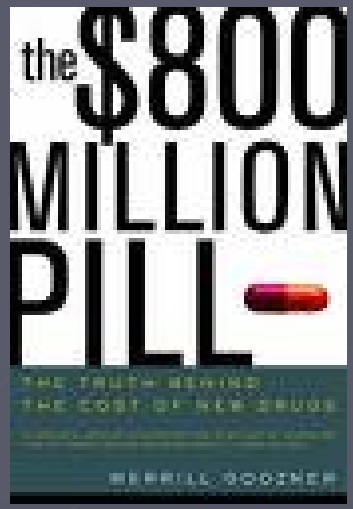
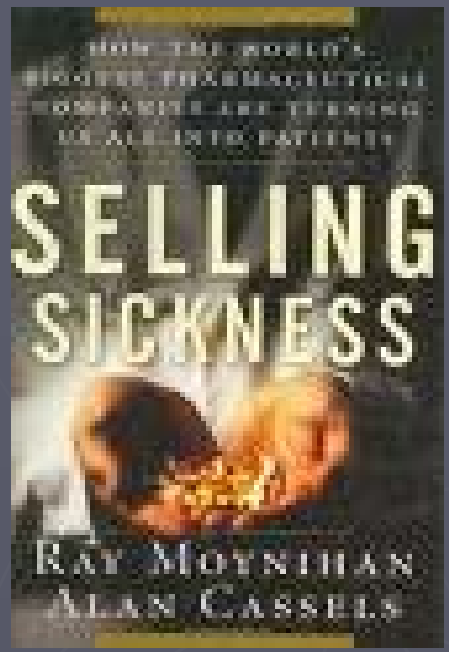
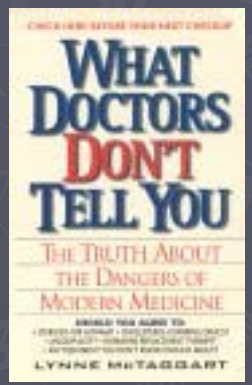
Promoting Integrity in Biomedical Research: Recent Controversies & Novel Remedies

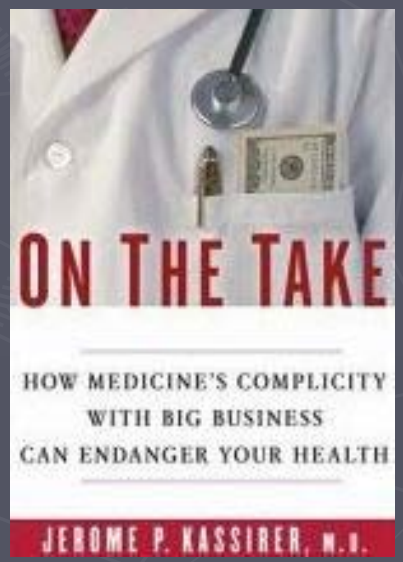
Trudo Lemmens
Faculties of Law and Medicine
Joint Centre for Bioethics
University of Toronto
Trudo.lemmens@utoronto.ca

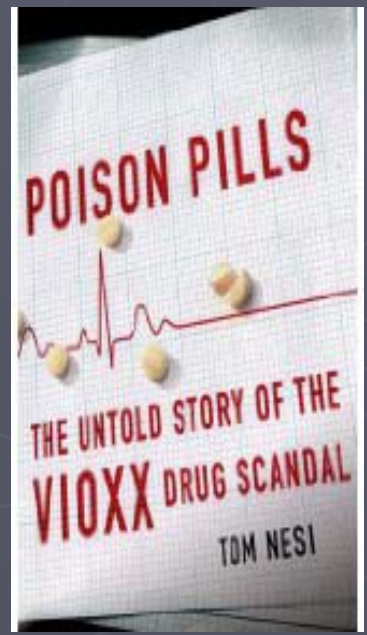

The Truth About
the Drug Companies
HOW THEY DECEIVE US
AND WHAT TO DO ABOUT IT
MARCIA ANGELL, M.D.

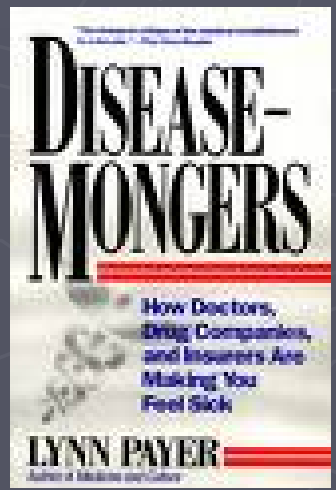

the $800
MILLION
PILL
MERRILL GOOZNER


SELLING
SICKNESS
RAY MOYNIHAN
ALAN CASSELS


WHAT
DOCTORS
DON'T
TELL YOU
THE TRUTH ABOUT
THE DANGERS OF
MODERN MEDICINE
LYNNE McTAGGART


ON THE TAKE
HOW MEDICINE'S COMPLICITY
WITH BIG BUSINESS
CAN ENDANGER YOUR HEALTH
JEROME P. KASSIRER, M.D.


POISON PILLS
THE UNTOLD STORY OF THE
VIOXX DRUG SCANDAL
TOM NESI


DISEASE-
MONGERS
How Doctors,
Drug Companies,
and Insurers Are
Making You
Feel Sick
LYNN PAYER

Interest Industry ≠ Public Interest

"for-profit industries do not share the same ethical norms to which physicians and other health care professionals must adhere. Their primary commitment is to create shareholder value, not maintain an altruistic commitment to patients."

