Yale University Open Data Access Project

A Model for Dissemination and Independent Analysis of Clinical Trial Program Data
Clinical Practice Guidelines We Can Trust
Finding What Works in Health Care
Standards for Systematic Reviews

These standards are for systematic reviews of comparative effectiveness research of therapeutic medical or surgical interventions

For more information visit www.iom.edu/srstandards
Systematic Reviews and Clinical Practice Guidelines Improve Healthcare Decision Making

- Define Clinical Problem
- Assemble Multidisciplinary Team
- Identifying, Assessing, and Synthesizing Evidence
- Developing Systematic Reviews
- Assembling Guideline Development Group
- Producing Systematic Review Report
- Producing Clinical Practice Guidelines
- Incorporating Expert Opinion and Patient Preferences and Characteristics
- Improved Health Outcomes and Quality of Care
- Use Guidance to Make Better Informed Decisions

We need better evidence and guidance to make informed healthcare choices.
What if....
COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECEOXB
AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

CLAIRE BOMBARDE, M.D., LOREN LAIN, M.D., AULEE REIN, M.D., DEBORAH SHAPIRO, D.P.H.,
RUSEN BURDES-VARGAS, M.D., BARRY DAVIS, M.D., P.D., RICHARD DAVY, M.D., MARCOS BOSE FERREZ, M.D., P.D.,
CHRISTOPHER J. HAWKES, M.D., MARC C. HOCHBERG, M.D., TAD K. KLEE, M.D.,
AND THOMAS J. SCHUMAKER, M.D., P.D., FOR THE VIGOR STUDY GROUP

ABSTRACT

Background. Each year, clinical upper gastrointestinal events occur in 2 to 4 percent of patients who are taking nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). We assessed whether rofecoxib, a selective inhibitor of cyclooxygenase-2, would be associated with a lower incidence of clinically important upper gastrointestinal events than is the nonselective NSAID naproxen among patients with rheumatoid arthritis.

Methods. We randomly assigned 8,076 patients who were at least 50 years of age or at least 40 years of age and receiving long-term glucocorticoid therapy and who had rheumatoid arthritis to receive either 50 mg of rofecoxib daily or 500 mg of naproxen twice daily. The primary end point was confirmed clinical upper gastrointestinal events (gastroesophageal perforation or obstruction, upper gastrointestinal bleeding, and asymptomatic gastrointestinal ulcers).

Results. Rofecoxib and naproxen had similar efficacy against rheumatoid arthritis. During a median follow-up of 9.0 months, 2.1 confirmed gastrointestinal events per 100 patient-years occurred with rofecoxib, as compared with 4.5 per 100 patient-years with naproxen (relative risk, 0.5; 95 percent confidence interval, 0.3 to 0.8; P<0.001). The respective rates of complicated confirmed events (perforation, obstruction, and severe upper gastrointestinal bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.8; P=0.025). The incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups.

Conclusions. In patients with rheumatoid arthritis, treatment with rofecoxib, a selective inhibitor of cyclooxygenase-2, is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a nonselective inhibitor. (N Engl J Med 2000;343:1520-8.) ©2000 Massachusetts Medical Society.

NONSTEROIDAL anti-inflammation drugs (NSAIDs) are among the most commonly used medications in the world. A major factor limiting their use is gastrointestinal toxicity. Although endoscopic studies reveal that gastric or duodenal ulcers develop in 15 to 30 percent of patients who regularly take NSAIDs, the chief concern is clinically important gastrointestinal problems, such as bleeding. It has been estimated that more than 100,000 patients are hospitalized and 16,500 die each year in the United States as a result of NSAID-associated gastrointestinal events.

