  - Option chosen:
    - User friendly and economical
    - Instructions, templates, Q&A
    - Applicants email documentation to YODA Project

Data Release in Practice

MEDTRONIC'S FULL DATASET IS NOW AVAILABLE

- **Required**
  - **PI registration**
  - **Proposal, COI, IRB approval/waiver, funding source**
  - **DUA educational module completion**
  - **Intent to create scientific knowledge**
- **Dissemination of findings must cite YODA Project as data source**
- **Research proposal will be made publicly available**

Data Release in Practice

- Share findings in peer-reviewed literature or a scientific meeting
- One year DUA expiration: renew or destroy
- Data is free
- No use of data for commercial purposes or pursuant of litigation
- No data distribution to third parties or public posting
- No attempts to re-identify individuals

Data Release in Practice

- Application received and logged
- Preliminary review for completeness
- General review (*not* scientific merit)
- Data granted or further information requested
- DUA instituted (1 year)
- Data transferred via Yale FTP System

Data Release in Practice

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Data Release: Enforcement

- DUA with Yale; enforceable by Medtronic
- Violations posted on website
- Possible surveillance efforts by Yale
- Users "check-in" at various time points
  - Project completion
  - Additional aims
  - Before DUA expiration
  - Before publication/presentation

Project Success

Clear Vision
Creativity
Trust
Honesty
Diplomacy
Skillful Negotiation

This project was possible because industry and academia chose to work together for the common good

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Request Medtronic rhBMP-2 Data

Medtronic has provided individual participant-level data (IPD) for each of their 17 clinical trials evaluating the efficacy or safety of rhBMP-2. The data are presented in a range of separate SAS-format data files for each trial according to the types of outcomes reported. Thirteen trials were randomized, controlled trials and four were single arm studies.

Medtronic also provided the following documentation, and any revision documents, for the 17 trials (please note- not all documents are available for each trial):

- Data Dictionary
- Trial Protocol
- Imaging Protocol
- Statistic Considerations Redacted
- Descriptions of derived endpoint variables
- Clinical Report Form
- Adverse Events Form
- Pre-Market approcal clinical study report redacted (where relevant)
- Pre-Market approval PAS final report redacted (where relevant)
- Final Report Redacted
- Clinical Study Report

SOFTWARE PROGRAMMING LANGUAGE

The data files total 2.5 GB in size. SAS version 9.1x is required to read the files.

QUESTIONS?

If you have questions please check the **FAQs** or email yodap@yale.edu. Please include contact information when submitting questions.

MEDTRONIC'S FULL DATASET IS NOW AVAILABLE!

Instructions for Submitting an Application (all steps must be completed)

1. **Click here** to submit your registration information. The following information is required:

Data Sharing:
Pros, Cons, and Challenges

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Data Sharing: Pros

- Fair and objective assessment of product research data
- Supports scientific competition, not marketing
- Untenable to withhold information about safety & effectiveness
- Will accelerate biomedical research
- Possibly restore trust in clinical research
- Fulfill obligation to research participants

Data Sharing: Pros

- Transparency
- Manufacturers will improve understanding of drug/device which may lead to a better treatment
- Taxpayer dollars fund NIH sponsored studies (especially important at universities)
- Pooled data may lead to new findings not identified in individual trials
- Decisions are made based on all relevant clinical evidence concerning a product

Data Sharing: Cons

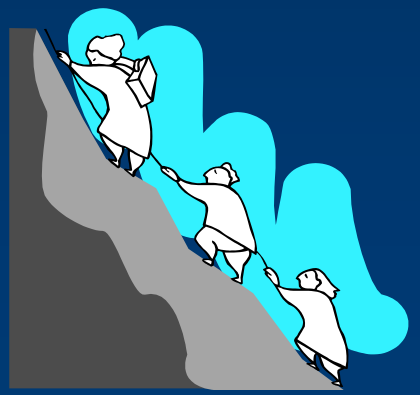
- Scientific success in universities (tenure)
- Substantial time and effort to collect data
- Research & Development is a competitive process
- Lack of standardized methods for data collection
- Some types of data may be difficult to interpret or may be misunderstood without access to the original methods
- Multiple analyses by various independent research groups may produce analyses with differing results

