Industry Supported RCT: Some Food for Thoughts

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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.”
Hundreds of Aspect Supported Trials!
Non Industry Supported Trial

The NEW ENGLAND JOURNAL of MEDICINE

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....
Research funded by drug companies is 'biased'.

Is this a Unique case?
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. The trials typically involved comparing the effectiveness of a drug to one that was already approved, or placebo, and assessing how the study's funding source might bias the outcome.
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.
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)

Yank, Rennie, Bero, BMJ, 2007;335;1202-1205
Any Other Studies?

*(136 trials in multiple myeloma found that more than 75% of IST reported results that favoured the new therapy over standard therapy)*

*(pharmaceutical company were about three times more likely to report in favour of the experimental therapy)*

*(trials with drug company support were much more likely to report in favour of the experimental therapy, 98% vs 79%)*.

*(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.
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

On the Take
How Medicine’s Complicity with Big Business Can Endanger Your Health
Jerome P. Kassirer, M.D.

The Truth About the Drug Companies
How They Deceive Us and What to Do About It
Marcia Angell, M.D.
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

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.
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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

How skeptical should we be about industry-sponsored studies?

David Chadwick, MD; and Michael Privitera, MD
How are we going to fix this?
Reporting Conflicts of Interest, Financial Aspects of Research, and Role of Sponsors in Funded Studies

Phil B. Fontanarosa, MD, MBA
Annette Flanagan, RN, MA
Catherine 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 and concerns about misleading reporting of industry-sponsored research. 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.

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 and are detailed in the current JAMA Instructions for Authors.

The Editors of JAMA require authors to disclose all financial and other interests that might be perceived as affecting the interpretation of their study results, from the time of submission through 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 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." 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

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

Kenneth J Rothman  Stephen Evans

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, 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.

*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 vs. placebo MI incidence

Absolute Risk Reduction = (1 - 0) = 1%

Relative Risk Reduction:
1.0 – 0.64 = 0.36 (36%)

NNT: 100 over 3 years (to benefit 1 MI)

HR = "Hazard Ratio";
similar to "Risk Ratio";

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avandia, which controls blood sugar</td>
<td>1,000+ to prevent heart attacks, other effects of diabetes</td>
</tr>
<tr>
<td>Zetia, which lowers cholesterol</td>
<td>1,000+ to prevent heart disease</td>
</tr>
</tbody>
</table>

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 from Atlanta, and Michael Mazzariello, 47, an attorney from New York, 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.
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.