The art and science of paper writing in clinical trials

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Clinical trials: Past, present, and future

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The publication imperative

Whereas:

Being able to research on human beings is a privilege, not a right, granted by society for the good its members;

The purpose of such research is to generate information for the benefit of humankind;

There is no lasting benefit to humankind absent repose of results of such research in the medical libraries of the world

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The publication imperative

Therefore

The sponsor and trialist, once a trial is undertaken, have moral obligations to publish results of trials regardless of the direction or nature outcome and to do so in a forthright and expeditious manner

and

Failure to do so represents a de-facto violation of the public trust

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What to publish?

The results for the primary outcome measure by treatment assigned

When to publish?

When the trial is finished, or during the trial when a treatment is stopped for lack of benefit or when the trial is stopped because of benefit

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Where to publish?

Peer-review, NLM indexed, medical journals

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Presentation vs publication?

Rule # 1: When it comes to results of trials, publish first, present later!

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Forms of presentation

- Presentation at scientific meetings (oral or poster)
- Press releases
- Website announcements
- Mailings

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Case studies

The WHI Hormone Replacement Trial
- Participants notified by letter starting 8 July 2002
- Press conference and release from NIH 9 July 2002
- Results published in full length article in JAMA 17 July

Vioxx
- Merck announces voluntary withdrawal of Vioxx 30 September following decision to stop the drug in a randomized trial (results not yet published)
- Results of an observational study suggesting risk of MI for Vioxx presented Aug 2004

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Reasons to publish first

1. Most efficient and expeditious means of dissemination of results
2. Presentation increases probability of not publishing
3. Presentation likely to increase time to publication
4. Authors defenseless when questions arise
5. Negative imprinting

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Exceptions to the rule

- Proprietary products (to reduce risk of "insider trading")
- When results are regarded as having immediate health implications

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The "rules" of randomized trials

Blackout (investigators do not see interim results by treatment group during the trial)
Independent treatment effects monitoring committee
Once randomized counted to the treatment group to which assigned
Primary analysis based on outcome measure specified when the trial was designed
Primary analysis based on all person enrolled and by treatment assignment regardless of adherence
All events counted to the treatment group of assignment regardless of time of occurrence

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Red herrings

- Generalizability
- Select study population
- Representativeness

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Subgroup analysis

- Meaningless in the absence of overall results by treatment group
- 1,000s done, few reported
- Most differences that are reported do not reproduce (ie, buyer beware!)
- The only legitimate subgroup variables are those observed prior to randomization

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Abuses

- Not playing with a "full deck"
- Analysis by treatment administered
- Considering only "evaluable patients"
- Elevating a subordinate variable to primary status

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10 easy steps to "success" in trials

1. Choose a "high tech" treatment for evaluation
2. Choose a surrogate outcome that "everyone" knows to be predictive
3. Do no quality control (to avoid finding things you do not want to know)
4. Toss out results for "nonadherent" patients
5. Limit analyses to "evaluable" patients and to "treatment-related" events

How to succeed in trials

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6 Analyze by treatment administered
7 Dredge to find a "significant" result; report ignoring the dredging
8 Seek media attention on presentation (except 60 Minutes)
9 Go on speaking tour touting results
10 Await call from Stockholm!

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The "usual" reading order

Title and masthead author listing
Conclusion
Abstract
References (especially to see if you are referenced)
Tables and figures
Methods section
Results section (when all else fails)
Discussion

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Title

Considerations

- Numbered titles?
- Design terms in title (eg, such as, *randomized*)?
- Subtitles?
- Study name as part of title?

