Industry Supported RCT: Some Food for Thoughts

Zeev N. Kain, MD, MBA, MA (hon), FAAP
Associate Dean for Clinical Research
Professor and Chair
Department of Anesthesiology and Perioperative Care
University of California, Irvine

My Disclosure

- Pharam $: Hoffman La Roche, Anesta, Aspect (2001 last support).

- NIH $: Since 1996

- Member of Editorial boards:
  - Anesthesiology, Pediatrics, J Clin Anesth, J Pediatr Psych, Anesth News

The Pharmaceutical Industry

- Of the 196 new chemical entities approved by the FDA between 1981 and 1990, 92% were developed by the pharmaceutical industry ($6B budget)
- Advanced significantly our scientific knowledge
- Increased life span
- $ for tx of diseases in developing countries
- Huge research budgets

A Bedtime Story : Awareness

Frequency of Anesthesia in the US:
21 Million per year in NA

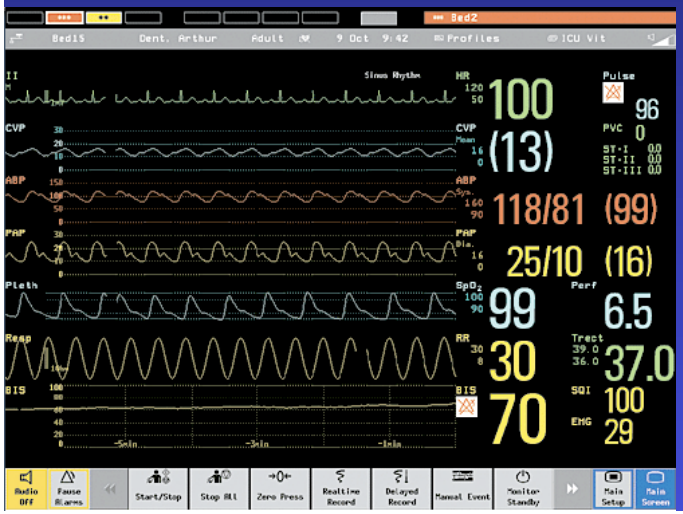
Incidence of Awareness:
1-2 per 1000? (define, measure)

Outcomes:
Psychological (immediate, delayed)

Solutions:
Old (HR, BP)
New (BIS)

Depth-of-Anesthesia Monitor: BIS

"The global market leader is the bispectral index system (BIS, Aspect Medical Systems), which relies on a proprietary algorithm for processing an EEG and alerts the anesthesiologist if the depth of anesthesia is inadequate."



Bispectral Index During Isoflurane Anesthes Pediatric Patients

Simon D. Whyte, MB, BS, FRCA, and Peter D. Booker, MB, BS, MD, FRC
Jackson-Rees Department of Anesthesia, Royal Liverpool Children's Hospital and the Li Anesthesia, United Kingdom

Validation of the Bispectral Index Monitor Du and Deep Sedation in Children

Nicole Brown McDermott, MD, Tamitha VanSickle, MD, Dominika Mc
Robert H. Friesen, MD

Department of Anesthesiology, The Children's Hospital and the University of Colorado Sch Denver, Colorado

PEDIATR
OFFICIAL JOURNAL OF THE AMERICAN ACADE

In this study, we tested the validity of the bispectral index (BIS) monitor during conscious and deep sedation of children by comparing it with the University of Michigan Sedation Scale (UMSS), a validated observational pediatric sedation scale. Eighty-six children <12 yr of age were enrolled in this observational study. The subjects underwent conscious or deep sedation administered by non-

during sedation; personnel ad cations and performing the p the BIS and UMSS scores. Sign BIS scores and UMSS scores w 0.0001), including in subjects −0.761, $P < 0.001$). Poor correl amine or an oral combinatio eridine w rrelates w ure of cons (A

Hundreds of Aspect Supported Trials !

