



Tomorrow's Doctors, Tomorrow's Cures™

Principles for Protecting Integrity In the Conduct and Reporting Of Clinical Trials

Susan Ehringhaus
David Korn

DBHSR

January 6, 2006

Principles for Protecting Integrity in the Conduct and Reporting of Clinical Trials

Approved by AAMC Executive Committee, January 6, 2006

Issue

Public concern is high regarding the timely and complete reporting of clinical trial results, primarily when the trials are sponsored by the drug, biologicals, or device industries. Because academic researchers and their institutions often play a prominent role in such trials, these concerns challenge the integrity of the academic medical research community as well as the sponsors of the trials.

Background

Despite a number of external initiatives that have heightened standards for reporting clinical trial results, the AAMC has been troubled by evidence that significant variation continues to exist within the academic community over the application of appropriate standards for analyzing and reporting the results of sponsored clinical research, especially clinical trials sponsored by industry. Accordingly, the AAMC, in collaboration with the Centers for Education and Research in Therapeutics and the BlueCrossBlueShield Association, has developed a set of principles, recommendations, and guidelines, rooted in sound science and sound ethics, to guide the medical schools, teaching hospitals, and professional societies that comprise the AAMC's membership and be broadly disseminated in the professional community. Assuming that broad consensus is reached within academic medicine, the sponsors will work to win acceptance of the principles by industry, the FDA and NIH, non profit sponsors of clinical trials, patient advocacy groups, and ultimately, the entire medical community.

As the first step in this process, the AAMC held a small invitational conference on June 22-23, 2005. Participants were selected primarily from the academic medical community for their experience in clinical research and research ethics, with special focus on expertise in the area of industry sponsored clinical trials. The charge to the conferees was to articulate a set of principles for academic medicine that should guide institutions and their researchers in the ethical and operational aspects of data access, analysis, and reporting of clinical research studies and would thereby help to assure integrity and credibility in the conduct and reporting of clinical trials. The conferees agreed to avoid what are routinely considered business or legal issues associated with clinical trials contracting (e.g., intellectual property, indemnification, and the like) and focused instead on study participation, access to data and analysis among investigators, reporting of results and publication, data sharing following publication, and trial registration.

The principles developed at the conference were endorsed by the AAMC's governance in September 2005 and shared widely with medical, scientific, and patient organizations, the FDA and NIH, non profit sponsors of clinical trials, patient advocacy groups, and senior biopharmaceutical executives, to identify areas of agreement and concern among those diverse stakeholders in clinical research. In response to comments, the document was revised to resolve ambiguous language and clarify certain technical

requirements. The revised principles were approved by the AAMC Executive Committee on January 6, 2006.

Consensus Principles

The following principles should apply to all clinical trials conducted in academic medical institutions regardless of the source of funding. They encompass single site as well as multisite studies, although operationalization of the principles may differ across study types and sizes. For purposes of these principles, “clinical trials” should be defined by reference to the ICMJE definition: “Any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome.” “Medical intervention” means “any intervention used to modify a health outcome”, including “drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like.”¹ This definition explicitly excludes phase 1 and early phase 2 studies (but not all late phase 2 studies), and it includes all phase 3 and 4 clinical trials, including studies of new indications for approved products.

Publications and Public Availability of Research Results

1. Researchers and their institutions have an ethical obligation when conducting human research to seek to make the results available publicly.
2. Contracts between sponsors and institutions for conducting clinical trials should require a good faith effort to publish the results of such trials in a peer reviewed journals in a timely fashion.
3. Contracts for clinical trials should contain a commitment of adequate funding to cover the full costs of the analysis defined in the protocol and the costs associated with publishing the results. This principle applies even when the study is terminated for any reason prior to meeting its pre-specified objectives.
4. All trials meeting the ICMJE requirements² for registration should make their results publicly available, by means of a link to any peer reviewed publications and by posting the results in an online accessible repository, within 18 months of submission of a manuscript for publication.
5. After publication of the results, the sponsor, the investigators, and their institutions should adopt a model for public sharing of the data underlying publications similar to that of NIH,³ which permits exceptions for confidential or proprietary information.