Troy Brennan & Michelle Mello, JAMA 2007; 297: 1255-1256

Wall-Street Journal: “For Bristol-Myer’s, Challenging Pfizer Was A Big Mistake”

- Bristol-Myer sponsored Harvard study comparing Pravachol with Pfizer’s Lipitor
- Conclusion: patients taking Lipitor have 16 % lower risk of cardiac arrest or death
- Pravachol: $ 2,8 Billion Sales in 2002

Structure of Presentation

- Recent (and not so recent) Controversies
  - Ghost Authorship
  - Publication and Reporting Bias
  - Misrepresentation
- Context: How Did We Get There?
- Remedial Strategies
- Promotion of Transparency: Registration of Clinical Trials & Results Reporting

Ghost & Honorary Authorship

- Ghost Author: Person who fulfills all the criteria for authorship but is not mentioned as author
  - "Individual who wrote the protocol, performed the statistical analysis, or wrote the manuscript, but is not listed as author or as member of a study group or writing committee, or in an acknowledgment." (Gotzsche *et al*., PLoS Medicine 2006)
- Honorary (Guest) Author: Person who is mentioned as author without fulfilling authorship requirements

Ghost Authorship: Is it Common?

Prevalence of Articles With Honorary Authors and Ghost Authors in Peer-Reviewed Medical Journals

Annette Flanagin, RN, MA; Lisa A. Carey, PhD; Phil B. Fontanarosa, MD; Stephanie G. Phillips, MS, PhD; Brian P. Pace, MA; George D. Lundberg, MD; Drummond Rennie, MD

Context.—Authorship in biomedical publications establishes accountability, responsibility, and credit. Misappropriation of authorship undermines the integrity of the authorship system, but accurate data on its prevalence are limited.

Objectives.—To determine the prevalence of articles with honorary authors

of fulfillment of authorship criteria,[7-9] we know of no large-scale, multijournal study on the prevalence of articles with honorary authors and ghost authors or

- A. Flanagin *et al*. JAMA 1998: analysis of 809 articles in leading medical journals (*JAMA, Ann. Int. Med., NEJM + 3 smaller journals*)
  - 11% ghost authors
  - 19% honorary authors

OPEN ACCESS Freely available online PLOS MEDICINE

Ghost Authorship in Industry-Initiated Randomised Trials

Peter C. Gøtzsche[1*], Asbjørn Hróbjartsson[1], Helle Krogh Johansen[1], Mette T. Haahr[1], Douglas G. Altman[2], An-Wen Chan[3]

1 Nordic Cochrane Centre, Copenhagen, Denmark, 2 Centre for Statistics in Medicine, Oxford, United Kingdom, 3 Department of Medicine, University of Toronto, Canada

Funding: AWC was supported by the Rhodes Trust. DGA is supported by Cancer Research UK. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

Academic Editor: Liz Wager, United Kingdom

Citation: Gøtzsche PC, Hróbjartsson A, Johansen HK, Haahr MT, Altman DG, et al. (2007) Ghost authorship in industry-initiated randomised trials.

ABSTRACT

Background

Ghost authorship, the failure to name, as an author, an individual who has made substantial contributions to an article, may result in lack of accountability. The prevalence and nature of ghost authorship in industry-initiated randomised trials is not known.

Methods and Findings

We conducted a cohort study comparing protocols and corresponding publications for industry-initiated trials approved by the Scientific-Ethical Committees for Copenhagen and Frederiksberg in 1994–1995. We defined ghost authorship as present if individuals who wrote the trial protocol, performed the statistical analyses, or wrote the manuscript, were not listed as

- Analysis of 44 industry-initiated trials Sweden:
  - 40 trial publications (91%) had ghost authors
    - In 7 of these: ghost author acknowledged
    - 33 trials (75%): no reference to ghost authors
  - 31 trials: statisticians as ghost authors

Guest Authorship and Ghostwriting in Publications Related to Rofecoxib

A Case Study of Industry Documents From Rofecoxib Litigation

Joseph S. Ross, MD, MHS
Kevin P. Hill, MD, MHS
David S. Egilman, MD, MPH
Harlan M. Krumholz, MD, SM

Context Authorship in biomedical publication provides recognition and establishes accountability and responsibility. Recent litigation related to rofecoxib provided a unique opportunity to examine guest authorship and ghostwriting, practices that have been suspected in biomedical publication but for which there is little documentation.

Objective To characterize different types and the extent of guest authorship and ghostwriting in 1 case study.

AUTHORSHIP IN BIOMEDICAL

manuscripts … were ***authored by sponsor employees*** but ***often attributed first authorship to academically affiliated investigators…*** . ***Review manuscripts were often prepared by unacknowledged authors and subsequently attributed authorship to academically affiliated investigators*** who often **did not disclose industry financial support** (*JAMA* 2008: Vol.299)

Draft Version and Final Version of Article Describing the Results of Protocol 078

Rofecoxib does not delay the onset of Alzheimer's disease: results from a randomized, double-blind, placebo-controlled study

External author?, W.H. Visser[1], E. Yuen[1], C. Assaid[1], M.L. Nessly[1], B.A. Norman[1], C.C. Baranak[1], C.R. Lines[1], S.A. Reines[1], G.A. Block[1] on behalf of the Rofecoxib Protocol 078 study group

---

A Randomized, Double-Blind, Study of Rofecoxib in Patients with Mild Cognitive Impairment

