

Clinical Trials: Challenges for Medical Journals

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Challenges

- Defining “clinical trial”
- Selective publication
- Authorship
- Conflicts of interest
- Staying true to the protocol
- Negative trials

What is a clinical trial?

- Hypothesis generating vs. hypothesis testing
- Exploratory vs. confirmatory
- Patients vs. healthy volunteers
- Drugs vs. other interventions

ICMJE Definition of Clinical Trial

“...any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and health outcome.”

Selective Publication



FDA Panel Urges Stronger Warning on Antidepressants

By GARDINIER HARRIS

Bethesda, MD, Sept. 14- Federal drug regulators should warn physicians and patients in the strongest possible terms that antidepressants not only cause children and teenagers to become suicidal but most have also failed to cure their depression, a federal advisory committee voted Tuesday...

1995 study of 2,157 life science faculty in top 50 NIH-funded Universities

19.8% of respondents **delayed publication** of articles for more than 6 months to serve proprietary needs:

- **to allow for patent application or negotiation**
- **to protect scientific lead**
- **to slow dissemination of undesired results**
- **to resolve intellectual property ownership disputes**

Blumenthal D, et al. JAMA. 1997;277:1224-1228.

Medical editors take steps to halt selective publication of studies

By Stacey Burling

In a move they hope will give doctors information to make better prescribing decisions—including the results of clinical trials that make drugs look bad—a group of prominent medical editors announced new rules yesterday for studies they will publish....

Trails Registration

- Entry of information about a clinical trial in a publicly accessible data base
- Registries include variable amounts of info on trial results
- Registration has been largely voluntary
- Often happens after trial is complete

Pros and Cons of Trials Registration

- Doctors and patients can find trials during enrollment
- Systematic review and meta-analysis authors can more easily locate relevant trials
- Editors can check that reports match original protocol
- Investigators worry that others will “steal” their ideas
- Sponsors worry about divulging proprietary information

ICMJE Policy on Trials Registration

ICMJE journals will not consider a manuscript reporting a trial that started on or after July 1, 2005 unless the investigators registered the trial in an acceptable registry **BEFORE enrollment of the first patients**

ICMJE advocates retrospective registration of trials begun before this date

Acceptable Trials Registries

- Accessible to public at no charge
- Managed by a non-profit entity
- Mechanism to ensure validity of registry data
- Electronically searchable

Minimum Registry Content

- Unique ID #
- Statement of intervention(s), comparison(s)
- Study hypothesis
- Definitions of all outcome measures
- Eligibility criteria
- Key trial dates
- Target # subjects
- Funding source
- Contact info for principal investigator

Examples of Existing Registries

- www.clinicaltrials.gov
- Controlled Clinical Trials
- Eurodract
- Industry registries

Authorship of Trials

Why Authorship Matters

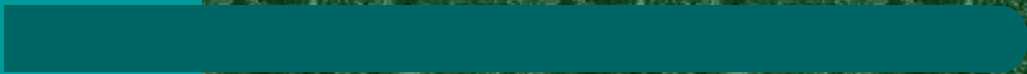
- Biomedical authorship has academic, social, and financial implications
- Readers want/need to know who did what
- Identifies who is accountable for the integrity of the work

Author:



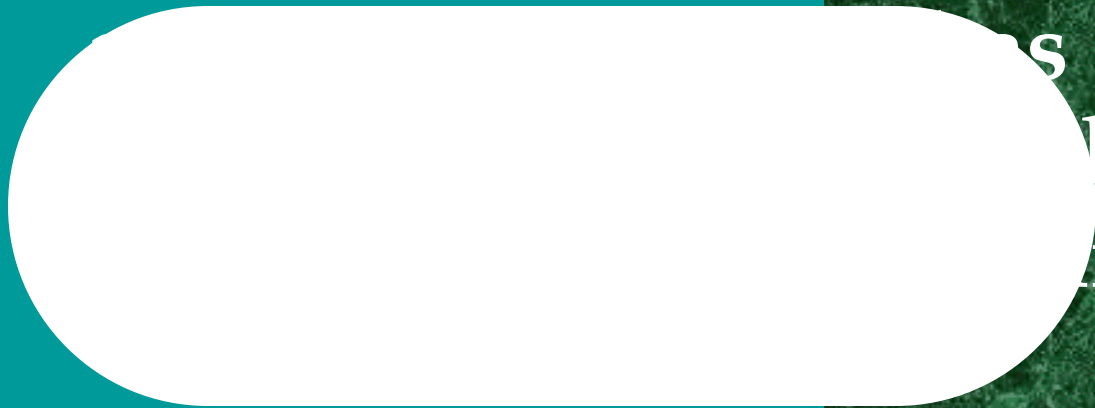
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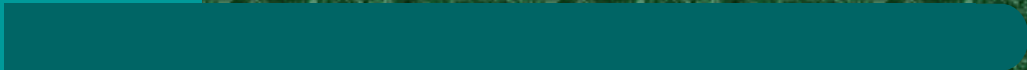


