Standards for CLINICAL RESEARCH WITHIN THE NIH INTRAMURAL RESEARCH PROGRAM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
October 2009

National Institutes of Health

Preface

The Standards for Clinical Research set forth some essential principles and processes for the conduct of clinical research in the intramural research programs of the National Institutes of Health. To achieve patient safety, efficient protocol implementation, and effective quality assurance and improvement requires adequate training of clinical investigators and sufficient infrastructure to support their endeavors. Consequently, the Standards should assist both new and experienced investigators as they apply good clinical practice in their research to achieve high-quality results.

The Standards were developed in January 2000 by the Clinical Center Medical Executive Committee, on which all the NIH institutes are represented by their clinical directors. They were endorsed by the scientific directors of the intramural research programs and the institute directors. Based on feedback from intramural clinical research programs and evolving standards within the human subjects research community, the MEC has reviewed and updated the Standards.

The NIH community remains committed to implementation of the Standards and evaluation of their application. It is important that every investigator involved in clinical research at NIH read, understand, and undertake training, as appropriate, to enable her or him to incorporate the Standards into everyday practice. It is equally important that the institutes, individually and collaboratively, assure the availability of all resources essential to the conduct of good clinical research.

The Standards for Clinical Research Within the NIH Intramural Research Program [http://www.cc.nih.gov/ccc/clinicalresearch/index.html] complements the Guidelines for the Conduct of Research in the Intramural Research Program at NIH and A Guide to Training and Mentoring in the Intramural Research Program at NIH [both available at http://www1.od.nih.gov/oir/sourcebook/ethic-conduct/ethical-conduct-toc.htm]. These statements encompass the NIH standards of training, ethics, and conduct for scientists.

John I. Gallin, M.D.
Director, NIH Clinical Center

Michael M. Gottesman, M.D.
Deputy Director for Intramural Research, NIH

Introduction

Adequate training and appropriate infrastructure to support principal investigators conducting clinical research are essential to patient safety, protocol implementation, and quality assurance and improvement—especially in interventional clinical trials. Indeed, even in natural history studies, such infrastructure can only enhance the quality of and access to the research by ensuring that data are collected as required by the protocol and are stored in a way that allows access to the information without dependence on any individual clinical researcher.

The International Conference on Harmonisation, a consortium of regulatory bodies for the European Union, Japan, and the United States (Food and Drug Administration), has issued a series of guidelines for good clinical research that has begun to define the resources required for clinical principal investigators (PIs).[1] A central requirement identified by the Conference is the availability of "an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely."[2] To assure patient safety and high quality in NIH intramural clinical research programs, the Medical Executive Committee of the NIH Clinical Center has developed the following essential standards for performing clinical research—categorized in seven subject areas:

1. **Clinical Informatics, Data Management, and Protocol Tracking**
2. **Biostatistics Support**
3. **Quality Assurance and Quality Improvement**
4. **Protocol Review**
5. **Human Resources and Physical Plant**
6. **Training and Education**
7. **Research Participants**

Standards

1. Clinical Informatics, Data Management, and Protocol Tracking

Rationale

Collecting clinical data is a complex task that must be integrated into the medical practices of the institution. To monitor the study's progress and patient safety, data collection is best done as data are generated. Data management organized and supported at the institute level is more efficient and reliable than that left to the individual investigator. There are often unforeseen uses for the kinds of information gathered in the conduct of a clinical trial, and a central database, with appropriate archiving, assures that this information remains the legacy of the institute.

Standard

Each institute sponsoring clinical research should develop a central clinical investigations database that maintains all data specified to be collected in the clinical study (either intervention or natural history). The clinical research information system being continually developed by the Clinical Center interfaces with and supports each institute's clinical research needs. A confederated database will enable information exchange, enabling access to and sharing of clinical and research information among all institutes. The institutes require data-management infrastructures to maintain their central data registries, to enhance existing databases, to provide eligibility checklists, to record patient randomization and entry into their protocols, to provide report generation, data warehousing, and data entry forms, and to monitor data collection.

2. Biostatistics Support

Rationale

The design of clinical trials should be based on sound statistical principles. Issues such as sample size, stopping rules, endpoints, and the feasibility of relating endpoints to objectives are pivotal to a successful trial. Typically, if the PI is not a skilled biostatistician, a biostatistician should be listed as an associate investigator on the protocol and should be involved in the protocol at all stages from design to analysis of results.

Standard

All clinical protocols must be reviewed by a qualified biostatistician prior to approval and implementation.

3. Quality Assurance and Quality Improvement

Rationale

The International Conference on Harmonisation is very clear on the responsibilities of research sponsors. The sponsor is defined as the organization that "takes responsibility for the initiation, management and financing of a clinical trial."[3] In the context of the intramural program, the research sponsor is each institute conducting intramural clinical research.