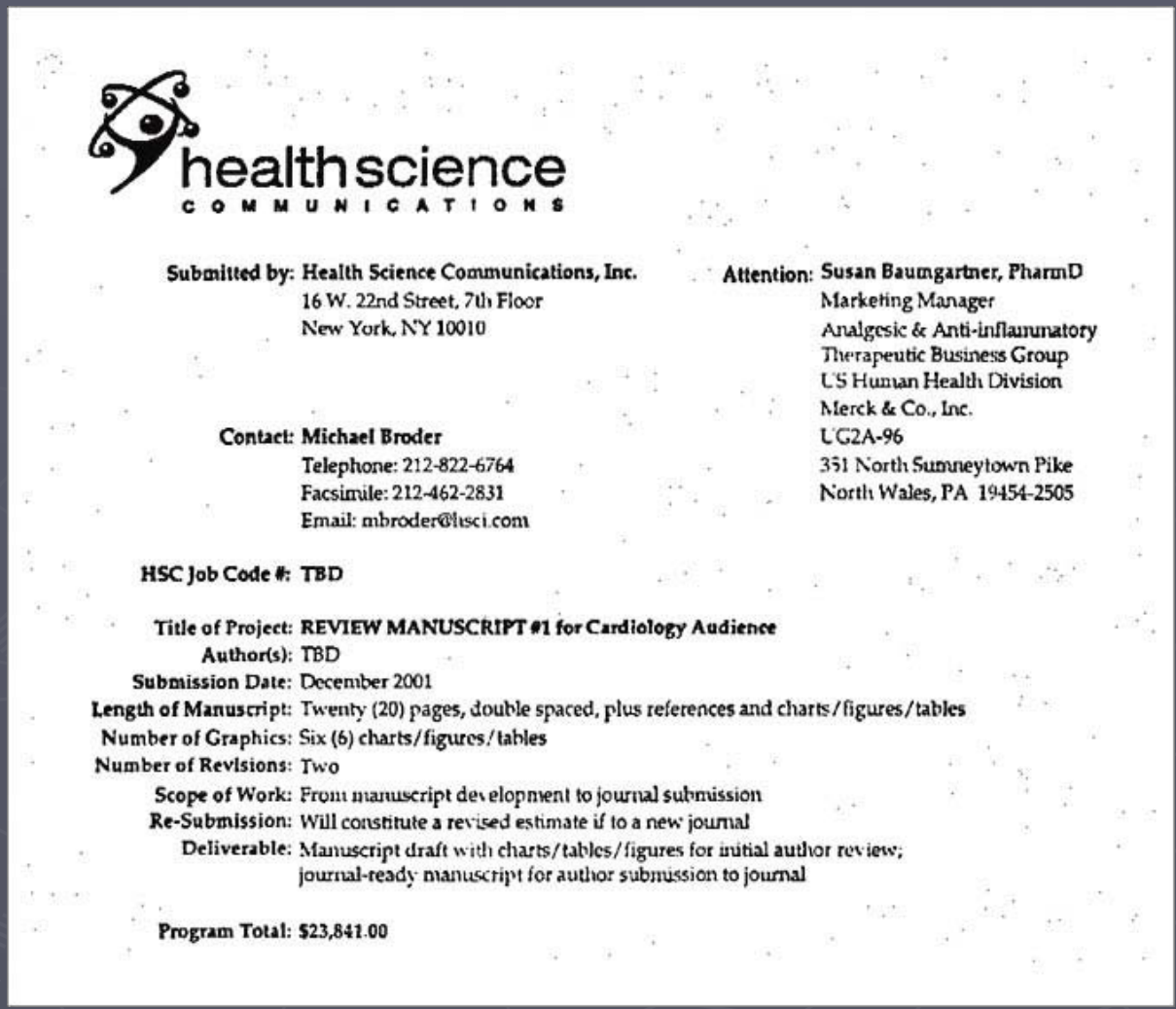
Leon J Thal[1], Steven H Ferris[2], Louis Kirby[3], Gilbert A Block[4], Christopher R Lines*[,4], Eric Yuen[4], Christopher Assaid[4], Michael L Nessly[4], Barbara A Norman[4], Christine C Baranak[4] and Scott A Reines[4], on behalf of the Rofecoxib Protocol 078 study group[5]

[1]University of California, San Diego, CA, USA; [2]New York University School of Medicine, New York, NY, USA; [3]Pivotal Research Centers, Peoria, AZ, USA; [4]Merck Research Laboratories, West Point, PA, USA

Ross, J. S. et al. JAMA 2008;299:1800-1812.

JAMA

Health Science Communications Inc Contract to Provide One 20-Page Review Manuscript With 6 Figures or Tables Intended for a Cardiology Audience for Merck Co Inc at a Cost of $23 841.00



health science
COMMUNICATIONS

Submitted by: Health Science Communications, Inc.
16 W. 22nd Street, 7th Floor
New York, NY 10010

Attention: Susan Baumgartner, PharmD
Marketing Manager
Analgesic & Anti-inflammatory
Therapeutic Business Group
US Human Health Division
Merck & Co., Inc.
UG2A-96
351 North Sumneytown Pike
North Wales, PA 19454-2505

Contact: Michael Broder
Telephone: 212-822-6764
Facsimile: 212-462-2831
Email: mbroder@hsci.com

