Implementing a Clinical Research Compliance Program

Kendra Dimond, Partner
Epstein Becker & Green
Washington, DC
202-861-0900

F. Lisa Murtha, J.D.
Chief Audit and Compliance Officer
The Children's Hospital of Philadelphia
215- 590-9156

Why is there a need for a compliance program for human subject research activities at an Academic Medical Center or University?

- Federally-sponsored Research
- Relocation of OHRP to Secretary Level
  - New office of research protection
- OHRP is defunct
- OIG Work plan FY1999 and FY2000
  - clinical drug trial billing
  - IRB (Institutional Review Board) Reviews
  - Allegations of Medicare/Research Grant Double Billing
  - Investigations that will address bribery, grant, contract and research fraud
  - FDA - Drug and Device Regulations
- Informed consent and reporting of serious adverse events
- IRB functionality

FAILURE TO MANAGE THESE ETHICAL AND REGULATORY ISSUES HAS RESULTED IN FINANCIAL AND REPUTATIONAL DAMAGE TO SOME OF THE WORLD'S MOST RESPECTABLE INSTITUTIONS

University of Minnesota
Misuse federal grants
$32 mil

Thomas Jefferson University
Research Fraud

University of Pennsylvania
Human Gene Therapy
Trials

University of Wisconsin
Madison PRISON
$10,000 Fine

Report on Medical
Errors

University of Oklahoma
Clinical Trial Shutdown

Duke University
Shutdown for
Clinical Trials

Consequences of Non-Compliance

- Fines and Penalties
- Shutdown of projects - Loss of research funding
- Institution considered “exceptional” by funding agency
- Loss of “expanded authorities” Federal Demonstration Partnership (“FDP”)
- Additional oversight/monitoring by the government
- Potential reduction in funding
- Professional integrity compromised
- Reputational risk

Protecting the Rights and Welfare of Human Research Subjects (Common Rule)

Compliance with federal regulations for the protection of human subjects is an obligation whenever biomedical or behavioral research is conducted or supported by any of 17 U.S. government departments or agencies, or whenever research is subject to regulation by the Food and Drug Administration (FDA).

Federal Regulations and Policy

- 45 CFR 46 – Basic DHHS Policy for Protection of Human Research subjects*
- Additional protections for vulnerable populations in subparts B-D

*Revised June 18, 1991

Federal Regulations and Policy (continued)

- "The Common Rule" - Federal Policy for the Protection of Human subjects - June 18, 1991

  Departments of Agriculture, Energy, Commerce, HUD, Justice, Defense, Education, Veterans Affairs, Transportation, and HHS, NSF, NASA, EPA, USAID, Social Security Administration, CIA and the Consumer Product Safety Commission.

Federal Regulations and Policy (continued)

- Additional Protections Included in 45 CFR 46:
- Subpart B – Additional DHHS Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant women, and Human In Vitro Fertilization
- Subpart C – DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects
- Subpart D – Additional DHHS Protections for Children Involved as subjects in Research

Basic Protections

- The regulations contain three basic protections for human subjects:
- Institutional Assurances
- IRB Review
- Informed consent

Assurances

- "Each institution engaged in research which is covered by this policy and which is conducted or supported by a Federal Department or Agency shall provide written assurance…that it will comply with the requirements set forth in this policy."
- Negotiated and approved by OHRP
- The institution must certify that the research has been reviewed and approved by an IRB. (45 CFR 46.103(b))
- Submitted to funding agency

Assurances

- Information to be included in the assurance:
- Statement of principles governing the institution
- Designation and roster(s) of the IRB(s)
- IRB procedures for ensuring prompt reporting

Assurances

Types of assurances:

- Multiple Project Assurance (MPA)
- Single Project Assurance (SPA)
- Cooperative Project assurance (CPA)
- Federal Wide Assurance (FWA)

Office of Human Research Protection (OHRP)

(Secretary-level office that oversees Human Subject Research)

Responsibilities

- Institutional Audits of Grants
- Implementation and interpretation of federal regulations and policy
- Education programs
- Negotiation of multiple project assurances
- Evaluation of compliance

Risk Factors in Human Subject Research

- Undefined roles and responsibilities (Administrators, Principal Investigators, Clinicians)
- Decentralized Administration
- Staff allegiance to Principal Investigator rather than institution
- Faculty or administrator conflict of interest situations
- Faculty disdain for administration or for regulation
- Lack of training in proper conduct of clinical trials

Principal Investigator's (PI) Responsibility in Conduct of Human Subjects Research

- Institution and PI ultimately responsible for conduct of grants and awards
- Insuring that there is informed consent from all research participants
- University warrants that it has proper system in place to protect human subjects
- PI acts as the agent of the grant recipient (i.e., the University)

Institutional Responsibilities

- Institutions bear full responsibility for all research involving human subjects covered under their Assurance
- All requirements of 45 CFR 46 must be met for all *federally-sponsored* research
- OHRP strongly encourages institutions to embrace the HHS regulations regardless of sponsorship, and to commit to this standard in their Assurance.