Data Sharing: Cons

- Culture where data are considered proprietary
- Inappropriate use by data users
- Patients may not want their private medical information shared
- Ethical dilemma: New use for data emerges after study complete (to which patients have not consented)

Data Sharing: Challenges

- Bad data = bad data
- What are the responsibilities of the original investigator or team?
- Where should the data be placed for others to access?
- What if there are subsequent questions and inquiries related to the original dataset?
- How to fairly give credit when many scientists all contribute significantly?
- Who bears the cost?
- Deidentification is complicated and expensive



Data Sharing: Challenges

No consensus on model

- Should data be posted on the web for download?
- What does an application process entail?
- Data recipient
  - Scientific background?
  - Specific credentials?
  - Academic affiliation?
- Should applications be reviewed for scientific merit?
  - By whom?
  - Associated costs?
- What kind of penalties are associated with misuse of data?
  - Forgo future use?
  - Litigation?
- Who polices data users and how?
  - Feasible to audit?

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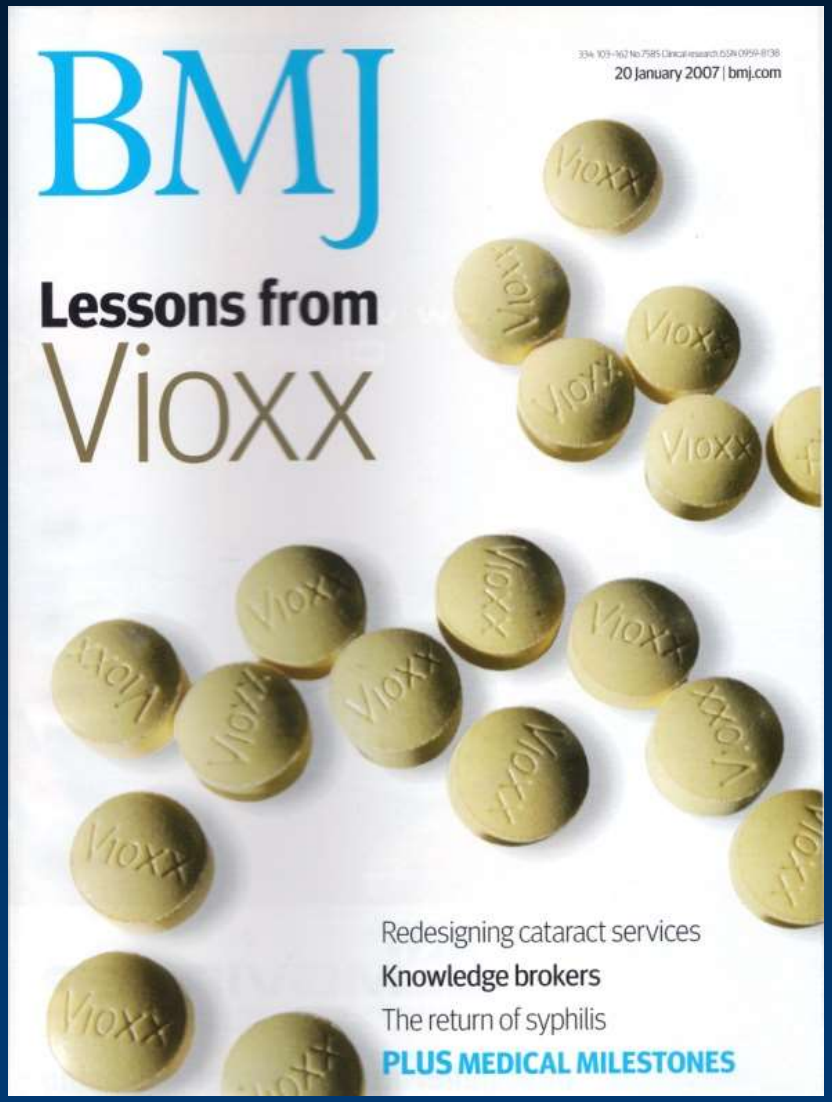