Create titles that:

- Are succinct but informative
- Indicate purpose
- Telegraph content and type of study

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The manuscript title

Avoid titles that:

- Contain too much detail
- Contain redundant terms, such as, *prospective*, in the phrase *prospective clinical trial*
- Are "cute" but uninformative
- Contain jargon, undefined abbreviations, or acronyms
- Contain uninformative words or terms, such as, *study, project, program, collaborative, cooperative*, as substitutes for more precise informative terms, such as, *clinical trial, multicenter*
- Contain terms of presumption or arrogance, such as, *definitive, unique, innovative*

Remember

- Importance of title as identifier and descriptor
- Use of title by indexers

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Title examples

JAMA: A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease: The International Verapamil-Trandoiapril Study (INVEST): A randomized clinical trial (27 words)

JAMA: Outcome of elderly patients with chronic symptomatic coronary artery disease with an invasive vs optimized medical treatment strategy: One-year results of the randomized TIME trial (26 words)

JAMA: Treatment of antidepressant-associated sexual dysfunction with Sidenafi (8 words)

JAMA: Effect of magnesium sulfact given for neuroprotection before premature birth (10 words)

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Vancouver Convention requirements for authorship

Persons must be able to show substantial contributions to *(a) conception and design, or analysis and interpretation of data; and to (b) drafting the article or revising it critically for important intellectual content; and on (c) final approval of the version to be published. Conditions (a), (b), and (c) must all be met.*[?] Acquisition of funding, the collection of data, or general supervision of the research group do not, by themselves, justify authorship credit.

International Committee of medical Journal Editors: Uniform requirements for manuscripts submitted to biomedical journals. New Engl J Med 336:309-315, **1997**.
Under the **Uniform Requirements for Manuscripts Submitted to Biomedical Journals** (also known as the **Vancouver Convention**)

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Authorship formats

Conventional
Ann L Jones, Fred A Brown, and Ian F Smith

Modified conventional
Ann L Jones, Fred A Brown, and Ian F Smith for the XYZ Trial Research Group

Corporate
The XYZ Trial Research Group
(Writing committee not identified)

Modified corporate authorship
The XYZ Trial Research Group
(Writing committee identified in footnote to title page or credits section, eg, *Ann L Jones, Fred A Brown, and Ian F Smith for the XYZ Trial Research Group*)

How many authors?

Not as many as typically listed!

"Authors" for 2003 multicenter trials in JAMA and NEJM

Authors	JAMA	NEJM	Total
4	2	2	4
5 - 8	6	5	11
9 - 12	12	18	30
13 - 16	11	6	17
17 - 24	3	7	10
25	1	2	3
Total	35	40	75
Mdn	11	12	
Conventional	12	8	20
Mod conventional	23	31	54
Corporate	0	0	0
Mod corporate	0	1	1

Credits for multicenter trials

- Provides information import to understanding trial (ie, should be regarded as essential part of manuscript)
- Should list centers (clinics, coordinating center and other key resource centers) and key personnel
- Should list key committee and composition; in regard to treatment effects monitoring committee listing should be of full committee with asterisk to indicate voting members

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The analysis database

- Establish a cut off date and stick to it!
- Check the accuracy of the data harvest (especially treatment assignment!)
- Write "rules" regarding outlier values and how missing data are dealt with
- Provide a "map" of the dataset and of mapping of form changes over the course of data collection
- Backup!

Quality control

- Independent replication of key counts
- Independent programming of key analyses
- Cross checking marginal in tables
- Verification of accuracy of reference citations
- Check of credit listings

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Manuscript checklists

Check content against CONSORT or other similar checklists published in textbooks on clinical trials when developing manuscript and again just before submission

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The Hansel and Gretel approach to paper writing

Accomplished by spreading sufficient crumbs along the way so you can find back (ie, figure out what you did), sometimes years after publication

Requirements
- Documentation and archiving of key analysis programs
- Archiving of interim and finished drafts
- Archiving and documentation of the analysis dataset

Mothballing

- Hard copy study forms for a minimum of 5 years following close of trial
- Data monitoring reports and related minutes stored for minimum of 10 years
- Electronic datasets stored for a minimum of 10 years; duplicate copies stored in separate locations
- Study correspondence file including correspondences related to manuscripts stored for a minimum of 10 years following close of trial

Dealing with editors

- Do not be talked into something you think is ill-advised
- Do not make changes on the fly absent thought or documentation
- Provide a detailed response as to how suggestions are handled including those not followed and why not
- Pay more attention to the editor than the reviewers!
- Remember: Editors are people too