Bispectral Index as a G

Karen S. Powers, Emily B. N
Elise W. van der Ja

British Journal of Anaesthesia **86 (2)**: 209–12 (2001)

EEG bispectral index and hypnotic component of anaesthesia induced by sevoflurane: comparison between children and adults

C.-S. Degoute[1]*, C. Macabeo[1], C. Dubreuil[2], R. Duclaux[3] and V. Banssillon[1]

[1]Department of Anaesthesiology and Intensive Care, [2]Department of ENT Surgery and [3]Department of Physiology (CNRS UPRESA 5020), Centre Hospitalo-Universitaire Lyon-Sud, France

**Corresponding author: Service d'Anesthésie-réanimation, Centre Hospitalo-Universitaire Lyon-Sud, F-69495 Pierre Bénite Cedex, France*

Non Industry Supported Trial

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 13, 2008 VOL. 358 NO. 11

Anesthesia Awareness and the Bispectral Index

Michael S. Avidan, M.B., B.Ch., Lini Zhang, M.D., Beth A. Burnside, B.A., Kevin J. Finkel, M.D., Adam C. Searleman, B.S., Jacqueline A. Selvidge, B.S., Leif Saager, M.D., Michelle S. Turner, B.S., Srikar Rao, B.A., Michael Bottros, M.D., Charles Hantler, M.D., Eric Jacobsohn, M.B., Ch.B., and Alex S. Evers, M.D.

Non Industry Supported Trial

- No reproduction the results of previous studies that reported lower anesthesia awareness with BIS monitoring,
- Awareness occurred even when BIS values within the target ranges.
- Findings do not support routine BIS monitoring as part of standard anesthesia practice.

The stock Market….

NewScientist SEARCH

NEWS | EXPLORE BY SUBJECT | SPECIAL REPORTS | LAST WORD | SUBSCRIBE | BLOGS | VIDEO |

BREAKING NEWS

The World's No.1 Science & Technology News Service

LATEST HEADLINES

Cosmic dust gives water a helping hand

Bird migration at mercy of

How information escapes from a black hole

'Self-digesting' biofuel plants could ease food crisis

Adapted aircon can track movement in the home

Treating animals like molecules aids census

ALL LATEST NEWS

PRINT EDITION

Subscribe

Is this a Unique case?

Research funded by drug companies is 'biased'

favour the sponsor's product, reveals a new study.

Researchers analysed 30 previous reports examining pharmaceutical industry-backed research and found the conclusions of such research were four times more likely to be positive than research backed by other sponsors.

"What we found was that in almost all cases there was a bias - a rather heavy bias - in favour [of a drug] when the study was industry funded," study leader Joel Lexchin told **New Scientist**.

The main reasons for this, say the team, may be that positive studies are more likely to be published than negative ones. Also, inappropriate comparison drugs may be used in these trials, skewing findings in favour of the tested product.

The new analysis is published in a special issue of the *British Medical Journal*, which focuses on the close relationship between doctors and the pharmaceutical industry.

UCSF study questions drug trial results

When drug companies sponsor research, their products more likely to perform well

Victoria Colliver, Chronicle Staff Writer
Tuesday, June 5, 2007

Money talks -- and very loudly when a drug company is funding a clinical trial involving one of its products, according to a study released Monday.

UCSF researchers looked at nearly 200 head-to-head studies of widely prescribed cholesterol-lowering medications, or statins, and found that results were 20 times more likely to favor the drug made by the company that sponsored the trial.

"We have to be really, really skeptical of these drug-company-sponsored studies," said Lisa Bero, the study's author and professor of clinical pharmacy and health policy studies at the university.

The research, reported in the online editions of PLoS Medicine, a San Francisco medical journal, focused on studies of six statins -- including Pfizer Inc.'s Lipitor, Merck & Co.'s Zocor and the generic drug Mevacor -- that had already been approved by the Food and Drug Administration.

Business & Finance

- Get Quote:

Detailed

Submit

Symbol Lookup

- Main Business & Finance Page: Stock quotes, portfolio, funds and more...
- Small Business Center: A new resource for small businesses. Get expert advice, forms and more.
- SFGate Technology: It's a high-tech world - - we just plug you into it...

Financial ties and concordance between results and conclusions in meta-analyses:

Objective: To determine whether financial ties to one drug company are associated with favorable results or conclusions in meta-analyses on antihypertensive drugs.

Setting: Meta-analyses: published up to December 2004

Outcome measures: The main outcomes were the results and conclusions of meta-analyses, with both outcomes separately categorized as being favorable or not favorable towards the study drug.

BMJ

Yank, Rennie, Bero, BMJ, 2007;335;1202-1205

Financial ties and concordance between results and conclusions in meta-analyses:

- 40% of all studies (124) had financial ties to a drug company.

- Multiple logistic regression analyses showed that one drug company remained more likely to report favorable conclusions (5.11, 1.54 - 16.92).

