Protecting the People who Volunteer to Participate in Research

Human Subject Protections
Medical Research Summit 3/2002

- Michele Russell-Einhorn, JD
- Director
- Clinical Research Consulting Team
- PricewaterhouseCoopers
- 301-897-4217
- Michele.Russell-Einhorn@us.pwcglobal.com

Session Objectives

- Review issues and present materials relating to the protection of human subjects in research
- Examine the requirements of the IRB review; responsibility, authority, jurisdiction
- Discuss the IRB review process

Research Involving Human Subjects

- “Research has to be based on the highest standards of responsible conduct, based on ethical principles by each and every individual taking part. Let me make it unmistakably clear, in case anyone has any doubts. If institutions and individuals fail to truly accept their responsibilities and in good faith work to achieve them, then they simply should not be permitted to engage in this endeavor.” (Dr. Greg Koski, Director, DHHS Office for Human Research Protections, August 2000)

Research Involving Human Subjects

- “What’s at stake is the integrity of research, and public confidence in that research.” (DHHS Secretary, Donna Shalala, May 2000)

Historical Overview

Historical Overview

- Nuremburg Code - Trials of War Criminals before the Nuremburg Military Tribunals Under Control Council Law No. 10, 1949
- Declaration of Helsinki - Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects, World Medical Association, 1964 (revised many times)
- Public Health Service (PHS) policy- Required the establishment of the National Advisory Health Council for the prior review of PHS sponsored research

Historical Overview

- National Research Act - Created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (July 12, 1974)
- Belmont Report - Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979

Federal Regulations Governing the Operation of IRBs

- Federal Policy for the Protection of Human Subjects (Common Rule)
- DHHS Regulations: 45 CFR Part 46
- DHHS Multiple Project Assurance (FWA)
- FDA Regulations: 21 CFR Part 50; 21 CFR Part 56
- Other Federal Agencies

The Common Rule

- A Federal Policy
- Applies to 17 Federal agencies and offices
- Does not apply to Federal agencies that have not signed the Common Rule (e.g., Department of Labor)

DHHS Regulations: 45 CFR Part 46

- Subpart A - codification of the Common Rule
- Subpart B - additional protections for pregnant women and fetuses (note new revision 12/13/01)
- Subpart C - additional protections for prisoners
- Subpart D - additional protections for children

DHHS Multiple Project Assurance

- An institution with a DHHS approved Multiple Project Assurance typically agrees to apply DHHS regulations to all research regardless of the funding source. This means that the additional protections set forth in Subparts B,C, and D would have to be applied to any research funded by a different government agency, even if that agency does not have similar additional protections.
- New Federalwide Assurance System

FDA Regulations

- FDA generally regulates but does not support or conduct research
- FDA regulations for informed consent are codified in 21 CFR Part 50; and for institutional review boards in 21 CFR Part 56
- FDA regulations apply to clinical investigators and regulate products, drugs, devices, and food and color additives

FDA Regulations

- Jurisdiction
  - Drugs, biologics, devices, color additives, food additives
- FDA vs DHHS regulations
- Drugs vs Devices
- Sponsor vs Investigator responsibilities
- Reporting requirements
- Use of a test article in unplanned emergency research
- IRB Review of Clinical Investigator's Brochure

FDA Regulations

- **Informed Consent -- 21 CFR 50**
    - Eight Required Elements
    - Written Documentation
    - Language Understandable to Subjects
    - No Coercion or Undue Influence
    - No Waiver of Subjects Rights

FDA Regulations

- **IRB Review -- 21 CFR 56**
  - Initial Review
  - Prospective Review of All Changes
  - Reporting/Review of Unanticipated Problems
  - Reporting/Review of Adverse Events
  - Continuing Review at Least Annually

FDA Regulations
Emergency Use of a Test Article

- **Without Informed Consent** -- 21 CFR 50.23(a)
  - Life Threatening Situation Necessitating the Use
  - Inability to Communicate with Subject for Legal Consent
  - Insufficient Time to Obtain Consent from Legally Authorized Representative (LAR)
  - No Alternative Therapy Available
  - Certification in Writing from Investigator and an other Nonparticipating Physician of the Above
  - Report to IRB Within 5 Working Days

FDA Regulations: Emergency Use of a Test Article

- **IRB Review** -- 21 CFR 56.104 (c)
  - Life Threatening Situation Necessitating the Use
  - Report to IRB Within 5 Working Days
  - Subsequent Use Requires IRB Review

FDA Regulations: 21 CFR 312
Investigational New Drug Application (IND)

- **Adverse Event Reporting**
  - **Investigator** must report **promptly** (immediately if alarming) to the **Sponsor any adverse effect** that may reasonably be regarded as caused by the drug (Sec 312.64)