Institutional Responsibilities (continued)

- Designate one or more Institutional Review Boards (IRBs) to review and approve all nonexempt research covered by an the Assurance
- Provide sufficient space and staff to support the IRB's review and record-keeping duties
- Ensure that appropriate Assurances and certificates of IRB review are submitted for all their federally sponsored research not only for themselves but also for cooperating performance sites

Institutional Official

- "The Buck Stops Here"
- Authorized to act for the institution
- Assumes on behalf of the institution the obligations in the Assurance – Institutional commitment to compliance
- Knowledgeable point of contact for OHRP
- Sets the "tone" for an institutional culture of compliance
- Confirms authority of and works in concert with IRB
- Responsive to IRB recommendations
- Provides IRB with necessary resources and staff

Institutional Review Board (IRB)

Membership:

- At least five members of varying backgrounds
  - Sufficiently qualified
  - Not solely of one profession
  - Gender diversity
- At least one non-scientist
- At least one non-affiliated member
- Expertise on “vulnerable populations”
- Outside consultants

What is an Institutional Review Board? (IRB)

A Committee whose primary mandate is to protect the rights and welfare of humans who are the subjects of research

Why do we have Institutional Review Boards? (IRB)

- PHILOSOPHY
- HISTORY
- REGULATIONS

Philosophical Basis for IRBs

The Belmont Report

Basic Ethical Principles:

- Respect for Persons
  - Individual autonomy
  - Protection of individuals with reduced autonomy
- Beneficence
  - Maximize benefits and minimize harms
- Justice

Historical Basis for IRBs

- NUREMBERG:

  During the Nuremberg War Crimes Trials, 23 German doctors were charged with crimes against humanity for “performing medical experiments upon concentration camp inmates and other living human subjects, without their consent, in the course of which experiments the defendants committed the murders, brutalities, cruelties, tortures, atrocities, and other inhuman acts.”

Historical Basis for IRBs

- The Nuremberg Code (1947)

  As part of the verdict, the Court enumerated some rules for “Permissible Medical Experiments”, now known as the “Nuremberg Code”.

These rules include:

- Voluntary consent
- Benefits outweigh risks
- Ability of the subject to terminate participation

Historical Basis for IRBs

- Tuskegee Syphilis Study:
- American medical research project conducted by the U.S. Public Health Service form 1932 to 1972, examined the natural course of untreated syphilis in black American men. The subjects, all impoverished sharecroppers form Macon county, Alabama, were unknowing participants in the study; they were not told that they had syphilis, nor were the offered effective treatment.

IRB Responsibilities

- Review and approve, require modifications, or disapprove all covered research
- Require that informed consent is in accordance with regulations
- Require documentation of informed consent or may waive documentation in accordance with regulations
- Notify investigators in writing of decisions
- Conduct continuing review of research no less than once per year

Criteria for IRB Approval

- Risks to subjects are minimized
- Risks are reasonable in relation to anticipated benefits
- Selection of subjects is equitable
- Informed consent is sought from each subject
- Informed consent is appropriately documented

Expedited Review

An IRB may use expedited review for:

- Research on list of eligible categories
- Minor changes in previously approved research
- Carried out by IRB chair or one or more experienced IRB members
- Reviewers can exercise all of the authorities of the IRB except disapproval
- All IRB members must be informed of research approved under expedited review

Purpose and Definition of Informed Consent

Informed consent is one of the primary ethical principles governing human subjects research; it assures that prospective human subjects will understand the nature of the research and can knowledgeably and voluntarily decide whether or not to participate.

Informed Consent Is...

- Risk/Benefit discussion with participants
- Voluntariness of participation
- Freedom to withdraw from study at any time
- Treatment
- Notification of serious adverse events
- Disclosure of PI’s financial interest in study

Performing a Risk Assessment For Human Subject Research Compliance

General Steps:

- Review human subject research policies and procedures or establish standard operating procedures
- Interview key administrative staff and Principal Investigators (3-5 awardees of large dollar volume research studies)
- Walk-throughs of clinical labs and administrative facilities
- Conflicts of Interest: Whose duty is it?

- PHS has suggested nine areas for Training and Education in the Responsible Conduct of Research. They are as follows:

Data Acquisition, Management, Sharing and Ownership

- Acquiring and maintaining research data
- Record keeping, electronic data collection, storage, data privacy and confidentiality
- Ownership

Mentor/Trainee Relationships

- Responsibilities
- Conflicts
- Collaboration and competition

Publication Practices and Responsible Authorship

- Collaborative work
- Assigning appropriate credit
- Appropriate citations
- Pressure to publish

Peer Review

- Peer review in determining merit for research funding and publications
- How peer review works in the grants process

Collaborative Science

- Setting ground rules
- Authorship disputes
- Sharing of materials and information

Human Subjects

- Ethical principles
- Informed consent
- Confidentiality and privacy of data and patient records
- Preparation of a research protocol
- Institutional review boards
- Proper conduct of the study
- Special protections for targeted populations

Research Involving Animals

- Ethical principles
- Federal regulations
- Treatment of animals

Research Misconduct

- Regulations that govern PHS-funded institutions
- Institutional misconduct policies
- Procedures for reporting misconduct
- Whistleblowers

Conflict of Interest and Commitment

- Definition of conflicts
- How to manage, reduce or eliminate
- Reporting obligations for financial relationships