- 37% of drug company articles had a poor concordance between results and conclusions (as compared to 0% of non profit)

BMJ

Yank, Rennie, Bero, BMJ, 2007;335;1202-1205

Any Other Studies?

Djulbegovic B, et al. The uncertainty principle and industry-sponsored research. *Lancet* 2000; 356: 635–38.
(136 trials in multiple myeloma found that more than 75% of IST reported results that favoured the new therapy over standard therapy)

Davidson RA. Source of funding and outcome of clinical trials. *J Gen Intern Med* 1986; 1: 155–58.
(pharmaceutical company were about three times more likely to report in favour of the experimental therapy)

Cho MK, Bero LA. The quality of drug studies published in symposium proceedings. *Ann Intern Med* 1996; 124: 485–89.
(trials with drug company support were much more likely to report in favour of the experimental therapy, 98% vs 79%).

Friedberg et al.. Evaluation of conflict of interest in economic analyses of new drugs used in oncology. *JAMA* 1999; 282: 1453-7.
(only 5% of industry-supported analyses reported unfavorable conclusions compared with 38% of not-for-profit sponsored studies)

Why is this Happening?

Publication issues?

Examples of Methods for Pharmaceutical Companies to Get the Results They Want from Clinical Trials

- Conduct a trial of your drug against a treatment known to be inferior.
- Trial your drugs against too low a dose of a competitor drug.
- Conduct a trial of your drug against too high a dose of a competitor drug (making your drug seem less toxic).
- Conduct trials that are too small to show differences from competitor drugs.
- Use multiple endpoints in the trial and select for publication those that give favourable results.
- Do multicentre trials and select for publication results from centres that are favourable.
- Conduct subgroup analyses and select for publication those that are favourable.
- Present results that are most likely to impress—for example, reduction in relative rather than absolute risk.

Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies

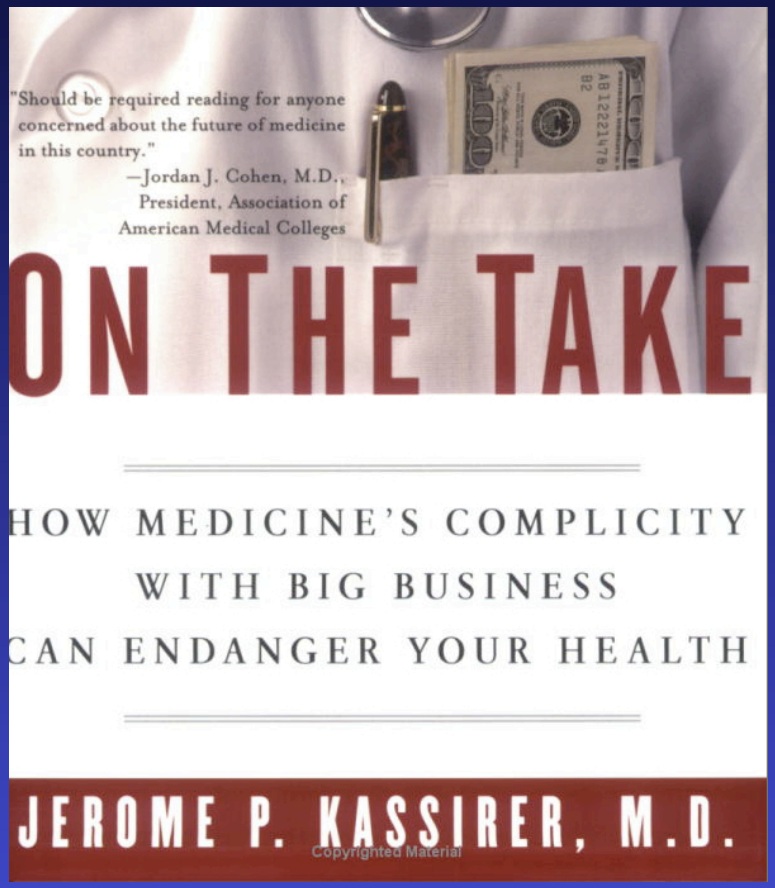
PLoS Medicine | www.plosmedicine.org May 2005 | Volume 2 | Issue 5 | e138