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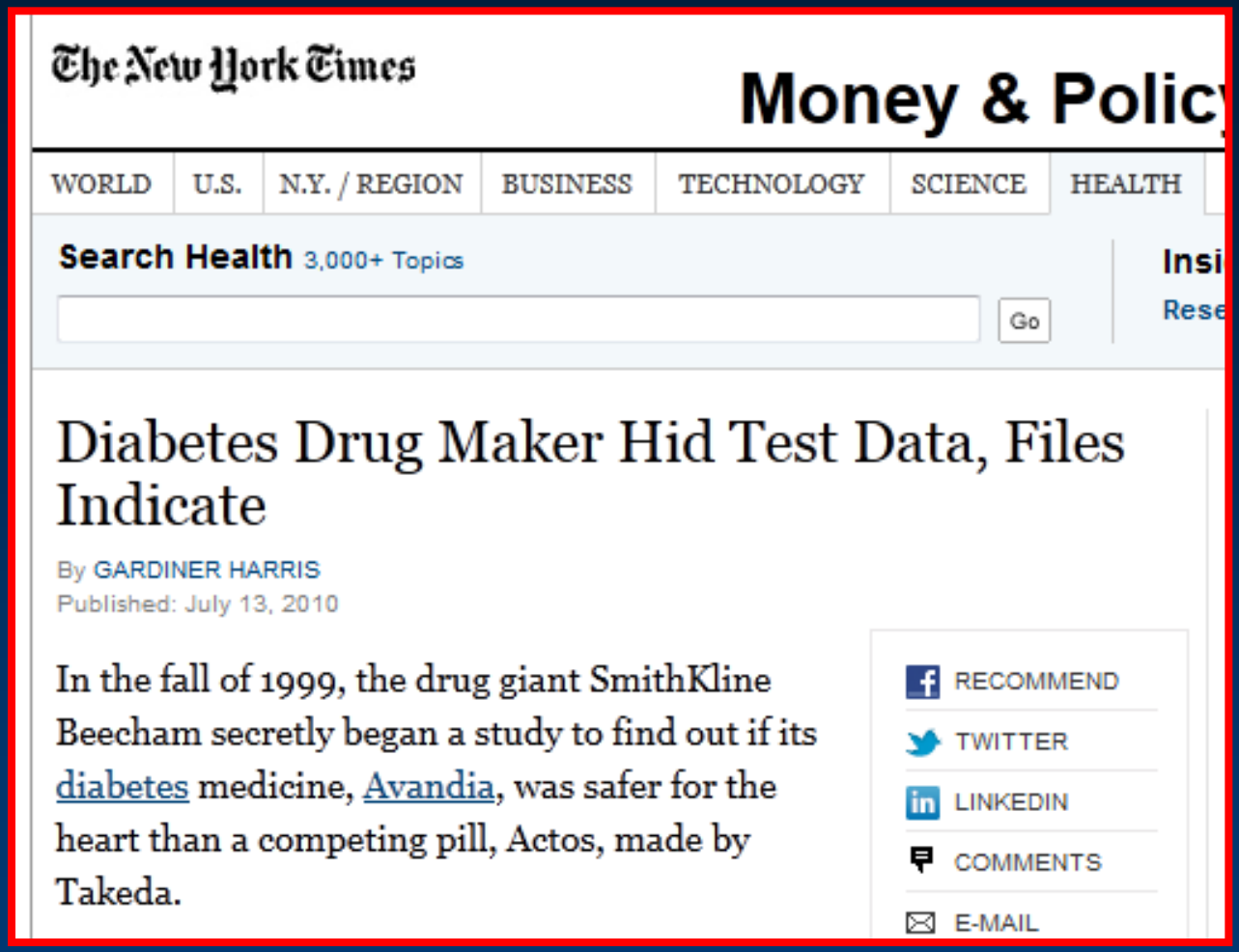
Did a Flu Drug Manufacturer Withhold Evidence From Drug Trials?