The sponsor "is responsible for implementing and maintaining quality assurance and quality improvement systems with written standard operating procedures to ensure that trials are conducted and data generated, documented, and reported in compliance with the protocol, good clinical practices, and the applicable regulatory requirements."[4] To accomplish this, institutes must have quality assurance/improvement programs to assure that each participating investigator is fulfilling his/her responsibilities. Quality assurance/improvement provides institutes with data about the quality of execution of their clinical research, and it provides investigators an opportunity to learn through external evaluation.

Some interventional trials should be overseen by an external expert committee (data safety and monitoring board [DSMB]) to assure that adverse events are recognized and reported and that protocols are implemented in conformance to the protocol design and are closed to accrual when endpoints are met or unanticipated adverse events occur. At a minimum, all randomized or masked (blinded) studies should be reviewed at least semiannually by a DSMB.

Standard

Each institute must have access to a quality assurance/improvement program with infrastructure that ensures that clinical trials are monitored adequately and centrally. The institute should determine the appropriate extent and nature of monitoring. This determination should be based on considerations of the study objectives, purpose,

design, complexity, blinding, size, and endpoints, and should include the following:

- Onsite protocol monitoring during clinical trials. Statistically controlled sampling is an acceptable method for selecting the data to be verified. For interventional trials, the institutes should demonstrate a capacity to review a minimum of 10% of patient records on selected clinical trials to assure data accuracy, protocol compliance, and adherence to regulatory requirements.
- Access to an independent DSMB for at least a semiannual overview of all randomized blinded studies.

4. Protocol Review

Rationale

All protocols involving human subjects must undergo review of scientific content by an institute scientific review committee. These protocol review committees assess scientific quality, the importance to clinical practice, and the appropriateness of the study to the sponsoring institute. Following the scientific review, all protocols must be reviewed by an institutional review board (IRB) or the Office of Human Subjects Research (OHSR) as required to establish and ensure patient safety and good ethical conduct of the study, including avoidance of conflicts of interest.

Standard

Each institute must provide:

- Scientific review by a written protocol review process.
- Infrastructure (e.g., administrative staff) to support an appropriately constituted IRB.

5. Human Resources and Physical Plant

Rationale

A cadre of skilled personnel is required to support the PI and provide oversight of clinical trials. The appropriate organization of a clinical trial team may differ depending on program objectives, but the team supporting a PI should comprise an appropriate mix of case managers, research nurses, physician assistants, nurse practitioners, data managers, and computer programmers.

Standard

Necessary personnel, office space proximal to patient care areas, and accompanying resources should be available to support the clinical research infrastructure.

6. Training and Education

Rationale

Training and education are first-order requirements to ensure that the Principal Investigators (PIs) and Associate Investigators (AIs) on clinical trials have a consistent and complete understanding of their responsibilities. Clinical protocol design requires a working knowledge of clinical trials methodology, biostatistics, and regulatory medicine. Similarly, monitoring the trial during its execution involves many distinct responsibilities—including reviewing each study subject's record to confirm his or her protocol eligibility, reviewing each study subject's record to determine compliance with the protocol, reporting adverse events to the IRB, determining necessary changes in the protocol and the informed-consent documents and submitting them as protocol amendments to the IRB, monitoring accrual to the study, and stopping the study when the requirements of the study design have been fulfilled or when it is clear that the rate of accrual fails to meet expectations.

Standard

- All clinical investigators (PIs and AIs) are required to take an overview training course, or equivalent, on the roles and responsibilities of clinical investigators. This course will be provided by the Clinical Center.
- All IRB chairs and IRB members (including lay members) will receive orientation materials and are required to take specialized training modules provided by the Clinical Center/OHSR.
- Continuing education will be provided for IRB members.

7. Research Participants

Rationale

Research participants are critical members of the clinical research team and are considered partners in the research process. A key responsibility of the Clinical Center and the investigator is to assure participants are educated about the protocols in which they are enrolled as well as about the clinical research process. Likewise, providing participants with opportunities to ask questions and voice concerns to the Investigator and the Clinical Center throughout the course of the research protocol is an essential aspect of a human subjects protection program.

Standard

- The organization will provide participants (and communities) with appropriate educational materials about the clinical research process (Clinical Center patient education materials; protocol specific patient education materials, Patient Recruitment and Public Liaison).
- Each informed consent document will provide participants with information about how to voice concerns or discuss problems related to their protocol participation (Patient Representative and study team members).
- The organization will periodically assess participants' perceptions of the clinical research experience and use those data to drive improvement activities (patient surveys, patient portal).

References

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance, April 1996 [http://www.cc.nih.gov/ccc/clinicalresearch/guidance.pdf].
[2] ibid., Section 4 — Investigator
[3] ibid., Section 1 — Glossary
[4] ibid., Section 5 — Sponsor

Cover drawing of Louis Pasteur, colleague and patient, courtesy of the New York Academy of Medicine