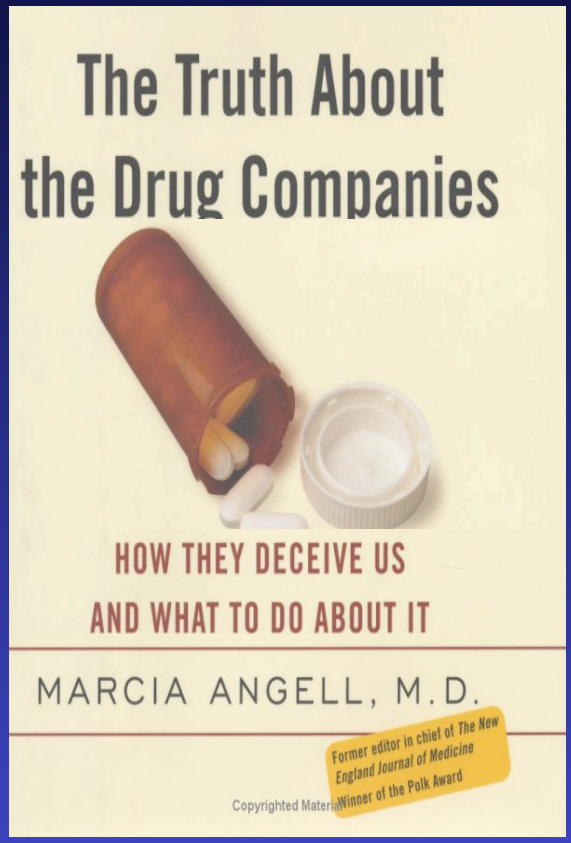
But surely the medical journals are protecting us?

Lapses at the New England Journal of Medicine

Richard Smith
Former Editor of the BMJ,
Journal of the Royal Society of Medicine,
2006;99:3801-1

NEJM: The Recent Editorial History





NEJM: The Recent Editorial History

- Jeff Drazen, had had financial connections with 21 drug companies between 1994 and 2000
- Drug advertisement profits to NEJM (and other)
- The Vioxx scandal (Drazen knew about the death in 2001), letter to the editor rejected.
- Publication of the error that was made after a consultation by a PR consultant input

Armstrong D. Bitter pill: how the New England Journal missed warning signs on Vioxx. Wall Street Journal 2006 May 15:A1

The New England Journal missed Vioxx warning signs

Monday, May 15, 2006
By David Armstrong, The Wall Street Journal

BOSTON -- In August 2001, a Seattle pharmacist called a radio show on which Jeffrey Drazen, the top editor of the New England Journal of Medicine, was appearing. On the air, the pharmacist, Jennifer Hrachovec, begged Dr. Drazen to update an article in the journal that touted the benefits of the painkiller Vioxx while playing down its heart risks.

Dr. Drazen was dismissive. "We can't be in the business of policing every bit of data we put out," he told Dr. Hrachovec.

Three years later, Merck & Co. pulled Vioxx from the market, citing higher risk of heart attacks and strokes in some patients. An estimated 20 million Americans took Vioxx, and more than 11,500 lawsuits have been filed against Merck alleging death and other damage from the drug.

NEJM: The Recent Editorial History

- Jeff Drazen, had had financial connections with 21 drug companies between 1994 and 2000
- Drug advertisement profits to NEJM (and other)
- **The Vioxx scandal (Drazen knew about the death in 2001), letter to the editor rejected.**
- **Publication of the error that was made after a consultation by a PR consultant input**

Armstrong D. Bitter pill: how the New England Journal missed warning signs on Vioxx. Wall Street Journal 2006 May 15:A1

THE DOCTOR'S WORLD

For Science's Gatekeepers, a Credibility Gap

By LAWRENCE K. ALTMAN, M.D.

The New York Times

"Journals have devolved into information laundering operations for the pharmaceutical industry",
Richard Horton, editor of the *Lancet*, in March 2004

Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies

PLoS Medicine | www.plosmedicine.org May 2005 | Volume 2 | Issue 5 | e138

NEUROLOGY 2006;67:378–379

Editorial

HIGH LIGHT

How skeptical should we be about industry-sponsored studies?

David Chadwick, MD; and Michael Privitera, MD

How are we going to fix this?