Most NSAIDs inhibit both cyclooxygenase-1 and cyclooxygenase-2, isoforms involved in the synthesis of prostaglandins. Cyclooxygenase-1 is constitutively expressed and generates prostacyclin involved in the maintenance of the integrity of gastrointestinal mucosa and platelet aggregation, whereas at sites of inflammation, cyclooxygenase-2 is induced to generate prostaglandins that mediate inflammation and pain. The antiinflammatory effects of nonselective NSAIDs (those that inhibit both cyclooxygenase-1 and cyclooxygenase-2) therefore appear to be mediated through the inhibition of cyclooxygenase-2; whereas their harmful effects in the gastrointestinal tract as well as their analgesic effects are believed to occur primarily through the inhibition of cyclooxygenase-1. Agents that selectively inhibit cyclooxygenase-2 have antiinflammatory and analgesic effects that are simi-
5. **Conclusion.**

To recap briefly, when the VIGOR Trial was unblinded, MRL scientists identified several possible explanations for the between-treatment difference in the incidence of cardiovascular events: Vioxx had a prothrombotic effect, naproxen conferred cardioprotection, or a combination of the two. Chance also could have played a role in conjunction with any of these explanations, or could possibly have explained the entire difference on its own. During the two weeks following the unblinding, MRL scientists concluded that the cardiovascular results of the VIGOR Trial were most likely explained by a cardioprotective effect of naproxen, and not by a prothrombotic effect of Vioxx.
Merck concluded that the cardiovascular effects seen in the VIGOR trial were most likely explained by a cardiovascular effect of naproxen.
HEALTH CARE REFORM

Pooled Analysis of Rofecoxib Placebo-Controlled Clinical Trial Data

Lessons for Postmarket Pharmaceutical Safety Surveillance

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<table>
<thead>
<tr>
<th>Month/Year</th>
<th>CV Event/Death RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/1998</td>
<td>1.35 (0.47-4.77)</td>
<td>0.63</td>
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</table>

**Health Care Reform**

Pooled Analysis of Rofecoxib Placebo-Controlled Clinical Trial Data

Lessons for Postmarket Pharmaceutical Safety Surveillance

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<td>2.16 (0.79-7.37)</td>
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<td></td>
<td>1.80 (0.71-5.40)</td>
<td>0.24</td>
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<tr>
<td>12/2000</td>
<td>2.18 (0.93-5.81)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

As of 12/00, same time as publication of VIGOR trial (Vioxx v. naproxen) where RR of MI was 5.00 (1.68-20.13)

**Health Care Reform**

**Pooled Analysis of Rofecoxib Placebo-Controlled Clinical Trial Data**

*Lessons for Postmarket Pharmaceutical Safety Surveillance*

### Table: CV Event/Death

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<th>Month/Year</th>
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<tr>
<td>06/2001</td>
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</tr>
</tbody>
</table>


---

As of 6/01, nearly 3 ½ years before Vioxx was withdrawn from market.

---

**Pooled Analysis of Rofecoxib Placebo-Controlled Clinical Trial Data**

Lessons for Postmarket Pharmaceutical Safety Surveillance

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<td>1.39 (1.07-1.81)</td>
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<tr>
<td></td>
<td>1.38 (1.08-1.77)</td>
<td>0.01</td>
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<tr>
<td></td>
<td>1.37 (1.07-1.75)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>11/2004</strong></td>
<td><strong>1.43 (1.16-1.76)</strong></td>
<td><strong>0.0007</strong></td>
</tr>
</tbody>
</table>

Not Just Vioxx

- Oseltamivir
- Reboxetine
- Rosiglitazone

Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

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

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</tbody>
</table>

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.
Call for full access to Tamiflu trial data to allow for independent scrutiny

Published: Tuesday, January 11, 2011 - 19:02 in Health & Medicine

Tom Jefferson and colleagues from the Cochrane Group argue that the current system for assessing the safety and effectiveness of drugs, based on published trial data only, is "wholly inadequate" and "ethically dubious." They propose a new approach that would allow in-depth scrutiny of the complete set of trial data for a new drug.

Their call comes after they reviewed the evidence for the antiviral drug oseltamivir (Tamiflu), and were unable to find sufficient published data to support the conclusion that oseltamivir reduces complications in healthy adults.

As a result, Roche (oseltamivir's manufacturer) publicly pledged to make full results for ten unpublished clinical trials available for scrutiny. Yet, to date, they have failed to fulfil this promise.