HSC Job Code #: TBD

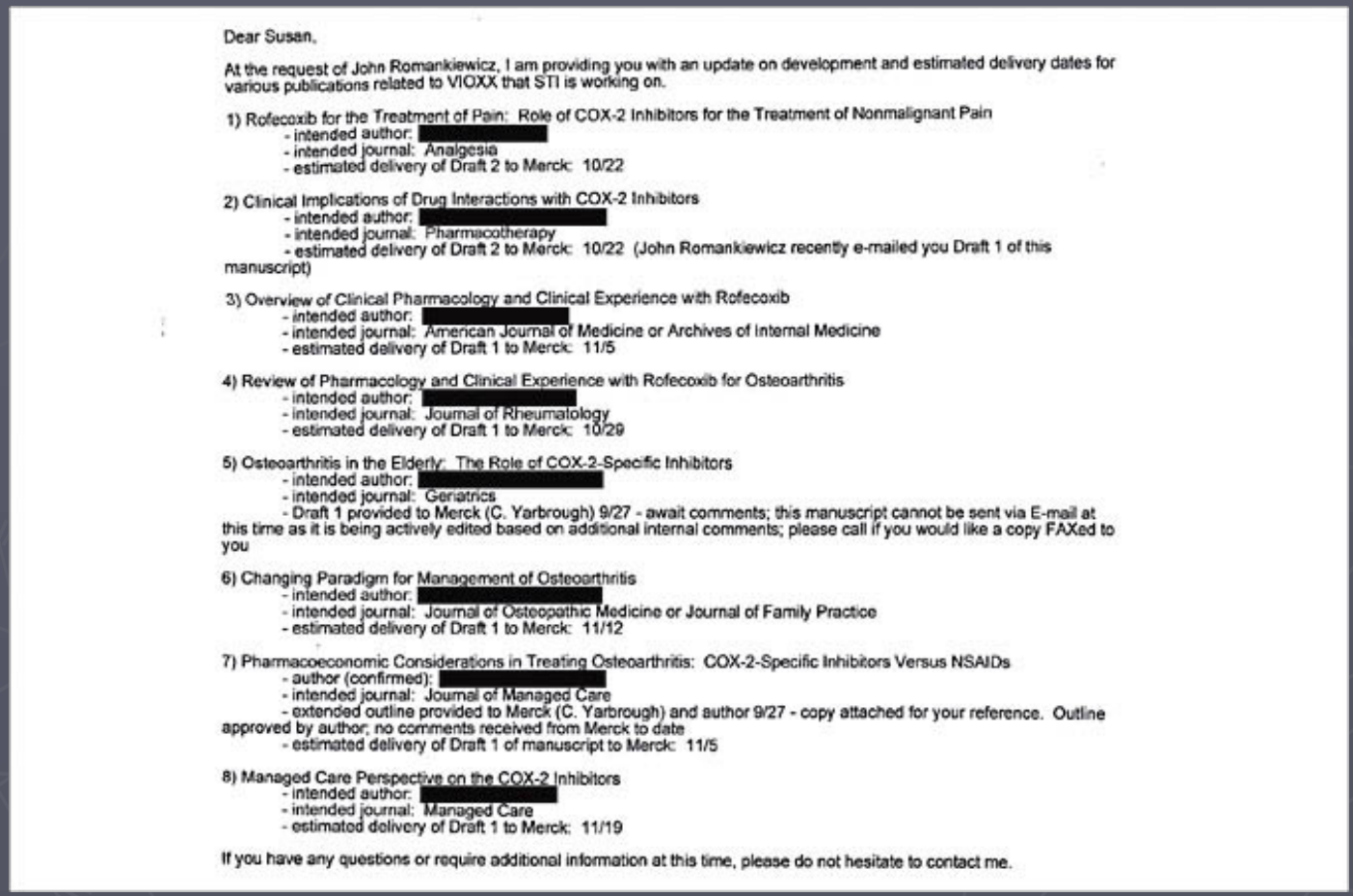
Title of Project: REVIEW MANUSCRIPT #1 for Cardiology Audience
Author(s): TBD
Submission Date: December 2001
Length of Manuscript: Twenty (20) pages, double spaced, plus references and charts/figures/tables
Number of Graphics: Six (6) charts/figures/tables
Number of Revisions: Two
Scope of Work: From manuscript development to journal submission
Re-Submission: Will constitute a revised estimate if to a new journal
Deliverable: Manuscript draft with charts/tables/figures for initial author review; journal-ready manuscript for author submission to journal

Program Total: $23,841.00

Ross, J. S. et al. JAMA 2008;299:1800-1812.

JAMA

October 1999 E-mail Between Representatives of Scientific Therapeutics Information Inc and Merck Co Inc Discussing Contracted Publications Related to Rofecoxib



Dear Susan,

At the request of John Romankiewicz, I am providing you with an update on development and estimated delivery dates for various publications related to VIOXX that STI is working on.

1) Rofecoxib for the Treatment of Pain: Role of COX-2 Inhibitors for the Treatment of Nonmalignant Pain
- intended author: [redacted]
- intended journal: Analgesia
- estimated delivery of Draft 2 to Merck: 10/22

2) Clinical Implications of Drug Interactions with COX-2 Inhibitors
- intended author: [redacted]
- intended journal: Pharmacotherapy
- estimated delivery of Draft 2 to Merck: 10/22 (John Romankiewicz recently e-mailed you Draft 1 of this manuscript)

3) Overview of Clinical Pharmacology and Clinical Experience with Rofecoxib
- intended author: [redacted]
- intended journal: American Journal of Medicine or Archives of Internal Medicine
- estimated delivery of Draft 1 to Merck: 11/5