JAMA®

Reporting Conflicts of Interest, Financial Aspects of Research, and Role of Sponsors in Funded Studies

Phil B. Fontanarosa, MD, MBA
Annette Flanagin, RN, MA
Catherine D. DeAngelis, MD, MPH

RESEARCH STUDIES IN BIOMEDICAL JOURNALS ARE INcreasingly scrutinized, not only for their scientific findings and clinical and public health implications, but also because of concerns related to conflicts of interest of investigators[1] and concerns about misleading reporting of industry-sponsored research.[2] The perception that conflicts of interest or financial concerns may have potentially detrimental effects on medical science has prompted medical journals to critically examine and more vigorously enforce policies for disclosure of potential conflicts and for reporting of relationships with industry.[3]

The need for transparency in reporting the financial conflicts of interest of authors and the relationships between investigators and funding sources has never been greater and is essential to help maintain confidence and trust in the scientific integrity of medical research articles. In this editorial, we review and update our policies for authors reporting conflicts of interest and disclosing financial support and other paid contributions for their work, as well as the requirements for reporting of industry-sponsored studies. Much of this information and the rationale for these policies have been described in previous editorials[4] and are detailed in the current *JAMA* Instructions for Authors.[3]

the time of publication. Authors also must report other financial interests that represent potential future financial gain, such as relevant filed or pending patents or patent applications in preparation. Although many universities and other institutions and organizations have established policies and thresholds for reporting financial interests and other conflicts of interest, *JAMA* requires complete disclosure of all relevant financial relationships and potential financial conflicts of interest, regardless of amount or value. Authors who are uncertain about what might constitute a potential financial conflict of interest should always err on the side of full disclosure and should contact the editorial office if they have questions or concerns.