Montesquieu

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The ICMJE

ICMJE Criteria for Authorship

1. **Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;**
2. **Drafting the article or revising it critically for important intellectual content;**

AND

3. **Final approval of the version to be published**

Contributions that Should Not Alone Earn Someone a Place on the Byline

- Acquisition of funding
- Collection of data
- Referral of patients
- Provision of study samples
- General supervision of the research group



Gift Authorship

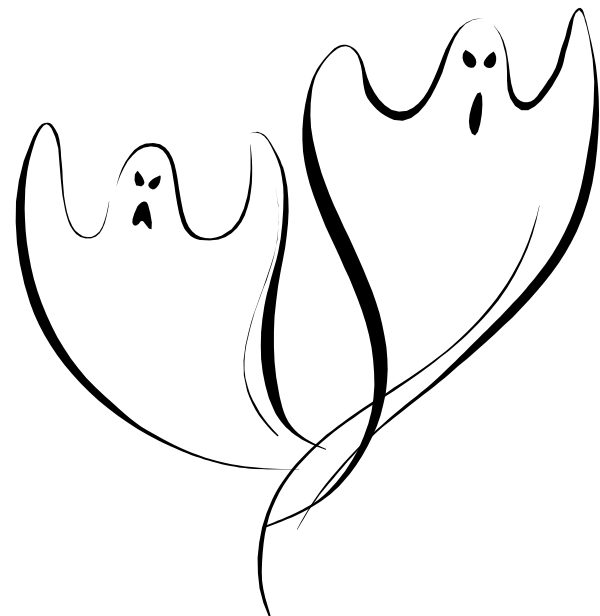
- **Some one who has not contributed substantially to the work is listed as a byline author**
- **Often a senior person whose name has cache**





Ghost Authorship

A “nobody” writer (the ghost) writes an article, then a “somebody” agrees to put his or her name on the byline



Fundamental Principles

- All persons designated as authors should qualify for authorship
- All those who qualify should be listed
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content

Large Multi-Center Groups

- Groups should identify individuals who accept direct responsibility for the manuscript (and meet authorship criteria)
- Journals will generally list other group members in the acknowledgements
- NLM indexes the group name and the names of individuals who accept direct responsibility for the article

Conflicts of Interest



What is Conflict of Interest?

- Researchers (or their institutions) have relationships with entities that have a vested interest in the outcome of the study
- These relationships could inappropriately influence (bias) researchers' actions



Sources of Conflicts



Personal

- friendships adversarial relationships
- academic competition
- intellectual passion

Financial

- employment
- ownership or options
- consultancies or honoraria
- grants, patents, royalties
- expert testimony