4) Review of Pharmacology and Clinical Experience with Rofecoxib for Osteoarthritis
- intended author: [redacted]
- intended journal: Journal of Rheumatology
- estimated delivery of Draft 1 to Merck: 10/29

5) Osteoarthritis in the Elderly: The Role of COX-2-Specific Inhibitors
- intended author: [redacted]
- intended journal: Geriatrics
- Draft 1 provided to Merck (C. Yarbrough) 9/27 - await comments; this manuscript cannot be sent via E-mail at this time as it is being actively edited based on additional internal comments; please call if you would like a copy FAXed to you

6) Changing Paradigm for Management of Osteoarthritis
- intended author: [redacted]
- intended journal: Journal of Osteopathic Medicine or Journal of Family Practice
- estimated delivery of Draft 1 to Merck: 11/12

7) Pharmacoeconomic Considerations in Treating Osteoarthritis: COX-2-Specific Inhibitors Versus NSAIDs
- author (confirmed): [redacted]
- intended journal: Journal of Managed Care
- extended outline provided to Merck (C. Yarbrough) and author 9/27 - copy attached for your reference. Outline approved by author; no comments received from Merck to date
- estimated delivery of Draft 1 of manuscript to Merck: 11/5

8) Managed Care Perspective on the COX-2 Inhibitors
- intended author: [redacted]
- intended journal: Managed Care
- estimated delivery of Draft 1 to Merck: 11/19

If you have any questions or require additional information at this time, please do not hesitate to contact me.

Ross, J. S. et al. JAMA 2008;299:1800-1812.

Reporting Mortality Findings in Trials of Rofecoxib for Alzheimer Disease or Cognitive Impairment

A Case Study Based on Documents From Rofecoxib Litigation

Bruce M. Psaty, MD, PhD
Richard A. Kronmal, PhD

CLINICAL TRIALS REGISTRATION IS now the standard expected by the International Committee of Medical Journal Editors.[1] The Food and Drug Administration Amendments Act (FDAAA), effective October 1, 2007, requires not only the registration of all phase 2 to phase 4 clinical trials of new drugs but also the submission of trial findings to a publicly available results database.[2] The purpose is to reduce the selective publication of entire trials or their results.

Sponsors have a marketing interest to represent their products in the best light. This approach conflicts with scientific standards that require the symmetric and comparable reporting of safety and efficacy data. Selective reporting of the results of clinical trials can misrepresent the risk-benefit profile of drugs. We summarize how the sponsor represented mortality findings associated with rofecoxib in clinical trials of patients with Alzheimer disease or cognitive impairment. We reviewed documents that became available during litigation related to rofecoxib involving Merck & Co, including internal company analyses and information provided by the sponsor to the FDA. We also evaluated information in 2 published articles that reported results of these trials. In one article (reporting results of protocol 091) published in 2004, 11 "non-drug related deaths" were reported (9 deaths among 346 rofecoxib patients and 2 deaths among 346 placebo patients). In another article (reporting results of protocol 078) published in 2005, 39 deaths were reported among patients taking study treatment or within 14 days of the last dose (24 among 725 rofecoxib patients and 15 among 732 placebo patients) and an additional 22 deaths in the off-drug period (17 in rofecoxib patients and 5 in placebo patients). However, these articles did not include analyses or statistical tests of the mortality data, and the 2 articles concluded that regarding safety, rofecoxib is "well tolerated."

JAMA, 16 April 2008, Vol 299 (15) 1813

Slide DJ McKnight

BRITISH JOURNAL OF PSYCHIATRY (2003), 183, 22–27

Interface between authorship, industry and science in the domain of therapeutics†

DAVID HEALY and DINAH CATTELL

Background Changes in the character of medical authorship.

Aims To compare the impact of industry-linked and non-industry linked articles.

Method We compared articles on sertraline being coordinated by a medical writing agency with articles not coordinated in this way. We calculated numbers of

Traditionally scientific authors generate, analyse and have access to raw data and prepare an article that disinterested observers would accept reflects an appropriate interpretation of those data. Authorship has been changing, however, and journals now accept that articles may be authored by individuals who have made a substantial contribution to the conception and design or the acquisition of data or analysis and interpretation of data in a

METHOD

This article distinguishes between traditior and non-traditional authorship on the ba of a judgement as to whether the autho are free in a traditional manner to sha with others the raw data from studies th author. We have assumed that autho working on company-sponsored artic are, in general, not at liberty to sha proprietary raw data and are even l likely to do so if they have not seen t raw data in the first instance. By raw da here is meant untabulated data; tabulati is arguably a primary and key act authorship. In pharmaceutical-compan sponsored clinical trials, this initial tabul tion is invariably performed either with the company or within a contract resear organisation that passes on tabulated da and trial reports to medical writi agencies. This practice, almost by defi tion, gives rise to a non-traditional fo

- Analysis of Impact Factor of Publications on sertraline (Zoloft ©): 85 papers CMD – 47 non-CMD
  - Current Medical Directions: Communications firm “dedicated to the development of innovative, high quality health care information.”
- **Conclusions**
  - CMD articles: all positive ⇔ non-CMD: 1/2 negative
  - CMD papers in best journals, highest impact factor; highest citation rate (*JAMA, Arch. Gen. Psych., Am. J. Psych., J. Clin. Psychoph*.)

ANXIETY

POST-TRAUMATIC STRESS DISORDER

Author—Title	Vendor	Status
Author TBD—(640) Sertraline vs. placebo in PTSD	Paladin	Poster presented at ECNP, 1997. Paper is completed, but revisions are needed.
Author TBD—(671) Title TBD	Paladin	Poster presented at ECNP, 1998. First draft completed, but additional analyses needed. Both 640 and 671 studies to be submitted soon. One will go to *New England Journal of Medicine* and the other to *JAMA*.