The Cochrane team's concern deepened after finding reports of ten serious adverse events in patients enrolled in two key manufacturer-funded trials that were not reported in journal publications arising from those trials.

Other recent cases, where the "true" effects of drugs have emerged only after all the evidence (including unpublished data) has been analysed, have further highlighted the importance of independent evaluation.

"The answer is to make the data freely available: we should accept nothing less than a full dataset," say the authors. "Before licensing a drug - and certainly before large purchase decisions are made - our governments and policy makers should ensure that all researchers can access data in sufficient detail to allow for the independent exploration and re-analysis of trials," they add.

Their proposed new approach involves compiling a complete list of drug trials, identifying all unpublished data, and making it publicly available for scrutiny.
Rosiglitazone Evaluated for Cardiovascular Outcomes — An Interim Analysis

Philip D. Home, D.M., D.Phil., Stuart J. Pocock, Ph.D.,
Henning Beck-Nielsen, D.M.S.C., Ramón Gomis, M.D., Ph.D.,
Markolf Hanefeld, M.D., Ph.D., Nigel P. Jones, M.A., Michel Komajda, M.D.,
and John J.V. McMurray, M.D., for the RECORD Study Group*

ABSTRACT

BACKGROUND
A recent meta-analysis raised concern regarding an increased risk of myocardial infarction and death from cardiovascular causes associated with rosiglitazone treatment of type 2 diabetes.

METHODS
We conducted an unplanned interim analysis of a randomized, multicenter, open-label, noninferiority trial involving 4447 patients with type 2 diabetes who had inadequate glycemic control while receiving metformin or sulfonylurea, in which 2220 patients were assigned to receive add-on rosiglitazone (rosiglitazone group), and 2227 to receive a combination of metformin plus sulfonylurea (control group). The primary end point
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.
Avandia: GlaxoSmithKline Cover-Up Turns Off Doctors

By LARA SALAHI (@LaraSalahiABC) and COURTNEY HUTCHISON, ABC Medical Unit
July 14, 2010

In the face of mounting evidence that GlaxoSmithKline withheld important safety data on their controversial drug Avandia, some doctors are abandoning use of this diabetes treatment.

Documents released Tuesday morning by the Senate Finance Committee suggested that for more than a decade, the drugmaker deliberately hid study results showing that Avandia could worsen certain risk factors for heart disease and was no better than its market competitor Actos.

The documents include several internal emails that record GlaxoSmithKline officials suggesting that certain unfavorable studies concerning the drug "never see the light of day to anyone outside of GSK."

"It's just not morally or ethically acceptable for companies to withhold data," says Dr. Steve Nissen, chair of Cardiovascular Medicine at the Cleveland Clinic and author of the original RECORD study, which raised public concern over Avandia's safety.
The MI Vanishes!

15 months after the MI!

The event was never referred for adjudication.

Why?
## CRF Review by FDA

About 1/8\textsuperscript{th} of cases in each arm reviewed

<table>
<thead>
<tr>
<th></th>
<th>Rosiglitazone</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Randomized &amp; treated - GSK &quot;ITT&quot;</td>
<td>2220</td>
<td>100%</td>
</tr>
<tr>
<td>CRFs reviewed (total 549)</td>
<td>278</td>
<td>13%</td>
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<tr>
<td>CRFs with problems</td>
<td>45</td>
<td>2.0%</td>
</tr>
<tr>
<td>Favoring rosiglitazone</td>
<td>44</td>
<td>2.0%</td>
</tr>
<tr>
<td>Favoring control</td>
<td>1</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

**Overall which arm is favored**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall which arm is favored</td>
<td>57</td>
<td>10.4% of 549</td>
<td>13</td>
<td>2.4% of 549</td>
</tr>
</tbody>
</table>

About 13% with endpoint problems >4:1 favoring rosiglitazone!
CV Follow-up + 14 Months

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Centre Number</th>
<th>Patient Number</th>
<th>Visit Date</th>
<th>Study Conclusion/Withdrawal</th>
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</thead>
<tbody>
<tr>
<td>49653/231</td>
<td></td>
<td></td>
<td>13 J an 09</td>
<td></td>
</tr>
</tbody>
</table>

**STUDY CONCLUSION /WITHDRAWAL**

Please complete this section only if the patient has completed Visit 27, or if they are withdrawing.

