

Why we need a uniform, comprehensive registry of clinical trials

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*The right to search for truth implies also a duty;
one must not conceal any part of what
one has recognized to be true. (A. Einstein)*

Evidence-based healthcare

- Depends on good evidence:
 - Formal summaries of research evidence (systematic reviews)
 - Reliable and complete sources of information

A sizable proportion of trial results remain unpublished

Population	Identification	Followup	Published %
JHU-MED ethics	1980	1988	81
JHU-PH ethics	1980	1988	66
NIH trials	1979	1988	93
Oxford ethics	1984-87	1990	73
Sydney ethics	1979-88	1992	59
NIH AIDS trials	1986-96	1996	55
Barcelona trials ethics	1997	2001	21
Danish RCTs ethics	1994-5	2003	37

Meta-analysis of association of various factors with publication

Studies: JHU-MED, JHU-PH, NIH, Oxford, and Sydney

Significant Results (yes vs no)

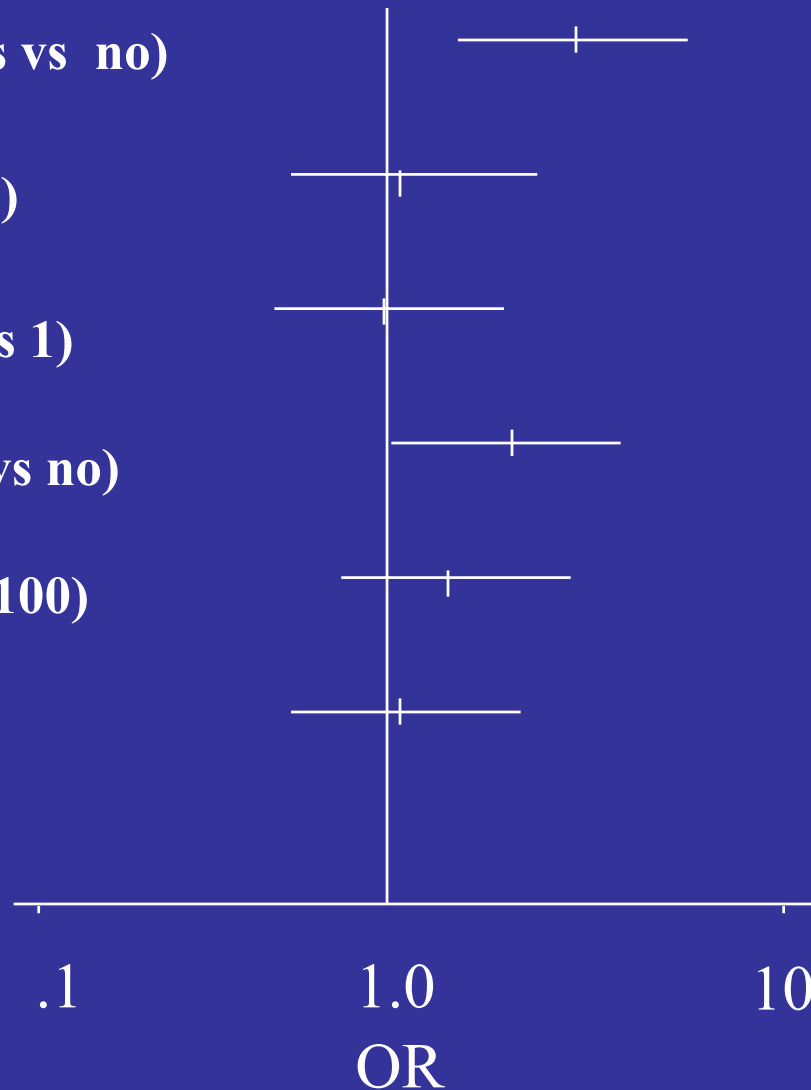
Clinical trial (yes vs no)

No. study groups (>1 vs 1)

External funding (yes vs no)

Sample size (≥ 100 vs < 100)

Sites (>1 vs 1)



Selective reporting of outcomes

Comparison of 102 trial protocols submitted in 1994-1995 to and approved by the scientific-ethics committees for Copenhagen and Frederiksberg Denmark, with 122 subsequent publications

Selective reporting of outcomes

Key findings

- Nearly two-thirds of the studies had a change in at least one primary outcome between the protocol and publication
- Statistically significant outcomes had a higher likelihood of being reported compared to non-significant findings

Publication bias is associated with study sponsor

- Systematic review of 30 studies of publication and industry support
- Research funded by industry
 - Less likely to be published than other research
 - More likely to have results favoring sponsor (OR= 4.05 [95% CI = 2.98-5.51]).

Why is failure to publish a problem?

- Ethical issues
 - Obligation to participants, the public, not fulfilled if knowledge about and from trials not disseminated
- Scientific issues
 - Publication bias – positive results published more often
 - Systematic reviews biased if unpublished information inaccessible
 - Over-reporting & ambiguity about unique trials
 - Participation by patients, doctors, researchers limited

September 2004 – ICMJE Statement

EDITORIAL

Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors

Altruism and trust lie at the heart of research on human subjects. Altruistic individuals volunteer for research because they trust that their participation will contribute to improved health for others and that researchers will minimize risks to participants. In return for the altruism and trust that make clinical research possible, the research enterprise has an obligation to conduct research ethically and to report it honestly. Honest reporting begins with revealing the existence of all clinical studies, even those that reflect unfavorably on a research sponsor's product.