stock

paid

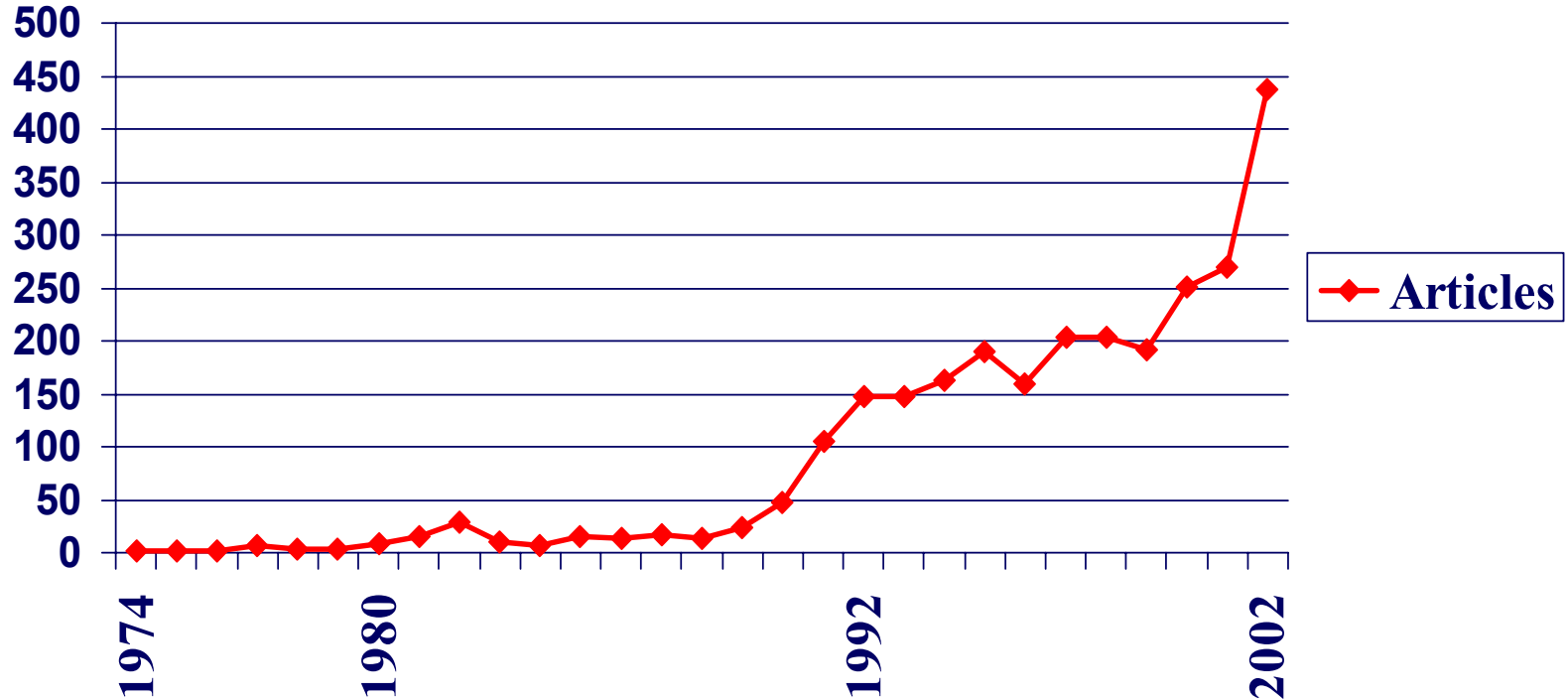
Public trust in the peer review process and the credibility of the published biomedical literature depend in part on how well researchers and editors handle **conflict of interest.**

Focus on financial conflicts

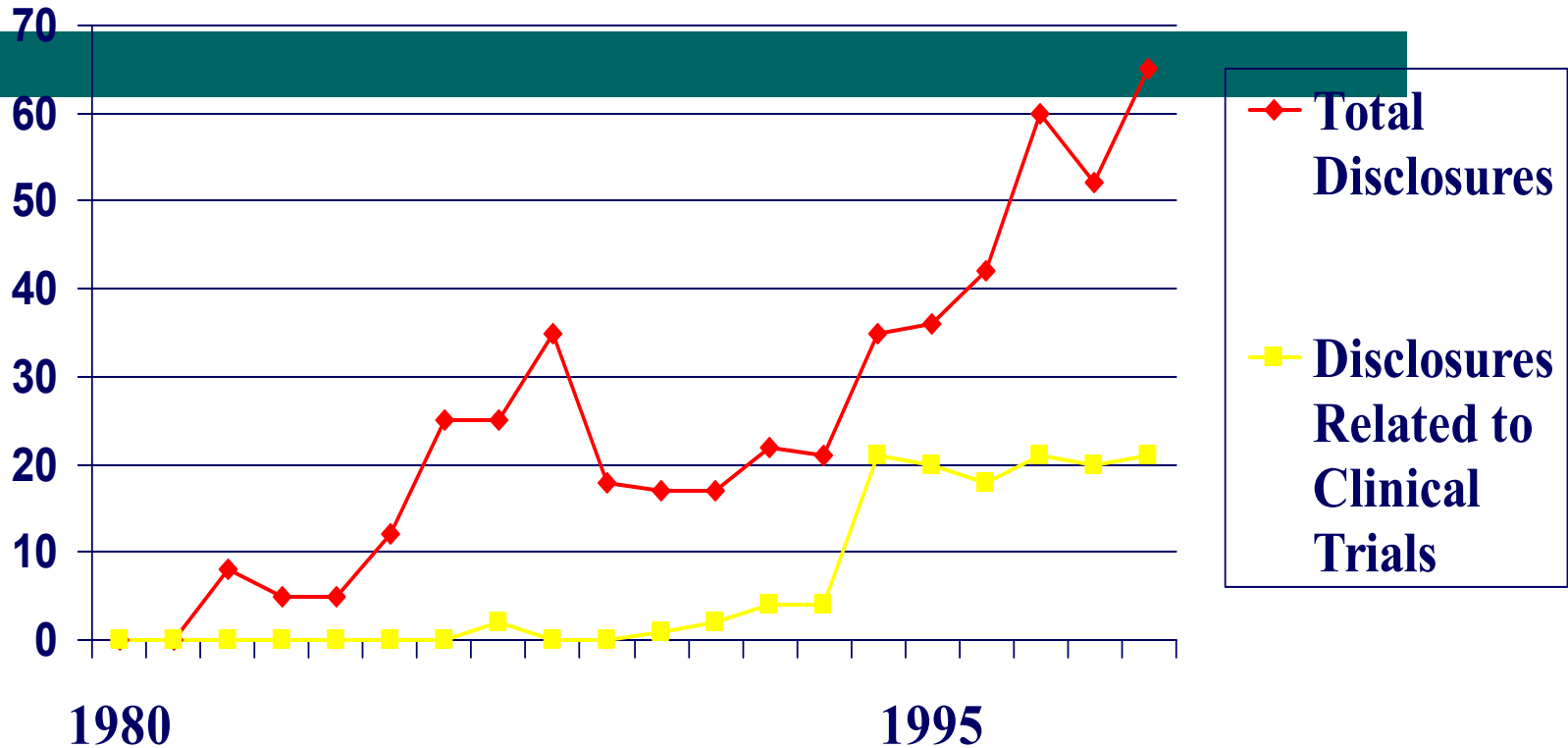
- Most easily identifiable
- Conflicts involving \$ are easy for those outside science to understand
- Financial conflicts are most likely to undermine the credibility of researchers, sponsors, journal, and science itself