Did the patient complete the CV Outcomes phase of the study?

- [ ] Yes
- [x] No

If 'No', please mark the primary cause of withdrawal. (Mark one box only).

- [ ] Adverse experience
- [x] Lost to follow-up
- [ ] Patient withdraw at his own request
- [ ] Other - specify

Date of final clinic or telephone visit: 06 Nov 07

**INVESTIGATOR’S SIGNATURE**

I certify that I have reviewed the data in this Case Report Form, including laboratory data and that in the Adverse Experience and Serious Adverse Experience sections (if appropriate) and that all information is complete and accurate.

Investigator’s Signature: [signature]

Date: 13 Jan 09

What the investigator reported: 06Nov07

What GSK used: 13Jan09!
46% of trials published!

ClinicalTrials.gov is a registry of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov gives you information about a trial’s purpose, who may participate, locations, and phone numbers for more details. This information should be used in conjunction with advice from health care professionals.
Read more...

▶ Search for Clinical Trials
Find trials for a specific medical condition or other criteria in the ClinicalTrials.gov registry. ClinicalTrials.gov currently has 80,696 trials with locations in 170 countries.

▶ Investigator Instructions
Get instructions for clinical trial investigators/sponsors about how to register trials in ClinicalTrials.gov. Learn about mandatory registration and results reporting requirements and US Public Law 110-85 (FDAAA).

▶ Background Information
Learn about clinical trials and how to use ClinicalTrials.gov, or access other consumer health information from the US National Institutes of Health.
Trial Registration and Results Reporting

• 1997 FDA Modernization Act, section 113, provided public access to information about ongoing clinical trials in which they may be able to participate
• Led to creation of ClinicalTrials.gov
• 2007 FDA Amendments Act broadened scope
2007 FDA Amendments Act

- **Expanded registry**: all studies must be registered at inception

- **Results database**: trial results uploaded within 12 months of study completion (24 if under review)
  - "Basic results": baseline characteristics, 1° & 2° outcomes, statistical analyses (overall & by arm)
  - Adverse events (serious & frequent)

- **But, no access to trial data** …
Replication in Field Biology: 
The Case of the Frog-Eating Bat

Michael J. Ryan

Studies conducted in the field offer unique opportunities to observe nature, but achieving true replication under natural conditions is challenging. As demonstrated by the discovery of frog eating by a charismatic bat, biology conducted in the field generally follows an interesting progression that includes discovery, demonstration, experimentation, and verification.

Darwin (1) proposed that elaborate courtship displays were maladaptive for survival but evolved because they enhanced mating success. He did not come to this conclusion from field observations or experimental verification of survival costs, but from examining a repeated pattern of sexual dimorphism among diverse taxa. He was right, and it was not by accident but by an informed observation of nature. Data supporting Darwin's insight accumulated in various ways. I review a series of studies to illustrate the different means by which we arrive at scientific conclusions in field biology.

Tungara frogs, Physalaemus pustulosus, make simple (whine only) and complex (whines with one to seven chucks) mating calls (2). When calling alone a male produces simple calls, and when in a chorus he makes complex calls, which are also more attractive to females (3). In our early studies of these frogs, we wondered why males do not always make complex calls. Harkening back to Darwin for inspiration, we assumed

Reproducible Research in Computational Science

Roger D. Peng

Computational science has led to exciting new developments, but the nature of the work has exposed limitations in our ability to evaluate published findings. Reproducibility has the potential to serve as a minimum standard for judging scientific claims when full independent replication of a study is not possible.