Subtle Impact of Interactions with Industry: Bias

- T.H. Stelfox et al. (1998): Analysis Calc. Channel Ant. Studies
  - 96% of authors of favourable studies; 60% of neutral articles; 37% unfavourable had ties with industry
- Friedberg (1999): 5% reports on new drugs sponsored by company unfavorable $\Leftrightarrow$ 38% independently supported unfavorable
- See also Meta Analyses by Bekelman et al. (JAMA 2003) & Lexchin et al. (BMJ 2003)

Publication Bias

- A.W. Chan *et al* (*BMJ* 2005: 330; JAMA 2004: 291; *CMAJ* 2004: 171)
  - Outcome reporting bias in clinical trials (both industry and CIHR sponsored trials)
- K. Lee *et al. PLoS* 2008: 5(9)
  - > 50% of supporting trials FDA-approved drugs remain unpublished > 5 y after approval

Case Study Publication Bias

- E.H. Turner et al., “Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy” 2008 *NEJM* 358: 252-60.
  - Published literature: 94% studies positive
  - Analysis 74 FDA registered studies
    - Overall: only 51% positive
    - 33 negative studies:
      - 22 not published
      - 11 ***published conveying a positive outcome***

Problems in Disclosing Adverse Events

- **Discussion** « Our systematic review, which included a total of 87 650 patients, documented an association between suicide attempts and the use of SSRIs. We also observed several major methodological limitations in the published trials. A more accurate estimation of risks of suicide could be garnered from investigators fully disclosing all events. »

D. Fergusson *et al.* BMJ 2005;330:396 (19 February), doi:10.1136/bmj.330.7488.396

Publication Controversies

- **Hormone Replacement Therapy**: Analysis Hemminki *et al*. 1997 and 2000 (*BMJ* and *Lancet*): "systematic synthesis of all data from well conducted small clinical (efficacy) trials would have revealed the effect of HRT on cardiovascular risk much earlier even than 1997… [but] many of the studies were unavailable."
- Blumsohn Controversy (*THES* 2005) related to risedronate (P&G): allegations of discrepancy between publication of data (with academic authors) and hidden results of study (analyzed in-house by P&G)

A.G. New York v. GlaxoSmithkline: June 2004

- Elliott Spitzer (AG): “GSK has engaged in repeated and persistent fraud by misrepresentation, concealing and otherwise failing to disclose to physicians information in its control concerning the safety and effectiveness of its antidepressant medication paroxetine in treating children and adolescents.”
- “GSK has allowed positive information …to be disclosed publicly, but has withheld and concealed negative information concerning the safety and effectiveness”

October 1998

SEROXAT/PAXIL
ADOLESCENT DEPRESSION
Position piece on the phase III clinical studies

EXECUTIVE SUMMARY

Results from the 2 placebo-controlled, phase III clinical trials designed to assess the efficacy and safety of Seroxat/Paxil in adolescents with major depression are now available.

Study 329 (conducted in the US) showed trends in efficacy in favour of Seroxat/Paxil across all indices of depression. However, the study failed to demonstrate a statistically significant difference from placebo on the primary efficacy measures. The second study (study 377), which was conducted in Europe, South America, South Africa and the United Arab Emirates, showed a high placebo response rate and failed demonstrate any separation of Seroxat/Paxil from placebo.

Data from these 2 studies are insufficiently robust to support a label change and will therefore not be submitted to the regulatory authorities. Results from Study 329 will be presented in abstract form at the ECNP meeting (Paris, November 1999) and a full manuscript will be progressed. There are no plans to publish data from Study 377.

LIPPINCOTT WILLIAMS & WILKINS

Journal of the American Academy of
CHILD & ADOLESCENT PSYCHIATRY

Volume 40(7) July 2001 pp 762-772

Efficacy of Paroxetine in the Treatment of Adolescent Major Depression: A Randomized, Controlled Trial

[Articles]

KELLER, MARTIN B. M.D.; RYAN, NEAL D. M.D.; STROBER, MICHAEL PH.D.; KLEIN, RACHEL G. PH.D.; KUTCHER, STAN P. M.D.; BIRMAHER, BORIS M.D.; HAGINO, OWEN R. M.D.; KOPLEWICZ, HAROLD M.D.; CARLSON, GABRIELLE A. M.D.; CLARKE, GREGORY N. PH.D.; EMSLIE, GRAHAM J. M.D.; FEINBERG, DAVID M.D.; GELLER, BARBARA M.D.; KUSUMAKAR, VIVEK M.D.; PAPATHEODOROU, GEORGE M.D.; SACK, WILLIAM H. M.D.; SWEENEY, MICHAEL PH.D.; WAGNER, KAREN DINEEN M.D., PH.D.; WELLER, ELIZABETH B. M.D.; WINTERS, NANCY C. M.D.; OAKES, ROSEMARY M.S.; MCCAFFERTY, JAMES P. B.S.

Conclusion article: Paroxetine is **generally well tolerated and effective** for major depression **in adolescents**

Alderman et al 1998 – “sertraline is **safe** and likely to be **effective** in pediatric patients.” (9%)

Ambrosini, Wagner et al 1999 – “sertraline is **effective, safe and well tolerated**” (5.7%)

Keller, Wagner et al 2001 – “study provide[s] evidence of the **safety & efficacy** of paroxetine in the treatment of adolescent depression (5.4%)

Wagner et al 2002 – “these results indicate that treatment of children and adolescents with paroxetine is **safe and generally well-tolerated**.

