Managing the Unmanageable: Conflicts of Interest and Bias in Research

Lisa A. Bero, Ph.D.
University of California, San Francisco
Conflict of interest: What is it?

• Circumstances that create a risk that professional judgments or actions regarding a primary interest will be unduly influenced by a secondary interest

• A risk--not necessarily the existence of biased judgment or action
Cycle of bias in research

Publication → Question → Population → Methods → Conduct → Publication
Why do we care about bias?

• Empirical evidence of bias
• Multiplicative effect in medical literature
  … and elsewhere
• Erodes evidence-base for health care decisions
• We may “do no good” or “more harm than good”
Why do we care about COI?

- Marketing = skepticism
- Research = trust
- Industry funding for research is substantial
- A growing number of researchers also have **personal** financial ties to their sponsors
- Financial ties = conflicts of interest
- COI associated with bias
Association of sponsorship and outcomes that favor the sponsor

MH pooled odds ratio = 4.051419 (95% CI = 2.978525 to 5.510779)

Why the association?

• Framing / social construction of the research question
• Designing the study
• Conducting the study
• Publishing the study (or not)
Drug Industry Documents

- Lawsuit against Parke-Davis by a former employee
- Company promoted gabapentin (Neurontin) off-label for unapproved uses
- Settlement agreement – documents available at http://dida.library.ucsf.edu

“publication strategy”

• Goal: to use research not as a means to gain FDA approval for new indications but “to disseminate the information as widely as possible through the world’s medical literature”
  – Ghost written articles
  – Seeding trials
Ghost Authors

• MECC offered substantial assistance in the development of manuscripts, reporting in a status report that “at [the author’s] request, we did an extensive literature search and submitted selected articles to him for reference…. We have offered him help in identifying and collecting his appropriate cases, analyzing data, writing a manuscript, or whatever he needs.”

• 7 published articles: 4 favorable, 3 neutral

• Only 1 article disclosed author tie with Parke-Davis
Uncontrolled open-label study; gabapentin titrated up to 3600 mg/day (twice the maximum FDA-approved limit)

700 physicians enrolled 2100 patients

Published report: “examined the effectiveness of gabapentin” in this dose range
IV. **Overview of 1996 Strategies**

The Neurontin 1996 promotional campaign expands on the positioning established for Neurontin in 1995. It asks physicians to use Neurontin earlier and emphasizes the need to titrate to effect by titrating Neurontin to higher doses.
Selective publication

- Marketing assessment: “The results of the recommended exploratory trials in neuropathic pain, *if positive, will be publicized in medical congresses and published.*” [italics added]
- “the results of [the negative trial] will not be published.”
- The positive trial was published, negative trial not found through PubMed/CL search.
DISTRIBUTION

O. Brandicourt, M.D. (PD, Product Planning, Morris Plains, NJ USA)

Neurontin® Marketing Assessments

Enclosed is the final version of the Marketing Assessment for Neurontin® in neuropathic pain and spasticity.

The results of the recommended exploratory trials in neuropathic pain, if positive, will be publicized in medical congresses and published, but there is no intention to fully develop this indication at this point. No investment is recommended for spasticity.
No overt difference in the trial methodology or the patients, which could explain the difference in the results between 945-77 and 946-177, has been detected. The question was raised whether it would be possible to investigate the patient history (primary care physician records) to determine if patient alcoholism could have been involved or patient screening was adequately performed.

ACTION: • The results of 945-177 will not be published, nor will the combined results of 945-77 plus 945-177 be published.
• The effort required to investigate the potential cause for the difference in results between 945-77 and 945-177 was deemed not feasible relative to the potential need for such explanation. It was decided not to pursue any further investigation to explain the difference.
• 945-78, the open-label extension of 945-77, which permits Neurontin doses to be increased as high as deemed necessary, will be completed by year end 1997.