The rise of computational science has led to exciting and fast-moving developments in many scientific areas. New technologies, increased computing power, and methodological advances have dramatically improved our ability to collect complex high-dimensional data. Large data sets have led to scientists doing more computation, as well as researchers in computationally oriented fields directly engaging in more science. The availability of large public databases has allowed for researchers to make meaningful scientific contributions without using the traditional tools of a given field. As an example of require long follow-up times. Such studies are difficult to replicate because of time and expense, especially in the time frame of policy decisions that need to be made regarding regulation.

Researchers across a range of computational science disciplines have been calling for reproducibility, or reproducible research, as an attainable minimum standard for assessing the value of scientific claims, particularly when full independent replication of a study is not feasible. The standard of reproducibility calls for the data and the computer code used to analyze the data be made available to others. This standard falls short of full
Legislation for trial registration and data transparency

Zhao-Xiang Bian*1 and Tai-Xiang Wu2

Abstract
Public confidence in clinical trials has been eroded by data suppression, misrepresentation and manipulation. Although various attempts have been made to achieve universal trial registration - e.g., Declaration of Helsinki, WHO clinical Trial Registry Platform (WHO ICTRP), the International Committee of Medical Journal Editors requirement - they have not succeeded, probably because they lack the enough power of enforcement. Legislation appears to be the most efficient and effective means to ensure that all researchers register their trials and disseminate their data accurately and in a timely manner. We propose that a global network be established. This could be accomplished in two steps. The first step is to legislate about trial registration and data transparency, such as USA's FDAAA Act 2007; and the second step to establish a global network to ensure uniform, international consistency in policy and enforcement of trial registration and data transparency.
Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers

Iain Hrynaszkiewicz¹*, Melissa L Norton¹, Andrew J Vickers², Douglas G Altman³

Abstract
In recognition of the benefits of transparent reporting, many peer-reviewed journals require that their authors be prepared to share their raw, unprocessed data with other scientists and/or state the availability of raw data in published articles. But little information on how data should be prepared for publication - or sharing - has emerged. In clinical research patient privacy and consent for use of personal health information are key considerations, but agreed-upon definitions of what constitutes anonymised patient information do not appear to have been established. We aim to address this issue by providing practical guidance for those involved in the publication process, by proposing a minimum standard for de-identifying datasets for the purposes of publication in a peer-reviewed biomedical journal, or sharing with other researchers. Basic advice on file preparation is provided along with procedural guidance on prospective and retrospective publication of raw data, with an emphasis on randomised controlled trials.

In order to encourage its wide dissemination this article is freely accessible on the BMJ and Trials journal web sites.
Sharing clinical research data in the United States under the health insurance portability and accountability act and the privacy rule

James D Miller

Abstract
Sharing of final research data from clinical research is an essential part of the scientific method. The U.S. National Institutes of Health require some grant applications to include plans for sharing final research data, which it defines as the factual materials necessary to document, support, and validate research findings. In the U.S., however, the Privacy Rule adopted under the Health Insurance Portability and Accountability Act impedes the sharing of final research data. In most situations, final research data may be shared only where all information that could possibly be used to identify the subject has been deleted, or where the subject has given authorization for specific research, or an Institutional Review Board has granted a waiver.
Editorial

Towards agreement on best practice for publishing raw clinical trial data
Iain Hrynaszkiewicz*1 and Douglas G Altman2

Address: 1BioMed Central Ltd, 236 Gray's Inn Road, London, WC1X 8HL, UK and 2Centre for Statistics in Medicine, University of Oxford, Wolfson College Annexe, Linton Road, Oxford, OX2 6UD, UK
Email: Iain Hrynaszkiewicz* - iain.hrynaszkiewicz@biomedcentral.com; Douglas G Altman - doug.altman@cs.m.ox.ac.uk
* Corresponding author

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Commentary

Whose data set is it anyway? Sharing raw data from randomized trials

Andrew J Vickers*

Address: Departments of Epidemiology and Biostatistics, Medicine, Urology, Memorial Sloan-Kettering Cancer Center, NY, USA
Email: Andrew J Vickers* - vickersa@mskcc.org
* Corresponding author

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Drug Study Secrecy Puts Lives at Risk
29 Nov 2011

Studies to test the safety and efficacy of drugs and medical devices are too often never made public, putting lives at risk. Head of Investigations at the British Medical Journal, Deborah Cohen reports

Transparency is at the heart of medical science. Every day decisions are made about when to stop and start treatment and how best to invest large sums of money in ways to protect the public from disease. All these rely on knowing as much as possible about the benefits compared to the risks of action or inaction.

