Course: EPIB 679-001 Clinical Epidemiology

Date: May 9 to June 3
8:35 – 11:40

Session 10: Ethics and clinical research
Dr. J. Brophy

The Yin and Yang of Clinical Trials
or
How to Avoid The Dark Side

Disclaimer

I have no known conflicts associated with this presentation and, to the best of my knowledge, am equally disliked by all pharmaceutical and device companies

Typical Disclosure RCT Investigator at ACC 2004 Scientific Meeting

Consultant: Abbot, AstraZeneca, Aventis, BMS, Centocor, COR/Millennium, Datascope, Eli Lilly, ESP Pharma, Genentech, Medical Simulator Corp., Merck, Procter & Gamble, Pharmacia, Roche, Sanofi-Synthelabo, Searle/Monsanto, Texas Biotechnology, The Medicines Company;
Research Support: Abbot, Accumbens, Aventis, Biogen, BMS, Centocor, COR/Millennium, Datascope, Eli Lilly, Genentech, Merck, Procter & Gamble, Pharmacia, Sanofi-Synthelabo, Searle/Monsanto, Texas Biotechnology;
Speaker’s Bureau: Aventis, BMS, Centocor, Eli Lilly, Sanofi-Synthelabo

Some possible sources of conflict

• Direct financial COI including fees for consultation, seminars, focus groups, stock options
• Indirect financial – lab and personnel support, university donations
• Future considerations -next major study
• Academic benefits from publications of major trials, prestige…

Can simple disclaimer eliminate these conflicts of interest?

The New York Review of Books

The Dawn of MefScience
By Richard Horton
• http://www.nybooks.com/
Conflicts of interest

“... a remarkable double standard, scientists absolve themselves from the dangers of often deep financial conflicts by the simple means of disclosure.... allowing scientists to wash their hands of criticism.

This situation cannot be justified.”

Conflicts of interest

- PUB MED has 465 references since 1999 identified by the keywords “conflict of interest”
- PUB MED same period 400 references for "Fabry disease", ultrarare X-linked lysosomal storage disorder associated with severe multi-organ dysfunction and premature death

Basic Premise for Today

- Clinical research and randomized clinical trials are a socially important, and scientifically valid activity that must be preserved against numerous threats

The Potential Threats

- Researchers
- Journal editors and reviewers
- Healthcare research consumers (i.e. you and me)
- Industry
- Academic institutions
- Government funding agencies
- Media
- Combinations of the above

Researchers

- Scientific fraud (rare but not zero)
- Ethics of recruitment
- Financial conflicts
  - Direct (infrequent)
  - Indirect (more common) laboratory support, consultant fees, speaker fees, eligible for next trial
- Other conflicts of interest
  - Professional advancement
  - Prestige

Does the name Jesse Gelsinger mean anything to you?
**Jesse Gelsinger Case Study #1**

- Healthy 18 year old volunteer
- Died Sept 1999 in a gene experiment at the University of Pennsylvania's Institute for Human Gene Therapy
- Researcher had $13.5 M equity in company
- University had $1.4 M equity position
- Didn’t meet entrance criteria
- Risks not explained

**Case Study #2**

- Lessons from the American experience with marrow transplantation for breast cancer
- Well meaning aggressive physicians equally aggressive lawyers and media
- It is also a story of professional interests, weak research, financial gain, politics, and fraud.

- BMJ VOLUME 324 4 MAY 2002

**Timeline**

**1ST Study**

- 1988 Annals report 172 women from 27 studies
- The summary response rate (defined as tumour shrinkage >50%) was 58%.
- There were no controls.
- There was no effect on mortality or morbidity

**Conclusions**

**JOURNAL ARTICLE:**
“Critical evaluation will require controlled trials…
“response rates that are probably superior to the best available with conventional therapies . . . although not yet associated with improved survival.”

**PRESS:**
“I think this shows that ABMT can be a very effective form of treatment”.

**Other issues**

- Breast cancer is a big story.
- Women's issues were prominent.
- Breast cancer was both common and feared.
- Transplantation was a source of hope—a technologically advanced procedure.
The Epidemiologist

- 1992, examination of all studies (non-randomized)
- Compared with standard Rx from RCT
- Conclusion survival rates after transplantation and conventional chemotherapy were essentially the same.

Cost-effective study

- CE analysis using efficacy data from case series and a hypothetical decision model suggested $100,000 (JAMA 1992)
- "Using reasonable assumptions, ABMT provided substantial benefit but at a cost that may be untenable."
- i.e. works but expensive

State of the Art or Experimental

- Insurance companies – experimental
- Courts - “To require that the plaintiff or other plan members wait until somebody chooses to present statistical proof . . . That would satisfy all the experts means that plan members would be doomed to receive medical procedures that are not state of the art.”
- 1992 one case awarded $89,100,000


- Insurance coverage “arbitrary and capricious.”
- Presumption of benefit
- Avoid “the relegation of patients to outdated and inferior treatments.”