II. Monotherapy

Based on the clinical data from 945-77 (efficacy and safety have already been shown) and the ongoing data from 945-82 (inconclusive results — doses not statistically different) must be included in the dossier for safety data, but is not considered a pivotal trial.
• 945-177 will be included in the dossier for safety data separate from and combined with 945-77.
• After review and discussion of the registration alternatives, national vs. mutual recognition vs. centralized, it was determined that national filings would permit individual countries to obtain faster registration (in some cases) while maintaining the current national labeling (considered favorable in some countries).

ACTION: • Based on these discussions it was decided to submit national application in Europe.
• The clinical expert report will be prepared by Dr. David Chadwick.
• It is anticipated that the Neurontin monotherapy claim will be fairly broad and similar to the following:

"Neurontin is an anti-epileptic for monotherapy or add-on therapy in patients with partial seizures or partial seizures with secondary generalization, including patients with newly diagnosed seizures at doses of 900 mg to 3600 mg per day in divided doses (TID)."* • PD Italy and France will need to renegotiate pricing when monotherapy will be registered if the labeling is not indication and dose specific. Specific labeling, i.e., "900 mg per day is the usual maintenance dose for naïve patients," could eliminate the need for price negotiations.
Are all the data submitted to the FDA published?

Objective: To identify and characterize discrepancies, if any, between clinical trial data submitted to the Food and Drug Administration (FDA) in approved new drug applications (NDAs) and the corresponding published trials.

Study Sample

All approved New Drug Applications (NDAs) for new molecular entities (NMEs) from 2001-2002 and all published clinical trials corresponding to the efficacy trials referred to within NDAs.
Redacted

1

pages of trade secret and/or confidential commercial information
## Ongoing Clinical Studies

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Study population</th>
<th>Number of subjects</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase IIIa Dose-ranging study of Org35140 SR (2.5, 4.0, 8.0, and 12 mg)</td>
<td>Patients, 675</td>
<td>2147</td>
<td>2147*</td>
</tr>
<tr>
<td>Phase IIIb Efficacy and safety of Org35140 SR (5 mg or 7.5 mg or 10 mg - dose according to body weight category) versus twice daily enoxaparin 1 mg/kg</td>
<td>Patients, 2200</td>
<td>1649</td>
<td>89</td>
</tr>
<tr>
<td>Phase IIIb Efficacy and safety of Org35140 SR (5 mg or 7.5 mg or 10 mg - dose according to body weight category) versus adjusted twice daily Org35140 SR</td>
<td>Patients, 2200</td>
<td>122</td>
<td>62</td>
</tr>
</tbody>
</table>

* May include blinded and unblinded data

** Completed: 2147 patients entered and 2147 completed

---

**Patient Exposure**

A summary of the duration of exposure for the ongoing studies in this safety update is provided in the following table.

For the Phase IIIb Study (63119), patients were to be treated with study drug (fondaparinux 2.5 mg, 4.0 mg, 8.0 mg, or 12.0 mg, or enoxaparin 1 mg/kg) for 3-7 days.
analysis also showed that PMs had an increased risk of shifting their QTc interval from normal to borderline or prolonged as compared to EMs.

A clinical pharmacology type study similar to LYAE conducted in genotypic PM children would provide important information regarding their risk of QTc prolongation. However, a negative study in this population would not likely eliminate all our concern about the LYAE signal. Given the ethical dilemma of conducting a clinical pharmacology trial in children, one could argue that in the interest of patient safety, the prudent recommendation would be to determine CYP2D6 metabolizer status prior to prescribing.

4 Labeling Recommendations

I concur with Dr. Boehm’s edits and additions to the proposed Strattera™ labeling. My additional comments follow below.

Judith A. Racoorin, MD, MPH
Safety Team Leader
 Included

- 33 New Drug Applications (NDAs) from 2001 - 2002 with 164 trials

- 1 – 13 efficacy trials per NDA, median 4
Of 164 Trials…

PUBLISHED within 5 years: 78% (128)

OF 33 NDAs….

ALL trials published: 52% (17)

NO trials published: 2 (with a total of 5 trials)
Reasons for not publishing…

“The data are in my opinion very worthwhile. Efforts were made a number of times to work on publishing the data, but it was never possible to find a time when both the PI and the company simultaneously had time available to commit.”

