NIH Requirements for Clinical Research

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January 18th, 2002
Salvador, Brazil
Overview

- International Clinical Research Has Many Masters
- Forces of change
- DHHS New Requirements
- GAO Required Changes
- NIH new requirements
- NIAID requirements
- DMID requirements
ORGANIZATIONS IMPACTING ON CLINICAL RESEARCH

...Masters

Department of Health and Human Services (DHHS)

NIAID-Supported International Clinical Research

Food and Drug Administration (FDA)

Office of Human Research Protection (OHRP)

NIH Office of Director

NIAID Office of Director

DMID/DIR Office of Director

Ethics Guidance e.g. NBAC

State/Local Regulations

Clinical Sites and IRBs

Manufacturers

International Conference on Harmonisation (ICH)

General Accounting Office

Foreign Regulatory Agencies (International)

Fogarty Center/State Department (International)

Office of Management and Budget (OMB)
The Force of Change

Executive Branch
President

DHHS

GAO

NIH
Director

NIAID
Dr. Fauci

DMD
DEA
DAIDS
DAIT
Intramural

PIPB

ICIDR
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- DMI D requirements
“The tragic death of Jesse Gelsinger focused national attention on the inadequacies in the current system of protections for human research subjects. …these inadequacies …. can also serve as a catalyst for change and improvement in clinical research. …. we must work together to reform the current system …. so that it can guarantee the greatest possible protection for every human subject, in every clinical trial and at every research institution in the country.”
DHHS Secretary Conclusions on the State of Human Subject Research

- US System of human subject protections is broken
- Reforms will take place
- NIH and researchers will implement the changes
DHHS Response to Perceived Weakness in Human Subject Research Oversight...Shalala

“I announced several additional steps to improve the safety of subjects in clinical trials; strengthen government oversight of medical research, including gene-transfer research; and reinforce clinical researchers' responsibility to follow federal guidelines”
"First, the NIH and the FDA will undertake an aggressive effort to improve education and training. The objective is to ensure that all clinical researchers, research administrators, IRB members, and IRB staff receive appropriate training in bioethics and other issues related to research involving human subjects. This training will be required for all clinical investigators who receive NIH funds and will be a prerequisite to the receipt of all NIH grants."
Second, the NIH and the FDA will issue specific guidelines on informed consent, reaffirming the expectation that research institutions and sponsors will audit records for evidence of full compliance. The new guidelines will also reassert the obligation of investigators to confirm the informed consent of participants when any serious trial-related event occurs that might affect a subject's willingness to participate.

The New England Journal of Medicine -- September 14, 2000 -- Vol. 343, No. 11,
“Third, in order to improve monitoring, the NIH will now require investigators who are conducting small-scale early clinical trials (phase 1 and phase 2 trials) to submit monitoring plans at the time they submit their grant applications. Researchers will be expected to share these plans with the IRBs. In addition, the FDA will soon issue new guidelines for data and safety monitoring boards (DSMBs).”
Shalala—Conflict of Interest

“Fourth, we will issue additional documents to clarify regulations relating to conflicts of interest.”

“Fifth, we will pursue legislation to enable the FDA to levy civil monetary penalties for violations of informed consent and other important research practices. The fines would be up to $250,000 per clinical investigator and up to $1 million per research institution.”

--Not yet

Shalala—OHRP renamed, moved from NIH to Office of the Secretary…..

“Along with these measures, the role of the OPRR is being expanded. Its responsibilities have been transferred to the Office of the Secretary, and it has been renamed the Office for Human Research Protections.”

The New England Journal of Medicine -- September 14, 2000 -- Vol. 343, No. 11,
Office of Human Research Protections (OHRP). What is new?

- Federal Wide Assurance
- Registration of IRB
- Emphasis on Education
What is an "Assurance" and When is an "Assurance" Needed?

- The Federal Policy (Common Rule) for the protection of human subjects at Section 103(a) requires that each institution "engaged" in Federally-supported human subject research file an "Assurance" of protection for human subjects.
- Additional Guidance on web
The Federal Wide Assurance

- The Assurance formalizes the institution’s commitment to protect human subjects.
- The requirement to file an Assurance includes both "awardee" and collaborating "performance site" institutions.
Procedures for Registering Institutional Review Boards and Filing Federal wide Assurances of Protection for Human Subjects (FWAs)

- On line registration. Web walks you through this process.
- Assurances approved under this process will cover all of the institution’s Federally-supported human subject research.
- Each legally separate institution will need its own Federalwide Assurance (FWA).
OHRP Website.... Federalwide Assurance

- What is an "Assurance" and When is an Assurance Needed?
  - Awards Personnel Notice
  - Awardee Notice
- Terms of Assurance
- Instructions for Filing Federalwide Assurances
  - Sample FWA Filing Document - RTF Format
  - Sample FWA Filing Document - HTML Format
- Modules Required for FWA Personnel
  - Sample Unaffiliated Investigator Agreement
  - Sample IRB Authorization Agreement
  - Sample Dept. of Veterans Affairs, ORCA Clearance Document
  - IRB Registration and Federalwide Assurance (FWA) Q & A
Why Register an IRB or IEC?