No medical treatment is perfect or suitable for everyone — that’s why balancing risks and benefits is crucial. But healthcare is big business; it’s where science meets big money and not all research evidence makes it into the public domain — specifically into medical journals where doctors and academics glean their information.

Medical history is replete with examples of the benefits of a treatment being overhyped and potentially serious side-effects being buried, leading to poor decisions. This wastes public money and can cost lives.
Scientists' Elusive Goal: Reproducing Study Results

By GAUTAM NAIK

Two years ago, a group of Boston researchers published a study describing how they had destroyed cancer tumors by targeting a protein called STK33. Scientists at biotechnology firm Amgen Inc. quickly pounced on the idea and assigned two dozen researchers to try to repeat the experiment with a goal of turning the findings into a drug.

It proved to be a waste of time and money. After six months of intensive lab work, Amgen found it couldn't replicate the results and scrapped the project.

"I was disappointed but not surprised," says Glenn Begley, vice president of research at Amgen of Thousand Oaks, Calif. "More often than not, we are unable to reproduce findings" published by researchers in journals.
No Cure

When Bayer tried to replicate results of 67 studies published in academic journals, nearly two-thirds failed.

- Fully replicated: 20.9%
- Partially replicated: 11.9%
- Not replicated: 64.2%
- Not applicable: 3.0%

Source: Nature Reviews Drug Discovery
Bottom Line

• Substantial number of clinical trials are conducted, but never published
• Even among published trials, a limited portion of the collected data is reported
• Thus, patients and physicians frequently make treatment decisions with access to only a fraction of clinical research data
What can we do?
A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned

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Abstract

BACKGROUND CONTEXT: Increasingly, reports of frequent and occasionally catastrophic complications associated with use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in spinal fusion surgeries are being published. In the original peer review, industry-sponsored publications describing the use of rhBMP-2 in spinal fusion, adverse events of these types and frequency were either not reported at all or not reported to be associated with rhBMP-2 use. Some authors and investigators have suggested that these discrepancies were related to inadequate peer review and editorial oversight.

PURPOSE: To compare the conclusions regarding the safety and related efficacy published in the original rhBMP-2 industry-sponsored trials with subsequently available Food and Drug Administration (FDA) data summaries, follow-up publications, and administrative and organizational databases.

STUDY DESIGN: Systematic review.

METHODS: Results and conclusions from original industry-sponsored rhBMP-2 publications regarding safety and related efficacy were compared with available FDA data summaries, follow-up publications, and administrative and organizational database analyses.

RESULTS: There were 13 original industry-sponsored rhBMP-2 publications regarding safety and efficacy, including reports and analyses of 780 patients receiving rhBMP-2 within prospective controlled study protocols. No rhBMP-2-associated adverse events (0\%) were reported in any of these studies (99% confidence interval of adverse event rate <0.5\%). The study designs of the industry-sponsored rhBMP-2 trials for use in posterolateral fusions and posterior lateral interbody fusion were found to have potential methodological bias against the control group. The reported morbidity of iliac crest donor site pain was also found to have serious potential design bias. Comparative review of FDA documents and subsequent publications revealed originally unpublished adverse events and internal inconsistencies. From this review, we suggest an estimate of adverse events associated with rhBMP-2 use in spine fusion ranging from 10\% to 50\% depending on approach. Anterior cervical fusion with rhBMP-2 has an estimated 40\% greater risk of adverse events with rhBMP-2 in the early postoperative period, including life-threatening events. After anterior interbody lumbar fusion rates of implant displacement, subsidence, infection, urogenital events, and retrograde ejaculation were higher after using rhBMP-2 than controls. Posterior lumbar interbody fusion was associated with radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes. In posterolateral fusions, the risk of adverse effects associated with rhBMP-2 use was equivalent to or greater than that of iliac crest bone graft harvesting, and 15\% to 20\% of subjects...
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.