Geller, Wagner et al 2002 – “paroxetine is a **safe and effective** treatment for OCD in pediatric pts”

Wagner et al 2003 – “sertraline is an **effective and well tolerated** treatment for children and adolescents with MDD”

(slide: D. Healy)

How Did We Get There?

- Huge Financial Interests of & Pressures on Pharmaceutical Sponsors
  - *E.g.* Vioxx
    - $2.5 billion annual sales
    - Loss in Value of Merck Shares on Day of Withdrawal: $ 30 billion
    - Financial Interests Journals: sale 900,000 reprints *NEJM* issue VIOXX: ~ $ 700,000

Relations of authors 44 CPG – with manufacturers product (JAMA 2002)

- 87 % some form of relation
  - 53 % honorarium/travel
  - 64 % speaker honorarium
  - 38 % employee/consultant
  - 58 % research support
  - 6 % equity
- Noteworthy:
  - 7 % thought that their relations influenced the recommendations
  - 19% thought that ***their co-authors' recommendations*** were influenced

Solution CPG conflicts?

- A.S. Detsky (NYT 2002): “We can’t stamp this out. The answer is to sensitize people to accept that it’s a problem.”
- “Our interviewees suggested that an author’s objectivity might actually be maintained by having multiple small relationships with different pharmaceutical companies.”

Financial Rewards Investigators

- Vioxx Litigation: Reveals Payment to Academic Authors for Authorship (*JAMA* 2008)
- Recent Congressional Hearings US: reveal failures to disclose significant payments from pharmaceutical companies and significant stocks (*NYT* Oct. 4, 2008):
  - Dr. C. Nemeroff (Emory): 2000-07: $ 2.7 million (1.2 million not declared to university; $ 960,000 of GSK)
  - Dr. A.F. Schatzberg (Stanford; President APA): $ 4.8 million in stock holdings in drug development company
  - Dr. J. Biederman & T.E. Wilens (Harvard): > $ 1.6 million
  - Dr. M. DelBello (Cincinnati): 2005-07: > $ 238,000

Slippery Slope: It Often Starts ‘Innocently’

- Membership of international expert advisory panel
- Key opinion leader and member speaker’s bureau
- Invitation to present at prestigious meeting
- Sponsor provides “draft slide presentation”
- Sponsor provides text presentation, then “draft publication” based on presentation…

What Can Institutions Do?

- Education and Sensitization. Examples:
  - obligatory courses on research integrity for all researchers in training (introduced UofT 2008)
  - “Researchers’ Oath” UofT 2007
- Develop (& SUPPORT) Appropriate Review Structure as well as Disciplinary and Regulatory Tools
  - Conflict of Interest Guidelines
  - Conflict of Interest Review
  - REBs and COI Committees
- Help Shape New Publication Culture: academic reward structures?

Association of American Medical Colleges: Reports 2001, 2002, 2008

- Disclosure of COI is necessary but not sufficient
- Institutional oversight needed: COI committees
- Presumption in Research: Significant COI Disqualifies Individual Researcher and/or Institution from Participating in Research
  - **Note: 'presumption' can be rebutted, but burden of proof rests with individuals & institutions that involvement is appropriate and necessary**

Other Regulatory Tools

- Sunshine Acts: Disclosure Obligation of Financial Relations Industry-Medical Profession
  - E.g. Minnesota, Vermont
- Professional Organizations
  - Conflict of Interest Regulations or Guidelines
  - Disciplinary Actions on basis of regulations or 'conduct unbecoming a physician'
    - E.g. Ontario College of Physicians and Surgeons Guidelines on Finder's Fees

Structural Transparency: Registration & Results Reporting

- 2005: International Committee of Medical Journal Editors: pre-trial registration condition for publication of trial results
- WHO International Clinical Trials Portal ***http://www.who.int/ictrp/en/***
- Ottawa Statements on Clinical Trials Registration and Results Reporting (2006-2007)

Results Reporting: An Ethical and Funding Agency Requirement

- CIHR: Policy on Access to Research Outputs, September 2007: Obligation to Report Research Results & Make Data Accessible (< 6 months)
- “deposit bioinformatics, atomic, and molecular coordinate data into the appropriate public database . . . immediately upon publication of research results”

(http://www.cihr-irsc.gc.ca/e/34846.html)

… an Increasingly Legal Obligation

- US FDA Amendment Act 2007:
  - Expands ClinicalTrials.gov Registry: obligation to register clinical trials (exc. Phase I)
  - Obligatory results reporting of clinical trials
    - FDA-approved drugs and cleared devices
    - "Basic" Results: Baseline Characteristics, Key Outcomes, Statistical Analyses (and Adverse Events)