Politics

- By 1994, 7 states had mandated coverage
- Federal government insists that all plans covering their workers provide coverage (350 plans and 9 million people)

The 1st Randomized Clinical Trial

- South African oncologists led by W R Bezwoda reported a complete response rate (no evidence of tumour) of 51% in women randomised to transplantation, compared with 4% in those receiving conventional therapy.
- The benefit in median survival was even more impressive: 90 weeks versus 45.
Randomized trials 1999

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients and Disease Stage</th>
<th>Follow-up</th>
<th>Bone marrow transplantation</th>
<th>Control</th>
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<tbody>
<tr>
<td>Randomized treatment</td>
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<tr>
<td>Probable leukemia</td>
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<tr>
<td>Test group (44)</td>
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<td>Fresh group (54)</td>
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<td>Acute lymphoblastic leukemia (53)</td>
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<td>Standard group (47)</td>
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Lessons

- Establish what is experimental
- Importance of good experimental design (RCT, hopefully >1)
- Premature to raise the question of cost effectiveness when effectiveness is unknown
- Realize that proponents are always more vociferous and potentially more biased than detractors

Conclusions

- “As a society we have to accept that rigorous evaluation of a new treatment is essential . . . Skipping this step may seem like a compassionate act, but it can have devastating consequences.”

The Potential Threats

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- Journal editors and reviewers
- Healthcare research consumers (i.e. us)
- Industry
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- “To a reasonable degree of probability ABMT has been proved to be ineffective and should be abandoned in favour of well justified alternative experimental approaches.”

The 1st Randomized Clinical Trial

- On site review team identified multiple problems
- Protocol and eligibility violations
- No signed consent forms.
- No access to the control patients.
- Logical inference “You could conclude that they might not exist.”
### Readers – Caveat Emptor

- Basic design issues
- Basic Analysis
- Results & Interpretation
- Discussion (spin)

- We won’t get fooled again (after this course)

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### Residents and Big Pharma

- Do you know if you are being bought?
- Can you resist being bought?
- Do you care if you are being bought?
- What about your free lunches?
- Do you believe in industry philanthropy?
- Should the sponsor choose the topic and the presenter?

### Residents and Big Pharma

- www.nofreelunch.org
- www.healthyskepticism.org

### Healthy Skepticism Inc

**Aim:** Improving health by reducing harm from misleading drug promotion

www.healthyskepticism.org
Dr Peter R Mansfield
University of Adelaide

### Population 1,100,000
Efficacy and safety of antidepressants for children and adolescents

1. Benefits of antidepressants are small. We estimated a 3 to 4 point difference on a scale that ranges from 17 to 113. (95% confidence 1 to 8 points)
2. Adverse effects common and sometimes severe.
3. “The magnitude of benefit is unlikely to be sufficient to justify risking those harms”
4. Benefits have been overstated and adverse effects understated.

Why do many doctors believe that antidepressant drugs work well?

A. Clinical experience: I prescribe the drug. The child/teenager gets better. I conclude the drug works.
B. Wishful thinking: Hope for clinically worthwhile advantages. + Ambiguity about efficacy only detectable with a statistical microscope. = Illusion of potency.

Other causes

- Improvement that would have happened anyway.
- Regression to the mean. (If something fluctuates and you catch it at an extreme it will usually be closer to the middle next time.)
- Non-drug effects of the medical encounter.
- A reason for believing that things will get better.
- The placebo effect.

Case study #5 - R&D or PR?
Prescient or lucky?

An industry view of RCT

Primary Endpoint

Overmedicalization?

Association of funding and conclusions

Off label marketing

Overmedicalization?

- In Canada, perindopril costs approximately $60 a month
- > $450,000 to save one life
- This insistence on pharmaceutical interventions has an indirect effect of shifting emphasis away from other healthcare interventions, which may result in greater health benefits at a fraction of the cost.

Association of funding and conclusions

- Association of funding and conclusions in randomized drug trials
  - JAMA 2003:290;921-28
- Conclusion: In for profit studies, experimental drug more likely to be recommended (OR 5.3, 95% CI 2.0-14.4). More positive results may be due to biased interpretation

Off label marketing

Pfizer to Pay $420 Million in Illegal Marketing Case
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Dancing with Porcupines - University–industry relationships

Dancing with the porcupine: rules for governing the university–industry relationship
Steven Lewis et al. CMAJ 2001

Dancing with Porcupines

- “The duty of universities is to seek truth. The duty of pharmaceutical companies is to make money for their shareholders.”
- Some university/industry partnerships described as “an unholy alliance whereby researchers and universities become handmaidens of industry”

Case study #8 & 9

- University of Toronto
  - Nancy Olivieri vs. Apotex
  - David Healy vs. Eli Lilly

Academic institutions

- Condensed version of common elements
- Drug sponsors would also are major donors to the University were unhappy with research findings and set out to (successfully) pressure the University to discredit these 2 researchers.
- University totally compliant to these pressures and ignored academic freedom

NEJM commentary

- Olivieri affair characterized as a “debacle …complicated by personal animosity, poor administrative judgment, and bad behaviour among academic colleagues”
- “growing evidence that things may not be much better, albeit less bizarre, elsewhere”

University–industry relationships

- “University/industry partnerships can imperil the fundamental values of academic freedom, research integrity, and patient safety.

Basic Premise for Today

- Clinical research and randomized clinical trials are a socially important, and scientifically valid activity that must be preserved against numerous threats

So, what’s the answer?

- First realize no quick fix
- Recognize and identify the threats
- Separate the culture of profit motive from the culture of caring for patients
- Produce informed consumers
- Other

In Class Preliminary Exam

Who described the role of the pharmaceutical industry as follows?

Not to provide the best possible care for people but in order to maximize profits.

Answers

- Karl Marx
- Roy Romanow
- Philippe Couillard
- Jay Brophy
- Pope John Paul II

### Answers

- Karl Marx
- Roy Romanow
- Philippe Couillard
- Jay Brophy
- Pope John Paul II


### That's all folks

Have a good summer