YODA Project Model

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

Yale University Center for Outcomes Research and Evaluation

Conferences to discuss issues associated with promoting access to individual clinical product data:
1. Creating standardized protocol for permitting access to product clinical data
2. Issues in conducting systematic review and meta-analysis of product data, including clinical trial and post-marketing surveillance data
3. Other issues: importance, strategies, gaps in statistical practice, practical concerns

Dissemination of conference proceedings via peer-reviewed journals and project Web site

Company releases to Coordinating Organization all clinical trial data (published/unpublished); post-market surveillance data; and spontaneous adverse events

Development and Refinement of Approach for Disseminating Data

Dissemination of findings

Dissemination of Primary Data

Review and Synthesis of Primary Data

Solicitation of proposals to conduct independent reviews

Selection of 2 research groups

Review Organizations conduct independent evaluations in parallel

Acceptance of requests for data using standardized protocol; review of proposals

Processing of requests for data access; request and application posted on Web site

Distribution of data

Requirement to submit results within 6 months of completion

Dissemination of findings
Why We Chose 'Open Science'

To accelerate research breakthroughs on brain diseases, the Allen Institute puts all its data online for use without fees.
Publication of clinical trial data: enough of the excuses!

Ryan Woodrow

Woodrow Medical Communications

I attended a MedComms Networking event last summer to listen to the thoughts of Ben Goldacre on the pharmaceutical industry. For those of you who don’t know Dr Goldacre, he is, according to his web page: “a best-selling author, broadcaster, medical doctor and academic who specialises in unpicking dodgy scientific claims from drug companies”. The briefing was fascinating. In particular, I was interested in Dr Goldacre’s arguments that the pharmaceutical industry are guilty of failing to publish all trial data (and in particular from negative trials), and that the industry fail to make enough data available for systematic reviewers and healthcare professionals to analyse. Dr Goldacre stated that this leads to publication bias and ultimately potential harm to patients (due to poor disclosure of adverse events) and unnecessary costs to us all (since the cheapest medications aren’t being used).
The Cochrane Collaboration Supports Free Access to all Data from all Clinical Trials

The Cochrane Collaboration is committed globally to providing the most reliable evidence of the benefits and harms of healthcare interventions. It publishes systematic reviews in The Cochrane Library and updates these regularly.

Selective reporting of trial results occurs frequently, leading to exaggerated findings of the beneficial effects of healthcare interventions and underestimates of their harms. As a consequence, many patients are unknowingly treated with interventions that have little or no effect, and may be harmed unnecessarily. This is unethical and has been said to violate the implicit contract between healthcare researchers and patients, where the aim of research is to improve treatment of future patients.

To ensure that all data from all clinical trials become publicly available, without undue delay, The Cochrane Collaboration calls for:

- All randomised clinical trials to be registered at their inception, before recruitment of the first participant (see the Cochrane statement on this here);
- All data from all randomised clinical trials, including raw anonymised individual participant data that do not allow identification of individual participants, and the corresponding trial protocols, to become publicly available free of charge and in easily accessible electronic formats;
- Governments to consider introducing legislation that makes it a requirement to provide these data from all trials to the public within 12 months from the end of the randomised phase of the trial, in accordance with most international calls for data sharing;
- Governments also to consider punitive measures for non-compliance: a requirement to continue to hold and make available core data indefinitely, or to pass such data to a central and accessible repository; and a recognition that ownership of trial data should be shared between sponsors, investigators and trial participants.

http://www.cochrane.org/about-us/our-policies/support-free-access-to-all-data-from-all-clinical-trials
ACCF/AHA/SCAI Practice Guideline

2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: Executive Summary

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions

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