To report this information, each author is required to sign and submit the following disclosure statement on the *JAMA* authorship form: "I certify that all my affiliations with or financial involvement, within the past 5 years and foreseeable future (eg, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, royalties) with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed."[3] Authors may include these disclosures on the *JAMA* financial disclosure form or should indicate that the disclosures are included in an attachment to the form or in the manuscript. In addition, authors who have no relevant financial interests should provide a statement indicating that they have no financial interests related to the mate-

Extra scrutiny for industry funded trials

BMJ

JAMA's demand for an additional hurdle is unfair—and absurd

Kenneth J Rothman Stephen Evans

2005;331;1350-1351

Suppose that a biomedical journal invoked a new policy requiring that all authors based in western Europe or North America would receive ordinary peer review, but authors from other countries would receive a peer review with additional hurdles. This policy may seem unfair, but suppose the journal claimed that research has shown that there is a greater prevalence of fraud, bias, and sloppy work among papers coming from these other countries.

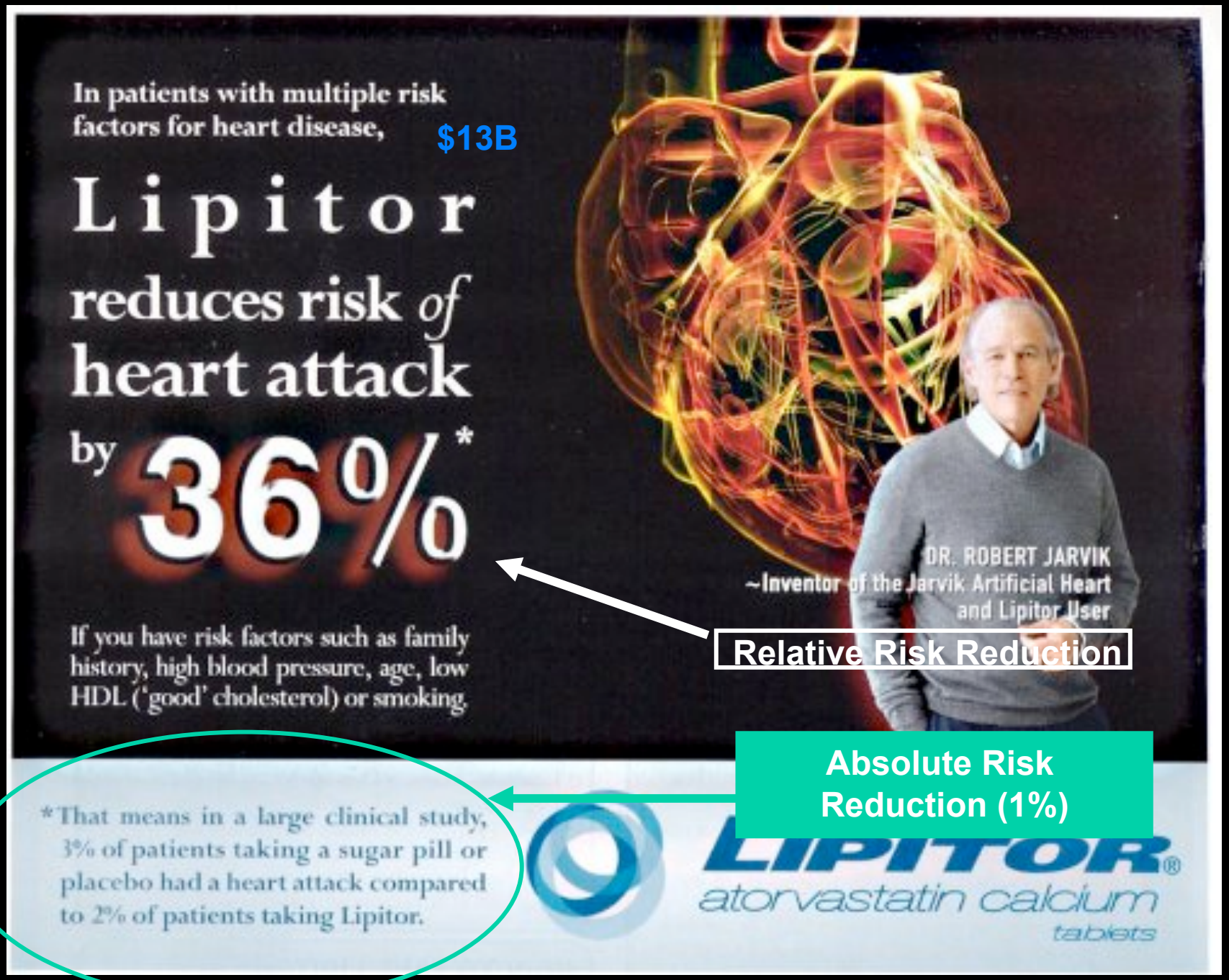
If these events actually transpired, we hope that other biomedical journals would rapidly point out that adopting such a policy would be unfair to authors from non-western countries, even if the premises for it were valid. Indeed, we hope that other editors would decide that it would be unethical to create any hierarchical system for submissions of papers to a biomedical journal. Peer review ought to rest on the content of a submission rather than solely on the basis of presumptions inferred from group affiliation such as nationality.