- To establish effective communication with IRBs and IECs working to protect human subjects
- At the present time, Registration is required only for IRBs and IECs designated under an OHRP Federalwide Assurance of Protection for Human Subjects.
- Other IRBs and IECs are encouraged to register voluntarily. IRB Registration is not currently required by FDA.
IRB Registration on line information.....

- Why Register an IRB or IEC?
- IRB Responsibilities
- IRB Knowledge of Local Research Context
- Instructions for Registering IRBs or IECs
- Sample IRB Registration Document - RTF Format
- Sample IRB Registration Document - HTML Format
- IRB Registration
IRB Registration on line information

- Approvals and Related Information
  - IRB/ FWA Documents Received  [last 45 days]

- Listings of Registered IRBs and IECs
  - Domestic IRBS (by State)
  - International IRBs/IECs (by Country)
  - All IRBs/IECs (by IRB Identifier)

- Listings of Institutions Holding OHRP Approved Federalwide
Regulation links on OHRP web site

- 45 CFR 46 - Protection of Human Subjects
- Research that may be Reviewed Through an Expedited Procedure
- Public Law 103-43, Sec. 498A Fetal Tissue Transplantation Research
- Statutory Basis for 45 CFR 46
- Presidential Memorandum on Protection of Human Subjects (2/17/94)
- Human Subject Regulations Decision Charts (9/98)
REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

Release Date: June 5, 2000 (Revised August 25, 2000)

- **Start date, Oct. 1, 2000**
- Before funds are dispersed for grants or contracts with human subject research must provide a description of education completed by all “key personnel” in the protection of human subjects.
- Key personnel include all individual responsible for the design and conduct for the study.
- Must be included in non-competing renewals.
Answers to Frequently Asked Questions for the Requirement for Education on the Protection of Human Subjects

- Key Personnel of all awards or on foreign subcontracts must comply with requirement.
- Applies to all non-competing renewals.
- Submitted only once per project/protocol
- Must be submitted for each project in program project grants, U19s, TMRC’s, TBRUs.
- Documents certifying that the education required has been met must be signed by an institution official.
NOTICE TO NIH GRANTEES/CONTRACTORS REGARDING LETTERS OR NOTICES FROM THE FOOD AND DRUG ADMINISTRATION

(FDA) Release Date: September 22, 2000 NOTICE: OD-00-053

In order to keep the NIH informed and comply with 45 CFR 74.51(f), the awardee institution must report FDA communications to the awarding Institute(s) or Center(s) **within 72 hours of receiving** a copy of the communication or upon being informed of the FDA communication, whichever occurs first.
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Inclusion of Women & Minorities

- It is the policy of NIH that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects. NIH Guide 23(11): March 18, 1994
- Cost not reason for exclusion.
- Of child bearing age not reason for exclusion.
Senators Harkin, Mikulski, Snow and Waxman asked GAO to assess NIH progress in conducting Women’s health over past decade.

GAO May report…

“A” for progress on training and effort

“F” for results
Two GAO Recommendations — Inclusion of Women and Minorities
May 2000

“Requirement be implemented that Phase III clinical trials be designed and carried out to allow for valid analysis of differences between women and men. Communicate this requirement to applicants and peer groups.”

“Training on requirement and purpose of system.”
NIH Response to GAO (update October 2001 on NIH website)

- Phase III studies must include analysis plans for minorities and gender.

- IRG’s will be asked to evaluate these plans. Will be reviewed and scored on how well you comply with inclusion of women.

- For all NIH grants, cooperative agreements, and contracts.
New PHS 398 Instructions: Section E:

- Inclusion of women & minorities is now part of Section E: Human subject research.
- Must include: a description of subject selection criteria and rational in terms of objectives and study design.
- Compelling rationale for proposed exclusion of any gender/racial group.
- Dates of enrollment (beginning and end)
New PHS 398 Instructions: Section E:

- A description of proposed outreach plans for recruiting women & minorities.
- Proposed sample composition.
NIH Response to GAO

1. Plans to conduct “Valid Analysis” by gender and/or racial/ethnic subgroups included in:
   - Research Plan submitted in application
   - Final protocol approved by IRB and NIH

2. The award will require that the results of analysis must be reported to NIH

3. Inclusion of the result of subset analysis is strongly encourage in all publications submissions.
NIH Defines Phase III CT…

**OD-00-048**

- Usually involves several hundred subjects

- For purpose of evaluating an experimental intervention in comparison with a standard or control or comparing two or more existing treatments.

- Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care.
When to include subset analysis......consider evidence from previous studies... If significant differences of clinical or public health importance in intervention effect

1. **Exist among subgroups.**
   - Design study to **measure significant differences** among subgroups as **primary outcomes**.

2. **Do not exist between subgroups**
   - Include women and minorities, but do not design study to measure significant differences between subgroups.

3. **Are neither supported nor negated between subgroups.**
   - Include subgroups so a valid analysis may be done, but **not required** to design to measure **significant differences** between subgroups.
Monitoring Adverse Events…communication between DSMB and IRB

- All multi-site trials with data safety monitoring boards are expected to forward summary reports of adverse events to each IRB involved in the study.

- DSMB summary recommendations must be sent to the IRB’s
Data Safety and Monitoring of Phase I and II trials, June 5th, 2000

1. A **general description** of the data and safety monitoring plan must be part of the research application.

2. This plan will be reviewed by the scientific review group and any comments and concerns will be included in an administrative note in the summary statement.
Data Safety and Monitoring of Phase I and II trials, June 5th, 2000

1. A detailed monitoring plan, however, must be included as part of the protocol and submitted to the local IRB and reviewed and approved by the funding Institute and Center (IC) before the trial begins.

2. Each IC should have a system for appropriate oversight and monitoring of the conduct of clinical trials to ensure the safety of participants and the validity and integrity of the data.
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Inclusion of Children
New in 1998

1. “It is the policy of the NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are specific scientific and ethical reasons not to include them”

2. Therefore, proposal for research must include a description of plans for including children.

3. If children will be excluded from the research, the application or proposal must present an acceptable justification for the exclusion.”

NIH Special Requirements
International Clinical Research

- State Department Clearance-1820
- FWA Project Assurance (registration IRB)
- IND not requirement at the moment…
  - Requires FDA Review
- Human subject training for all significantly involved personnel.
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NIAID CLINICAL TERMS OF AWARD

Introduction

- NIAID Clinical Terms of Award (CTA) were introduced in June 1999.
- The CTA outline information, approvals, and reporting requirements required by the NIAID when funding human subject research.
- By accepting NIAID funds under the CTA, the investigator agrees to comply.
CTA Overview—3 parts

- Objectives of NIAID CTA
- Information required for NIAID review and approval prior to initiating a study
- Reporting requirement
Objectives of NIAID CTA

- Ensure compliance with laws and regulations governing clinical research
- Assist both the NIAID and investigators in monitoring compliance with established standards.
- Compliance with Principles of Good Clinical Practice
CTA: Submission to NIAID for Review and Approval Prior to Study Initiation

- Safety monitoring plan, e.g. DSMB (data safety & monitoring board) ISM,
- Protocol, informed consent
- Adverse event monitoring and reporting plans
- Site monitoring plans
- Institutional Review Board Approval
**NIAID Review of Submitted Materials**

- **Time line:** within 3 weeks
- **Investigator must respond to NIAID concerns in writing**
- **Protocol review:** 2 methods
  - Committee review—most of PIPB submissions go through ICTDR Protocol review process
  - 3 staff review
Reporting Requirements: 3 categories

- Demographics
- Safety
- Changes in study protocol or study status
**Reporting Requirements**

- **Demographics**
  - Interventional studies (clinical trials) every 6 months
    - Gender, ethnicity, children, adults
    - Cumulative
  - Non-interventional (clinical studies) annually, included in progress reports
Reporting Requirements

Safety

- Serious adverse events
- If IND any reports sent to FDA, must be sent to NIAID within 24 hours
- If non-NIAID DSMB, any open DSMB reports within 30 days
Reporting Requirements

- Changes in study status: within 3 days
  - Protocol amendments
  - Terminations of study protocol
  - Temporary suspension of study
  - Any change in informed consent or IRB status
  - Any problems or issues which may affect human subjects
Guidance includes definitions of severity

- Relationship or association with use of study agent or participation in the study
  - Definite: temporal ass. Repeat on rechallenge
  - Probable: temporal ass. With improvement upon withdrawal, no explained by subjects clinical state
  - Possible: less clear temporal association, other etiologies possible
  - None: no temporal association, related to other etiologies, or subjects known clinical state.
Where to Get More Information

- Other training sessions, e.g. GCPs training session after ICTDR meeting
- ICSSC.org, NIAID web
- Program officer
- Please call PIPB with questions or concerns
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Monitoring—Force ICH, NIH, NIAID Terms of Award

- All NIH-supported trials require site monitoring (NIH Guide 6/98)
  - ICTDR network all interventional trials
  - All NIH-supported trials need to follow monitoring plans (NIH Guide 6/00)

- Safety Monitoring
  - ICTDR DSMB: reviews late phase II and phase III and others at their discretion.
Summary

- Be Aware of new requirements for human subject research.
- Comply with the requirements.
- Document compliance.
- Remember that program staff is your ally.
- Additional information on web!