¹ DeAngelis, C. et al., *Is This Clinical Trial Fully Registered*. JAMA. 2005; 293: 2927-9. DeAngelis, C. et al., *Clinical Trial Registration: a Statement from the International Committee of Medical Journal Editors*. N.Engl.J.Med. 2004; 351:1250-1.

² Ibid. The World Health Organization is leading an international effort to promote registration of clinical trials, but has not yet gained consensus on the issue of “masking” of certain elements in the minimum data set required for registration. Because of continuing uncertainty, the WHO effort is acknowledged but not included as an alternative to the ICMJE registration requirements.

³ http://grants.nih.gov/grants/policy/data_sharing/.

Registration of Clinical Trials

6. Within 21 days of initiating enrollment of participants, any clinical trial covered by these principles should be fully registered pursuant to the ICMJE requirements⁴ for registration. Registration must include the assignment of a unique identifying number to each clinical trial.
7. Registration should be accomplished either in clinicaltrials.gov or in another public, non-profit, international registry and should include all the elements required by that registry.
8. Insofar as is feasible, trial registration data should be regularly updated to include a link to all published reports associated with the study.

Lead Investigator and Steering Committee

9. A multisite clinical trial, at the outset, should identify a lead or principal investigator and a steering committee to represent the full body of investigators.

Publication and Analysis Committee

10. A multisite clinical trial, at the outset, should establish a publication and analysis committee [hereinafter P&A committee]. It is essential that the P&A committee be independent of the sponsor's control, have access to the full data set, understand and implement the prespecified analysis plan, and have the resources and skills both to interpret that analysis and perform additional analysis if required. In order to prevent any appearance of undue influence by the sponsor, the P&A committee should contain a majority of participating, non-sponsor-employed investigators, with appropriate skills in analysis and interpretation of clinical trials. The P&A committee and the steering committee may have the same membership.
11. The P&A committee in multisite clinical trials (or the principal investigator of single site studies), through a qualified expert of its choosing, preferably a member of that committee, should have the right to access any data generated during the study that the committee deems necessary to ensure the integrity and validity of the study and its full reporting.
12. The P&A committee in multisite clinical trials (or the principal investigator in single site studies) should require that the sponsor of the study perform its analysis of trial data in a defined period of time. The committee (or PI) should be able to conduct its own analysis through an expert selected by it, to the extent it deems this necessary. Whenever feasible, the expert should be agreed upon by the P&A committee and the sponsor.
13. The sponsor should share with the P&A committee all analyses called for by the study that the sponsor conducts of any biological materials it receives during the course of the study.

⁴ See note 1.

14. The P&A committee or PI should make a good faith effort to disseminate the results of the study through peer reviewed mechanisms.

Individual Publication

15. Site-specific publications in multisite trials have an unavoidable potential for bias. Because they are almost never part of the original analytic plan, they are often misleading, and should be strongly discouraged. However, to respect an academic institution's commitment to academic freedom, site-specific analyses should nonetheless be permitted with conditions. Accordingly, an individual site investigator in a multisite trial should be free to analyze and publish data from the individual site, consistent with sound principles of science and analysis, but *only* after review and comment by the P&A committee and *only* after publication of the study as a whole, or, in the absence of acceptance of the full publication, within 2 years from the specified end points or earlier termination of the study.

