Ethics and Regulations in Clinical Research

MCTS C03 (3 credits)
Tuesday Evenings, 4:30-7:30pm
RWJMS Clinical Academic Building, Room 3403,
New Brunswick, NJ
Course Director: Michael J. Leibowitz, M.D., Ph.D.
Ethics and Regulations

- Ethical issues need to be considered in all clinical studies. Each study is unique and there often are differing opinions on critical issues.

- On the other hand, Regulations protect subjects, and these must be followed. These may vary between countries, states, and institutions.
Course Format

- Lecturers include academic and industrial researchers, many with extensive clinical research experience.

- Grading
  - Mock IRB & suggestions for protocol revision
  - Student seminars
  - Term papers
  - CITI (Collaborative IRB Training Initiative) certification (on-line)
Ethical Scientific Conduct & Conflict of Interest

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Definition of Scientific Misconduct

- Fabrication
- Falsification
- Plagiarism
- Other definitions (not meeting the standards of the scientific community) no longer widely used
Experimental Data

- Who owns them?
- Dated and signed
- Not removable or erasable
- How keep computerized data?
Publishing a Paper

- Authorship is the “coin of the realm”
- When you ready to publish? Tell a complete story, reproducible data, significant contribution
- Author/contributor: significant contribution to the design, experimentation, and reporting of the work
- Rewards and responsibilities of authorship: credit and blame
- New initiative to identify contribution of each contributor (not exactly same as author) of a paper (Rennie et al., JAMA 278:579, 1997)
Fabrication and Falsification

Unlike plagiarism, obviously wrong and requires conscious action by the wrong-doer.

How can this be prevented?

- Supervisors
- Reviewers
- Other researchers
- Responsible Conduct of Research course
- Is reducing pressure feasible and would it work?
Failure to Publish Negative Results

Many more positive than negative results published

Is this due to influence of sponsors or other factors?

Importance in clinical research greater than in other fields
Definition: Plagiarize

“to steal or pass off as one’s own (the ideas or words of another)”

“to present as one’s own an idea or product derived from an existing source.”

Webster’s Seventh New Collegiate Dictionary
Definition: Copyright

“the exclusive legal right to reproduce, publish and sell the matter and form of a literary, musical or artistic work.”

Note that this includes scientific publications.

Webster’s Seventh New Collegiate Dictionary
Who owns a publication?

- All authors?
- Senior (first) author?
- Submitting (PI) author?
- Employer(s) of authors?
- Funding agencies?
- Publisher?
Why is plagiarism the most widespread infraction despite being the easiest to detect?

- Many authors may not know the rules!
- Computers make plagiarism easy!
- “Self-plagiarism” is still plagiarism!
How to use the work of others appropriately

- Reference
- Citation
- When is permission needed? From whom?
“The rightsholder did not grant rights to reproduce this item in electronic media. For the missing item, see the original print version of this publication.

**Figure 3.** cat-scratch disease showing inflammation of the lymph node.


P.M. Rabinowitz et al., American Family Physician 76: 1318 (2007).
Plagiarism Checking Sites

Multiple sites and programs are listed at:

http://plagiarism.phys.virginia.edu/links.html
Conflict of Interest
Definition of Conflict of Interest

According to D.F. Thompson, a conflict of interest occurs when secondary interests (financial and many others, such as promotion, fame, family, etc.) unduly influence professional judgment concerning a primary interest (patient well-being, research and education).

This may be an actual or potential personal or institutional conflict, or the APPEARANCE of such a conflict.

Bayh-Dole Act (1980) mandates commercialization of govt.-funded university research discoveries.
Why Such a High Standard?

- Observers cannot easily determine what influences an investigator
- Science, funding agencies and the public depend on trust of research reports; any doubt is potentially disastrous
Does funding source matter?

603 consecutive papers and presentations on leg orthopedic prostheses:

– Total hip replacement implants
  - Commercially funded: 93% positive
  - Independently funded: 37%

– Total knee replacements
  - Commercial: 75% positive
  - Independent: 20% positive

– Investigators receiving royalties reported no negative outcomes

How widespread is COI?