among authors. We presume that the intent is well motivated, in the sense that the editors at *JAMA* have recognised the potential for a problem—perhaps bias, fraud, or shoddy work—in submissions funded by industry. *JAMA*'s draconian solution, however, punishes the innocent along with the guilty, and denigrates the reliability and professionalism of industry-employed statisticians, whose credentials *JAMA* apparently considers insufficient.

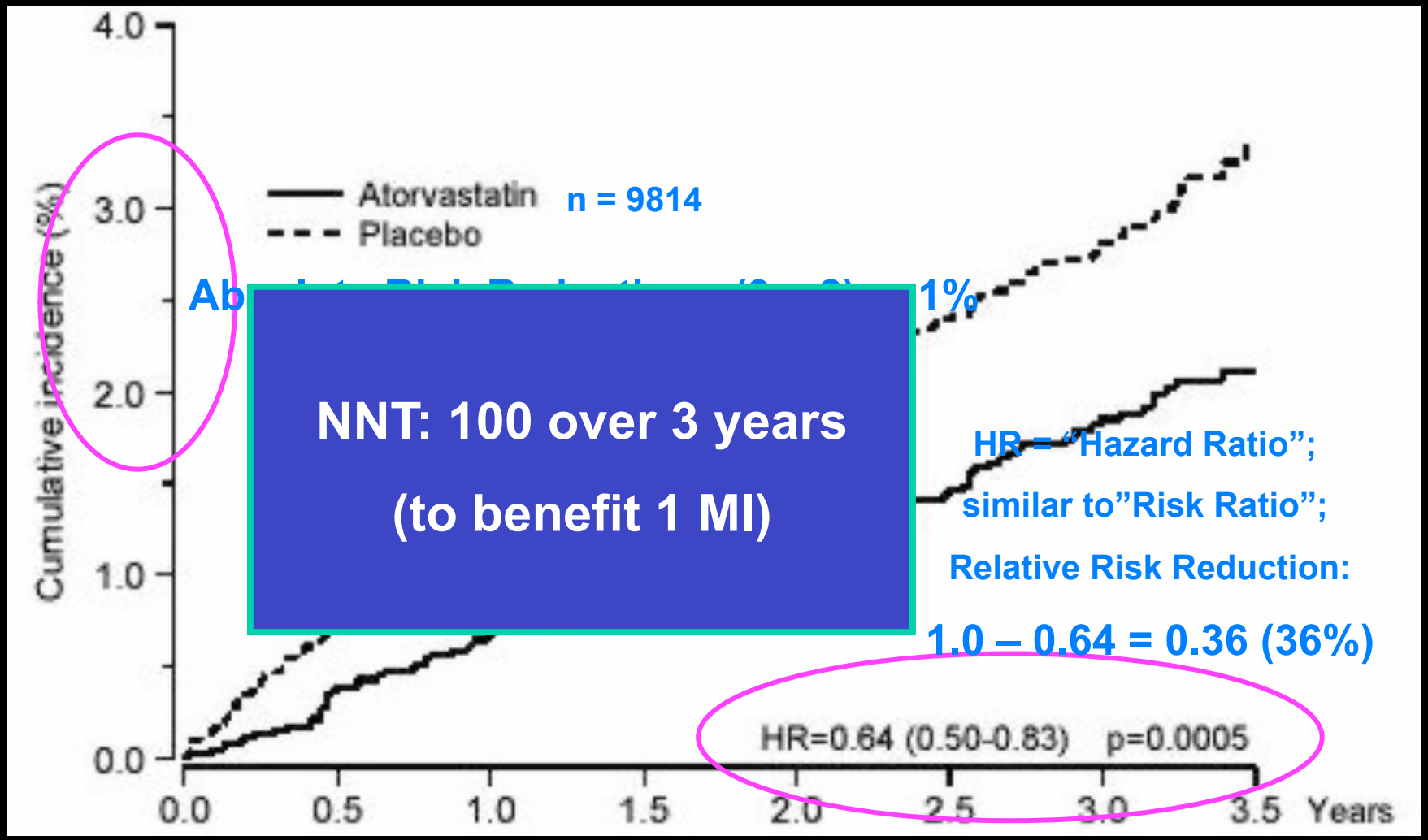
Following these new instructions raises many questions that require arbitrary distinctions. The instructions require an academic statistician either to conduct or to bless the analysis. But what is the mark of a qualified statistician? A degree? Certification by the Royal Statistical Society? And who is academic? A retired professor who becomes an industry consultant? A retired industry statistician who joins a university? Once paid by industry, would an academic statistician remain independent? Will mail order universities be acceptable, or must the universities meet specific accreditation requirements?

So how are we going to fix this?

- Appropriate controls
  - Control dosing issues
  - External validity (age, gender, SES)
- Surrogate endpoints
  - Short term vs Long term
  - Clinically relevant
- The role of academic CROs
- Tight control of study data, analysis, and interpretation by the commercial sponsor is undesirable
- independent data and safety monitoring committee


In patients with multiple risk factors for heart disease,
$13B
Lipitor
reduces risk of heart attack
by 36%*
If you have risk factors such as family history, high blood pressure, age, low HDL ('good' cholesterol) or smoking.
DR. ROBERT JARVIK
~Inventor of the Jarvik Artificial Heart and Lipitor User
Relative Risk Reduction
Absolute Risk Reduction (1%)
*That means in a large clinical study, 3% of patients taking a sugar pill or placebo had a heart attack compared to 2% of patients taking Lipitor.
LIPITOR®
atorvastatin calcium
tablets

Lipitor vs. placebo MI incidence



Sever et al; "ASCOT" Lancet 2003; 361: 1149

THE NUMBER NEEDED TO TREAT

How well do drugs work? Ads and news stories usually say that a medicine slashes the risk of, say, heart attacks by a big number, like 50%. But that often overstates the benefit, because it fails to provide the absolute risk. If only 2 people in a group of 100 are expected to have a heart attack, then a drug that cuts the rate by 50% prevents just 1 heart attack when taken by all 100 people. That's why researchers favor using the "number needed to treat"

"What if you put 250 people in a room and told them they would each pay $1,000 a year for a drug they would have to take every day, that many would get diarrhea and muscle pain, and that 249 would have no benefit? And that they could do just as well by exercising? How many would take that?"

Dr. Jerome R. Hoffman

who have risk factors such as high blood pressure		conditions	precise NNT can't be calculated.
Avandia, which controls blood sugar	1,000+	to prevent heart attacks, other effects of diabetes	The drug reduces blood sugar, but that does not translate into fewer problems, such as kidney failure, nerve damage, amputations.
Zetia, which lowers cholesterol	1,000+	to prevent heart disease	Companies admit that it has not been shown to reduce heart disease or heart attacks.