Authorship

16. Ghost or guest authorship is unacceptable. Authorship implies independent, substantial, and fully disclosed participation in the study and in the preparation of the manuscript. It is acceptable for employees of the sponsor to participate in drafting and publication activity, but only if their roles are fully disclosed.
17. Institutions conducting clinical trials should adopt as policy the standards of authorship defined by the ICMJE.
18. Where applicable, investigators should use the CONSORT principles⁵ as guidance for publication of trial results.
19. Investigators should fully disclose, and journals should publish, the existence of all relevant financial interests, including consultancies of any investigator, in all communications of trial results.
20. Any manuscript submitted for publication should accurately disclose the role of each author in conducting the study and preparing the manuscript. Such information should also be disclosed in any public presentation of study results, to the extent practicable.
21. Manuscripts submitted for publication should disclose all previous publications involving the same protocol or database.
22. Manuscripts submitted for publication should be accompanied by the protocol and pre-specified analysis plan and all dated amendments to them, and any deviations to the pre-specified plan should be identified and discussed.

⁵ Altman, D. et al., *The Revised CONSORT Statement for Reporting Randomized Clinical Trials: Explanation and Elaboration*. *Annals of Internal Medicine*. 2001; 134: 663-94. Ioannidis, J. et al., *Better Reporting of Harms in Randomized Trials: An Extension of the CONSORT Statement*. *Annals of Internal Medicine*. 2004; 141: 781-8.

Conferees

Robert Alpern, M.D.

Dean

Yale University School of Medicine

Michael B. Amey

Associate Dean, Research Administration

Johns Hopkins University School of Medicine

Robert Califf, M.D.

Clinical Research Institute

Duke University Medical College

Arthur L. Caplan, Ph.D.

Chair of the Department of Medical Ethics

Director, Center for Bioethics

University of Pennsylvania

Gail H. Cassell, Ph.D.

Vice President of Infectious Diseases

Eli Lilly and Company

Kay Dickersin, Ph.D.

Professor

Johns Hopkins Bloomberg School of Public Health

Robert N. Golden, M.D.

Vice Dean

Professor and Chair of Psychiatry

The School of Medicine

University of North Carolina Chapel Hill

Harry B. Greenberg, M.D.

Senior Associate Dean for Research

Acting Co-Chairman, Department of Medicine and Microbiology and Immunology

Stanford University School of Medicine and the VAPHCS

Stephen I. Katz, M.D., Ph.D.

Director

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Drummond Rennie, M.D.

Deputy Editor, JAMA

Adjunct Professor

University of California, San Francisco

Robert R. Rich, M.D.

Vice President and Dean

School of Medicine

University of Alabama at Birmingham

Brian L. Strom, M.D., M.P.H.

Chair and Professor

Dept. of Biostatistics and Epidemiology

Director

Center for Clinical Epidemiology and Biostatistics

University of PA School of Medicine

Robert Temple, M.D.

Associate Director for Medical Policy

Food and Drug Administration

DHHS/FDA/CDER/OMP

Janet Wittes, Ph.D.

President

Statistics Collaborative

Alastair J.J. Wood, M.D.

Associate Dean

Professor of Medicine

Clinical Pharmacology Division

Professor of Pharmacology

Vanderbilt University

Principal Staff

David Korn, M.D.
Senior Vice President
Division of Biomedical and
Health Sciences Research
Association of American Medical Colleges

Susan Ehringhaus, J.D.
Assistant Vice President, Associate General
Counsel for Regulatory Affairs
Division of Biomedical and
Health Sciences Research
Association of American Medical Colleges

Coordinators

Allan M. Korn, M.D., F.A.C.P.
Senior Vice President
Office of Clinical Affairs/Chief Medical
Director
BlueCross BlueShield Association

Howard Dickler, M.D.
Director for Clinical Research
Division of Biomedical and
Health Sciences Research
Association of American Medical Colleges

Donald R. Stanski, M.D.
Scientific Advisor
Center for Drug Development Science
Food and Drug Administration
Professor of Anesthesia
Stanford University

Other Attendees

Naomi Aronson, Ph.D.
Executive Director
Technology Evaluation Center
BlueCross BlueShield Association

Kevin A. Schulman, MD
Professor and Vice Chair
Department of Medicine
Duke University School of Medicine

Kim Wittenberg, M.A.
Clinical Research Associate
Division of Biomedical and
Health Sciences Research
Association of American Medical College