Unfortunately, selective reporting of trials does occur, and it distorts the body of evidence available for clinical decision making. Researchers (and journal editors) are generally most enthusiastic about the publication of trials that

show favorable results. To address this problem, the ICMJE has created a public trials registry. Trials must register at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by September 13, 2005, before considering the trial for publication. We speak only for ourselves, but we encourage editors of other biomedical journals to adopt similar policies. For this purpose, the ICMJE defines a clinical trial as 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 a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (for example, phase I trials),

What is needed?

A virtual, global unified register

- Standardization across registers
- Minimum dataset
- Centralized processing and dissemination
- Unique trial IDs

What do we have?

Many independent trials registers

- No standardization across registers
- Variations in the data included
- No centralization
- At least 3 unique trial ID systems



TrialsCentral

Your source for online clinical trials information

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May 15, 2005

TrialsCentral™ provides free and confidential access to listings of clinical trials. This information about current clinical research studies helps to support informed, evidence-based decision making in health care.

The [Clinical Trials](#) page has an easy-to-use database of clinical trials registers. Search by health condition, such as cancer or diabetes, and by geographic location of the trials.

The [Frequently Asked Questions](#) (FAQ) page can help you learn more about clinical trials. You may want to read this before beginning your search for trials.

The [Resources](#) page has links to further health care information sites, including medical dictionaries, published [or recent] articles, and links to other evidence-based health care sites.

[Contact us](#) with comments, questions, or to report problems with the site.

Please complete the [Questionnaire](#) if you maintain a database of clinical trials. Join us at TrialsCentral™ in our efforts to make clinical trials information more accessible to everyone.



This site is dedicated to [Diana Anderson](#).

Who is doing what internationally?

International Registers/Unique IDs

- **ISRCTN (Current Controlled Trials)** - publicly-funded trials from UK, Canada, Netherlands; MRC-UK; Wellcome Trust; WHO; others
- **ClinicalTrials.gov** (US National Library of Medicine) – mainly US-funded trials, drug trials, and other, voluntary, registrants

National Registers

- Japan
- Chile
- Colombia
- Brazil
- Spain

“Secret” registers

- EUDRACT

US legislative action

- US 2005 – FACT legislation to expand clinicaltrials.gov - limited to drugs, biologics, devices
- Increasing number of US states (Nevada, North Dakota, New Jersey, Maryland pending) enacting laws to enforce existing law

International action

Ottawa Statement

- Principles (BMJ April 23, 2005)
 - Over 100 individual and organizational signatories so far
 - Additional signatories invited
 - Translation (so far) into French, Japanese, Italian
- Operationalization
 - Writing in progress, meeting at Society for Clinical Trials, Portland Oregon, May 23, 2005

Ottawa Statement

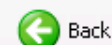
General timeline for process of trials registration

Stage of trial

- Initial trial protocol
- ↓
- Final protocol with changes
- ↓
- Participant recruitment begins
- ↓
- Data collection completed
- ↓
- Final results
- ↓
- Published/unpublished results

Action

1. Obtain unique ID
2. Provide Unique ID on consent forms and other trial documentation
3. Register and release minimum protocol items and consent forms
4. Register and release protocol amendments
5. Ensure public availability of full protocol and data collection forms
6. Register and release published and unpublished results
7. Link publication citations to trials registers



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Ottawa Statement on Trial Registration

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The Ottawa Statement, Part One: Principles for international registration of protocol information and results from human trials of health-related interventions

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WHO Unified Trials Register

Technical Consultation 25-27 April 2005

Agreed

1. Which trials to register

Any research project that prospectively assigns human participants or groups to one or more health-related interventions to evaluate the effects on health outcomes

- All health and health care interventions, not only medicines and medical devices
- Exploratory studies need not be registered
- When unsure, register

2. When to register

- As early as possible, ideally before recruitment of the first participant
- Informed consent form should include a trial ID

WHO Unified Trials Register

Technical Consultation 25-27 April 2005 (cont'd)

3. Minimum data set

At time of registration

- Unique IDs, funding sources, sponsors, contact persons, ethics review, condition under study, eligibility criteria, study type, start state, recruitment status

Delayed release of information in special cases (to be discussed further)

- Official scientific title
- Intervention(s)
- Target sample size
- Primary and secondary outcomes

WHO Unified Trials Register

Technical Consultation 25-27 April 2005 (cont'd)

Agreed (tentative)

4. Results disclosure:

- ICH E3 synopsis, adding ID and removing conclusions
- Results linked to registration
- Open access
- English summary
- Sponsor responsible for disclosure
- License holder responsible for updates

WHO Unified Trials Register

Technical Consultation 25-27 April 2005 (cont'd)

Agreed (tentative)

5. Where to register

- Open access to minimum dataset without barriers
- Open registration free of charge or minimal cost
- Searchable via Internet
- Validated information – responsibility of registrant
- Not-for-profit or for-profit distinction unnecessary

What next?

- **Contribute to international trials registration effort**
 - Register your trials and obtain a unique ID!
 - Insist that industry trials in which you participate are registered
 - Include Unique ID on consent forms
 - Work with your research ethics committee to require registration
- **Contribute to the Ottawa Statement**
 - Sign Principles if you have not
 - Contribute to Operationalization Statement (May 23-Portland)
- **Ensure that your journals require trial registration for publication**