- Survey of medical school/teaching hospital faculty (1663 at 50 schools, 2007)
  - 52% had “any relationship” with industry
  - 41% had relationship that contributed to most important research
  - 20% had industrial funding (48% clinical trials)
  - Average industry funding per year: $33,417
  - Average industry funding of clinical trial PI’s: $110,869

DE Zinner, EG Campbell, JAMA 302:969-76 (Sept. 2, 2009)
COI Importance in Clinical Research

- Potential of harm to subjects
- Study defects may harm future patients as well as future research
- Exposure reduces public trust, reducing willingness of public to serve as subjects
- Risk of lack of faith by funding sources
- BASIC research still has rules, but not as strict as CLINICAL research
Secondary Interests Define Types of Conflicts

- Institutional conflict of interest
  - Growing problem as universities profit from inventions

- Intellectual bias

- Conflict of commitment

- Individual investigator conflicts: financial easiest to recognize and measure, but there may be others
Financial Conflict of Interest

Any monetary value including, but not limited to:

- Salary or other payments (e.g. fees or honoraria); NIH threshold=$10K/year
- Equity; NIH threshold $10K or 5%
- Intellectual property rights (patents or royalties
- Investigator or a spouse or relative
- Other institutions may use different thresholds
  (Harvard threshold is *de minimis* level)
Remedies for COI

- Self-regulation: Has not worked!
- Disclosure: “Sunshine as a disinfectant”
  - May cause subject stress and anxiety
  - Is it sufficient? Will subjects understand?
- Mediation/Management: blind trust, proceeds to charity, outside supervisor for research, etc.
- Prohibition: Some conflicts are prohibited by journals or institutions, not manageable
Disclosure

- May not be sufficient, but is required
- Early disclosure can prevent later embarrassment!
- Includes all payments (received or planned), equity interest, fiduciary responsibility, personal financial interest including relatives (spouse, parent, child, siblings, domestic partner, including “step,” “half,” “in-law,” etc.)
- Size and nature of a financial conflict of interest affects how it should be managed
Who Needs to Disclose?

- Investigator = principal investigator and any other person who is responsible for the design, conduct, analysis or reporting of research.
- Not just PI, it can be anyone (key personnel, even tech) who is involved in design, conduct, or reporting of sponsored research
- Term also includes investigator’s spouse and family
Federal COI Reporting Requirements

- At time of application, all investigators must submit information to institution.
- Prior to expenditure, institution reports COI to NIH & assures management, reduction or elimination of COI.
- Financial COI identified after initial report must be reported within 60 days of discovery and managed, reduced or eliminated.
How to Decide if COI is a Problem?

- $ amount of payment/equity
- Responsibility of investigator in entity with a competing interest (Board Member greater than consultant)
- Decision making power in the research. COI influences decisions.
Examples Allowed at UMDNJ

- UMDNJ employee receiving royalties from publications or licensure of inventions
- Equity in a company whose sole purpose is to accommodate employee’s outside consulting
- Nominal compensation for service to professional associations, review panels, presentations of scholarly work, accreditation reviews
Decision-making is the problem in conflict of interest

- What to test
- Placebo vs. active control
- Endpoint selection
- Inclusion/exclusion criteria
- Design of informed consent document
- Rules for stopping trial for proven efficacy or adverse events
- Decision on stopping trial due to evidence from other trials
- Which eligible patients will be enrolled
Reporting of Negative Results

- Essential in clinical research
- Often against the interests of the corporate sponsor
- It is generally unacceptable for a sponsor to ban (or impede or delay) the publication of negative results.
- Required registry of clinical trials (Internal. Comm. Med. J. Editors, 2005) may alleviate this problem, but not eliminate; publications are more visible than registry.
Selective Outcome Reporting Remains a Problem

323 trials in cardiology, rheumatology, GI in 10 top journals in 2008

- 45.5% registered before end with outcomes
- 27.6% not registered
- 13.9% registered after completion
- 10.8% without clear outcomes
- 31% discrepancy between outcomes registered and outcomes published (reported new outcome or did not report original outcome)

S. Mathieu et al., JAMA 302:977-84 (Sept. 2, 2009)
Other COI Issues

- Fees for patient recruitment. General covering costs OK, but profit is a problem
- Finder’s fees (payment for referral of patients) considered unethical (illegal in clinical practice)
COI Resources

- UMDNJ Policies
  [http://www.umdnj.edu/oppmweb/university_policies/Academic_affairs/PDF/00-01-20-89_00.pdf](http://www.umdnj.edu/oppmweb/university_policies/Academic_affairs/PDF/00-01-20-89_00.pdf)

- 42 CFR Part 50, Subpart F

- AAMC site
  [http://www.aamc.org/research/coi/start.htm](http://www.aamc.org/research/coi/start.htm)

- NJ Law: NJSA 52:13D-19.1