Articles on Conflict of Interest MEDLINE /PubMed, 1974 - 2002



Financial disclosures of faculty principal investigators at UCSF, 1980 -1999



37% of 225 researchers had >1 disclosure
(2.6% in 1985; 7.1% in 1997)

Boyd and Bero. *JAMA*. 2002;284:2209-2214.

Scope of Financial Interests

- Systematic review - 37 studies
- Prevalence - 1 in 4 investigators have industry affiliations
- Association between industry sponsorship and pro-industry conclusions (OR 3.6)

Berkelman et al JAMA. 2003;289:454-465

Ugly Examples

- Deferiprone (iron chelation therapy) worsened hepatic fibrosis - company delayed publication 3 years (*NEJM*. 2002;347:1368)
- Synthroid shown to be bioequivalent to generic thyroxine - company delayed publication 3 years (*JAMA*. 1997;277:1238)
- HIV Immunogen not effective - company sued UCSF for \$8M over publication; arbitration ruling in favor of university (*JAMA*.2000;284:2193)

How does one manage conflicts sensibly?

- **Recognition** that conflicts of interest exist and can influence the design, conduct, and reporting of clinical research
- **Collaboration** between public, researchers, physicians, academic medical centers, biomedical journals and industry

Summary of the ICMJE Policy

- **All in the research/review/publication process must disclose whether or not potential conflicts exist**
- **Personal and institutional conflicts require disclosure**
- **Disclosure for all publication types**
- **Editors may use information in editorial decisions**
- **Editors should publish information on potential conflict of interest**

Summary of the ICMJE Policy

- Report the role of the sponsor in the design, conduct, and reporting of the study
- Decline to consider papers unless the authors can attest that they had full access to the data and control over the decision to publish

Staying True to the Protocol





U.S. News & World Report Archive
ARTICLE PREVIEW

SEPTEMBER 17, 2001

True, False, Whatever

Stacey Schultz

Catherine DeAngelis is not happy. The editor of the Journal of the American Medical Association knows that she is responsible for publishing deliberately misleading research that could have untoward consequences for thousands of patients. A year ago, she ran the results of a six-month study of the popular arthritis drug Celebrex; that showed the drug caused fewer gastrointestinal problems than comparable medications. But when the Food and Drug Administration reviewed the same trial...

Safeguards Against Protocol Impropriety

- Trials registration
- Vigilant reviewers
- Protocol submission/review

“Negative” Trials



MYTH:

Journals aren't interested in publishing negative trials

TRUTH:

Journals aren't interested in publishing inconclusive trials

Things That Can Lead to Inconclusive Trials

- Insufficient sample size
- Insufficient length of follow up
- Early termination of study

Ways to Increase the Appeal of Inconclusive Trials

- Recognize inconclusive findings
- Confidence intervals and discussion of clinically meaningful Effect sizes
- Documentation that researchers stuck to the protocol
- Use inconclusive results to define/focus next steps in the area