Posted By Dr. Mercola | **December 24 2009** | **21,886 views**

Doctors have alleged that Roche, the manufacturer of Tamiflu, has made it impossible for scientists to assess how well the anti-flu drug stockpiled around the globe works by withholding the evidence the company has gained from trials.

A major review of what data there is in the public domain has found no evidence Tamiflu can prevent healthy people with flu from suffering complications such as pneumonia.

Tamiflu may shorten the bout of illness by a day or so, the investigators say, but it is impossible to know whether it prevents severe disease, because the published data is insufficient. Roche has failed to make some of the studies carried out on the drug publicly available.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Diabetes Drug Maker Hid Test Data, Files Indicate
By GARDINER HARRIS
Published: July 13, 2010
In the fall of 1999, the drug giant SmithKline Beecham secretly began a study to find out if its diabetes medicine, Avandia, was safer for the heart than a competing pill, Actos, made by Takeda.
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EDITORIALS

Missing clinical trial data: setting the record straight

Urgent action is needed to restore the integrity of the medical evidence base

RESEARCH, p 816
ANALYSIS, pp 809, 811

Elizabeth Loder associate editor, *BMJ*, London WC1H 9JR
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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and

Like us, you have probably grown accustomed to the steady stream of revelations about incomplete or suppressed information from clinical trials of drugs and medical devices.[1] If so, this issue of the *BMJ* features a pair of papers that will dismay but not surprise you. Researchers for an official German drug assessment body charged with synthesising evidence on the antidepressant reboxetine encountered serious obstacles when they tried to get unpublished clinical trial information from the drug company that held the data, an experience from which they draw several lessons.[2]

Once they were able to integrate the astounding 74% of patient data that had previously been unpublished, their conclusion was damning: reboxetine is "overall an ineffective and potentially harmful antidepressant".[3] This conclusion starkly contradicts the findings of other recent systematic reviews and meta-analyses published by reputable journals.[4-8] These studies presumably met prevailing standards for the conduct of meta-analyses. Yet we now know that they did not provide a properly balanced view of the harms and benefits of reboxetine. Why? Because they did not combine all of the existing evidence from clinical trials. Furthermore, the difficulties clinical trial data become available. At present, however, we do not know the extent to which integration of missing data would support or refute key portions of the existing evidence on which doctors, patients, and policy makers rely.

As Wieseler and colleagues point out, the Food and Drug Administration Amendments Act of 2007 and parallel European efforts will increase the accessibility of clinical trial results and make it more difficult to conceal information.[2] But they do not solve the problem of our current evidence base, which contains incomplete and questionable evidence. So what can be done? At the moment there are no organised efforts to identify missing information and integrate it into the existing evidence base.

The *BMJ* has a particular interest in the impact of unpublished data on the overall verdict regarding the effectiveness of medical treatment. Because we think that it is important to re-evaluate the integrity of the existing base of research evidence, the *BMJ* will devote a special theme issue to this topic in late 2011. A detailed call for papers will follow, but we mention this now because we hope that researchers with such

Bottom Line

- **Facilitates fair and objective assessment of trial data, as opposed to speculative analysis based on incomplete data**
- **Promotes transparency**
- **Compete on science, not marketing**
- **Untenable to withhold information about product effectiveness and safety**

Bottom Line

- Reinforcement of open scientific inquiry
- Verification, refutation, or refinement
- Promotion of new research on data
- Encourages multiple perspectives
- Reduces duplicative data collection
- Respects efforts of volunteers/subjects

Source: Institute of Medicine "Vaccine Safety Research, Data Access and Public Trust" 2005.

Project Leadership

- **Harlan Krumholz, MD, SM**
  Principal Investigator
  Yale University
- **Cary Gross, MD**
  Co-Investigator
  Yale University
- **Joseph Ross, MD, MHS**
  Co-Investigator
  Yale University
- **Kevin J. Bozic, MD, MBA**
  Associate Professor and Vice Chair
  University of California, San Francisco
- **Ezekiel J. Emanuel, MD, PhD**
  Vice Provost and Levy University Professor
  University of Pennsylvania

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