Penalties for Non-Compliance

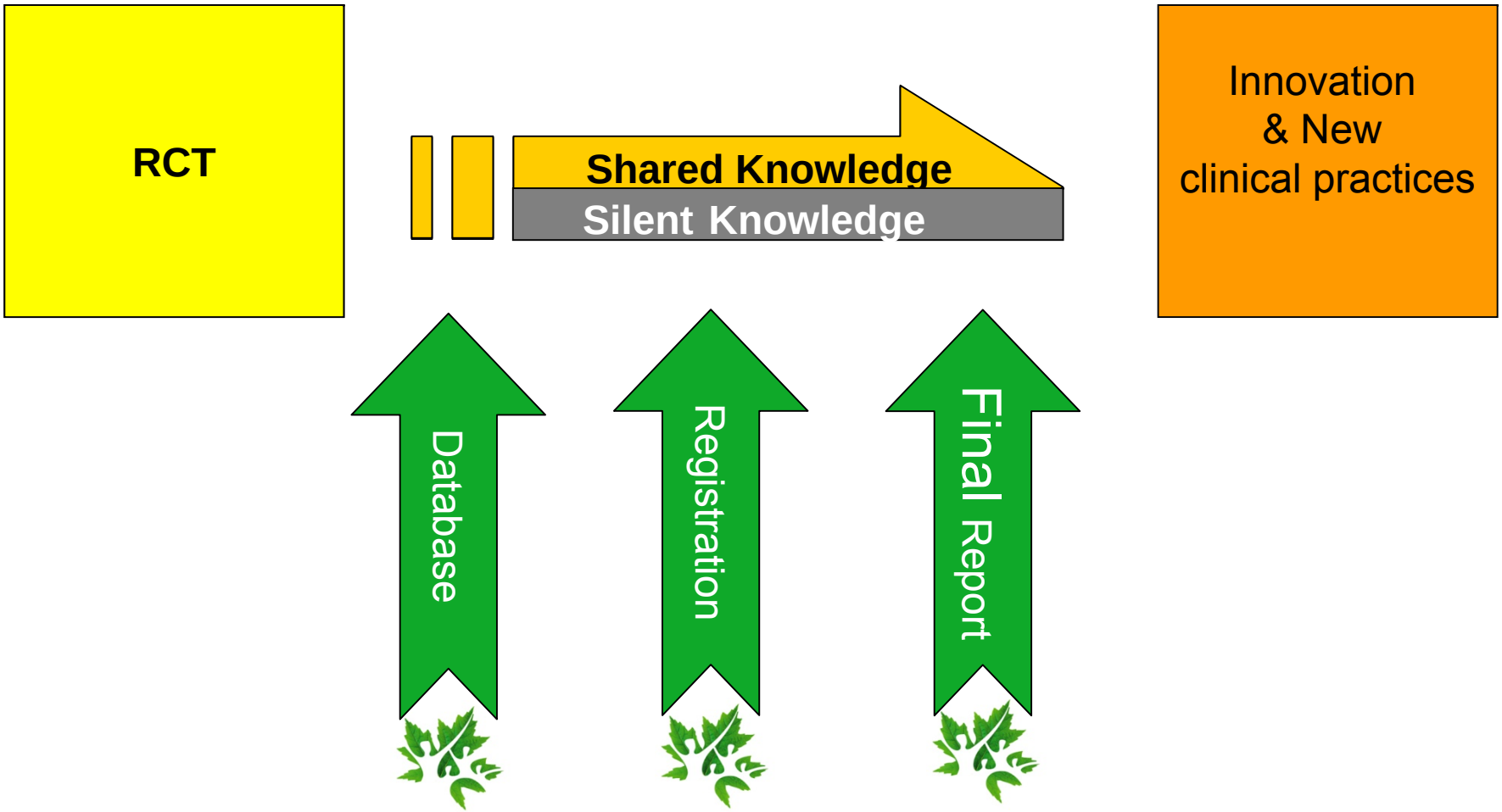
- Withholding of federal funding (e.g., from NIH, VA, others)
- Monetary fines -- Up to $10,000 per violation and $10,000 per day
- Notices of non-compliance posted in registry/results database

What can ethics committees do?

- Require registration in recognised registry (WHO/ICMJE)
  - require the registration number
  - use the summary data posted on the registry- compare with the protocol
  - Look at the results registry to assess scientific validity and value of trial
  - verify the possible redundancy of the proposed trial

CIHR

(Slide: K. Krleža-Jerić)



Limits of Registration System

- Enforceability registration requirement?
  - ICMJE: enforcement related to publication
  - WHO: no enforcement other than 'moral authority'
- Penalties Necessary: Register Trials for Serious & Life-Threatening Diseases US: significant non-compliance (prior to FDA Amendment Act!): Only 48% of 127 cancer trial protocols sponsored by pharmaceutical companies were submitted to the registry (Derbis J, et al (2003): reported by Turner PloSMedicine 2004.
- **Access to raw data?**
- **Sponsor still controls clinical trials**

- « The findings from this case study suggest that additional protections for human research participants, including new approaches for the conduct, oversight, and reporting of industry-sponsored trials, are necessary. A clinical trials system in which sponsors fund the trials that are conducted by independent investigators would provide additional protections.”

BM Psaty & KR Kronmal, “**Reporting Mortality Findings in Trials of Rofecoxib... »** *JAMA.* 2008;299(15):1813-1817.

More Radical Reform

- M. Angell & S. Krimsky: Independent Drug Testing Agency to Separate those with financial interests in outcome of research and those who design, conduct, analyze and publicize results
- W. Ray & M. Stein, “Reform of Drug Regulation—Beyond an Independent Drug-Safety Board” 2006 *NEJM* 194-201 (354(2): New Independent Drug Agency, funded by tax on pharmaceuticals:
  - *Center for Drug Approval*
  - *Center for Post-Marketing Studies*
  - *Center for Drug Information*

Conclusion

- Strengthen Regulatory Tools COI
- Promote Transparency
  - Financial Relations
  - Research Results
- Separation of academic & regulatory interests AND RESEARCH CONDUCT from industry interests