“Unfortunately I do not think this complete study has ever been published. It is clearly important that this should be published. I have been and continue to be in contact with [company name] to see how this can be published.”
## Predictors of Publication

<table>
<thead>
<tr>
<th>Trial Characteristic</th>
<th>OR (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable primary outcome (s)</td>
<td>4.77 (1.33-17.06)</td>
<td>0.018</td>
</tr>
<tr>
<td>Active control (vs. placebo only)</td>
<td>3.37 (1.02-11.22)</td>
<td>0.047</td>
</tr>
</tbody>
</table>


Papers include more outcomes favoring the test drug

- 179 primary outcomes reported in NDAs
  - 41 were omitted from the papers
- Papers had 138 outcomes also reported in NDAs (77%)
  - PLUS 15 additional outcomes that favored the test drug
  - PLUS 2 other neutral outcomes
Outcomes omitted and results changed

- 43 outcomes in the NDAs did not favor the test drug
  - 20 were not included in the papers
  - 5 changed statistical significance, with 4 changing to favor test drug in the paper

- * changes in outcomes occurred in 36 (22%) trials found in 19 (58%) NDAs
What do we do about funding bias?

Ban         →  Manage         →  Disclose

New models of funding
Registries
IRB approvals
COI committees
Reviewing Conflicts

• Disclose to institution
  – Who, what, when, how much, how often?
• Review by institution
  – COI committee?
• Management strategy
• Monitoring / enforcement of management strategy
Why a committee?

• “What are the problems of having financial relationships with sponsors? This should not be an issue to even discuss. If the investigators decide to take on a project with any sponsors or a sponsor is willing to fund a project, that is a FAVOR to the university.”

• “I recognize that I am in conflict, but believe that I can handle it. If I couldn’t handle the conflict, I wouldn’t have gotten involved.”

• “There is no conflict. I am the best one to determine if there is a conflict.”

• “I can manage the conflict.”
Factors considered by COI committees

- Length or nature of involvement with sponsor
- Type of sponsor
- Separation between sponsored project and investigator’s paid activities
- Risks to human subjects
- Risk of bias
- Potential benefit of the research
Managing conflicts

• Strategies to eliminate conflicts:
  – Resign from management position / other work with company
  – Resign as Principal Investigator
  – Eliminate all financial ties (clinical trials and systematic reviews)
Managing conflicts

• Strategies to mitigate conflicts:
  – Publicly disclose financial interests
  – Reduce equity holding to under 5%
  – Clearly separate research from paid consulting activities
  – Oversight committee
What do we know about disclosure?

- Most frequently used strategy to “manage” financial conflicts of interest
- Difficult to enforce / is not done
- Does not prevent bias in research
- Makes those giving advice *more* biased
- Makes readers more critical
- Necessary *but not sufficient*
Examine conflicts of interest in medical research, education, and practice and in the development of clinical practice guidelines

Develop analyses and recommendations to inform policies to identify, limit, and manage conflicts of interest in these contexts without damaging constructive collaborations with industry
IOM Recommendations: Disclosure

• Standardize disclosures to institutions
• Minority Report: Standardize disclosures to the public
• Require pharmaceutical, medical device, and biotechnology companies to publicly report payments to physicians and other
IOM Recommendations: Medical research

• Research institutions should adopt policy that investigators generally may not conduct research with human subjects if they have a significant financial interest in the outcome of the research
IOM Recommendations: Medical education

• Prohibit gifts, ghostwriting, speakers bureaus
  – Limit drug samples, consulting, sales reps
• Provide education on relationships with industry and conflicts of interest
• Develop new system of funding accredited continuing medical education that is free of industry influence and provides high-quality education
IOM Recommendations: Institution-level conflicts

• Institutions should create policy and board-level committee to identify and respond to conflicts of interest at the institutional level
• NIH/PHS: require grantees to adopt institutional conflicts of interest policies
Conclusions

- Conflicts of interest exist
- Conflicts of interest are associated with bias in research
- Strategies to protect against bias are needed
  - Disclosure is not enough
  - In some cases, conflict should be eliminated
  - Institutions need mechanisms to manage conflicts of interest