Data: Bandolier, Therapeutics Initiative, *BusinessWeek*

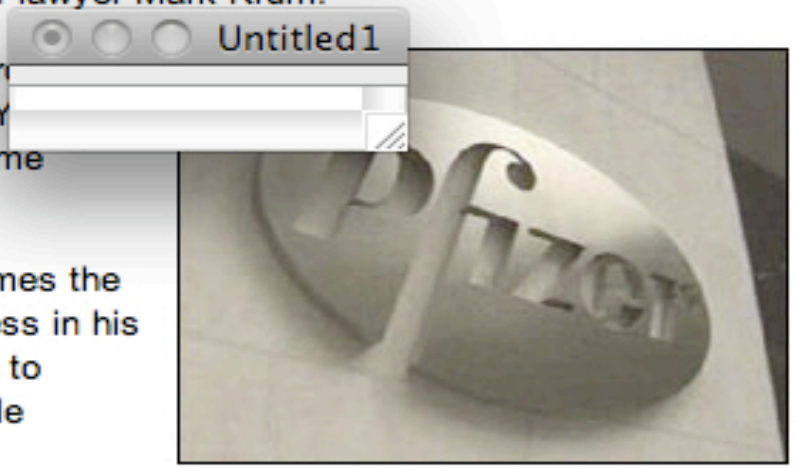
Pfizer sued over alleged Lipitor side effects

Two plaintiffs say cholesterol-cutting blockbuster caused nerve and muscle damage, memory loss. Pfizer says the drug is safe.

By Aaron Smith, CNNMoney.com staff writer
June 8, 2006: 1:03 PM EDT

NEW YORK (CNNMoney.com) - Lipitor, the world's top-selling drug from the world's leading pharmaceutical company, has been targeted by two lawsuits blaming it for memory loss and damage to the nervous system.

The plaintiffs also have accused Pfizer (down $0.49 to $23.42, Research), maker of the cholesterol-cutting drug, of having "failed to inform consumers and the medical profession of serious side effects associated with the statin Lipitor," according to a statement from plaintiff lawyer Mark Krum.



Plaintiffs Charles Wilson, 60, a former insurance executive fr
Atlanta, and Michael Mazzariello, 47, an attorney from New Y
filed the lawsuits Wednesday night in New York State Supreme
Court.

Wilson took Lipitor for 17 months from 2002 to 2003 and blames the drug for memory loss, nervous-system damage, and weakness in his arms and legs, which caused him to leave his job, according to Krum. Mazzariello blames Lipitor for memory loss and muscle damage, said Krum, and he needs a cane to walk.

ECONOMICS, EDUCATION, AND HEALTH SYSTEMS RESEARCH
SECTION EDITOR
RONALD D. MILLER

EDITORIAL

The Legend of the *P* Value

Zeev N. Kain, MD, MBA

Center for the Advancement of Perioperative Health and Department of Anesthesiology & Pediatrics & Child Psychiatry, Yale University School of Medicine, New Haven, Connecticut

Although there is a growing body of literature criticizing the use of mere statistical significance as a measure of clinical impact, much of this literature remains out of the purview of the discipline of anesthesiology. Currently, the magical boundary of $P < 0.05$ is a major factor in determining whether a manuscript will be accepted for publication or a research grant will be funded. Similarly, the Federal Drug Administration does not currently consider the magnitude of an advantage that a new drug shows over placebo. As long as the difference is statistically significant, a drug can be advertised in the United States as "effective" whether clinical trials proved it to be 10% or 200% more effective than placebo. We submit that if a treatment is to be useful to our patients, it is not enough for treatment effects to be statistically significant; they also need to be large enough to be clinically meaningful.

related to this complex problem. Please note that a detailed discussion of the underlying statistics involved in this topic is beyond the scope of this editorial.

When examining the report of a clinical trial investigating a new treatment, clinicians should be interested in answering the following three basic questions:

1. Could the findings of the clinical trial be solely a result of a chance occurrence? (i.e., statistical significance)
2. How large is the difference between the primary end-points of the study groups? (i.e., impact of treatment, effect size)
3. Is the difference of primary end-points between groups meaningful to a patient? (i.e., clinical significance)

It was Sir Ronald A. Fisher, an extraordinarily in-

So how are we going to fix this?

- independent data and safety monitoring committee
- Publication issues and control
- Disclosure of all interests

Myth:

You should believe everything you read in a medical journal.

Reality:

Life is not that simple.