FDA Regulations 21 CFR 312 Investigational New Drug Applications

- **Sponsor** must notify **FDA** of any adverse experience associated with the drug that is both serious and unexpected
  - Serious Adverse Drug Experience = death, life-threatening, hospitalization, persistent/significant disability/incapacity, congenital anomaly / birth defect (Sec 312.32)
  - Unexpected Drug Experience = any adverse drug experience, the specificity or severity of which is no consistent with the current investigator brochure or IND application (Sec 312.32)

FDA Regulations: 21 CFR 812 Investigational Device Exemption (IDE)

- **Significant vs Non-Significant Risk Devices** (Sec 812.2)
  - **Significant Risk Device =** Investigational device that presents a potential for serious risk to the health, safety, or welfare of subjects, including implants
  - **Non-Significant Risk Device =** Investigational devices that does NOT present the potential for serious risk to the health, safety, or welfare of subjects
  - Once IRB-approves the research as not involving a Significant Risk Device, the research is considered to have an approved IDE, unless the FDA has notified the sponsor otherwise.

FDA Regulations: 21 CFR 812 Investigational Device Exemption (IDE)

- **Adverse Event Reporting**
  - **Investigator** must report any unanticipated adverse device effect to **Sponsor and the IRB** as soon as possible and within 10 working days (Sec 812.150)
  - **Sponsor** must report any unanticipated adverse device effect **to FDA, all reviewing IRBs, and investigators** (Sec 812.150)
  - **Unanticipated Adverse Device Effect =** any serious adverse effect on health or safety, or any life-threatening problem or death, caused by or associated with a device if not previously identified in nature, severity, or degree of incidence in the investigational plan or application (Sec 812.3)

Central Regulatory Protections

- Federal Policy (Common Rule)
- HHS Regulations (45 CFR Part 46)
- FDA Regulations (21 CFR Parts 50 & 56)
  - Informed Consent
  - Review by an Institutional Review Board (IRB)

Other Federal Agencies

- Some federal agencies have codified the Common Rule
- Some federal agencies have additional protections (VA requires compensation for research - related injuries)
- Some federal agencies have no regulatory requirement for informed consent and institutional review board review

Institutional Responsibility for Human Subjects Research

- Authorized institutional official
- IRB chair
- IRB members
- IRB administrators
- Investigators
- Study Coordinators
- Data Safety Monitoring Boards

IRB

- Mission is to protect the rights and welfare of individuals participating in research involving human subjects
- To approve, disapprove, modify, suspend protocols as necessary to comply with regulations and policies concerning the protection of human subjects in research
- The determination of the IRB must be final within the institution: officials of the institution may not approve the research if it has not been approved by an IRB. 45 CFR 46.112

Composition of the IRB

- Number of Members: minimum of 5 members
- Diverse in gender and racial background
- Sufficiently qualified in experience and expertise
- One scientific member
- Community representative
- Non-scientific member
- Expertise in vulnerable populations for regular review of such research

IRB Review Process

- Who determines exemptions
- Expedited review
- Full review
- Continuing Review
- Review of unanticipated risks to subjects and adverse events

Full Board Review

- The entire IRB reviews the materials.
- Continuing review must be conducted by the full board unless an there is a category that permits expedited review.

Expedited Review 45 CFR 46.110

- Conducted by chair or designee on IRB.
- Only minimal risk and fits into a category on Nov. 1998 list.
- All provisions apply.
- Can only approve research.
- Must be reported to full IRB.
- 45 CFR 46.110 (b)(2) allows for expedited review of minor changes in previously approved research if no more than minimal risk.

Continuing Review 45 CFR 46.109(e)

- Required to occur within one year (no grace period)
- IRB must review all relevant materials
- Initial review=research had not yet begun; Continuing review is opportunity to see what has happened once the research started.
- More than status reports should be reviewed

IRB Review includes...

- risk/benefit analysis
- informed consent
- ethical basis of research
- fair and equitable selection of subjects
- privacy and confidentiality
- monitoring
- participant compensation

IRB review includes...

- recruitment procedures
- new information
- analysis of unanticipated risks

IRB Meetings and Record Keeping

- All members receive complete set of materials
- Adequate time to review materials
- Minutes of meetings must be comprehensive
- Attendance and votes should be recorded
- OHRP recent approval of teleconferencing if each participating member (i) has received all pertinent material prior to the meeting; and (ii) can actively and equally participate in the discussion of all protocols

IRB Member Resources

- IRBForum (McWirb) Discussion Forum
- Public Responsibility in Medicine and Research
- Applied Research Ethics National Association
- Office for Human Research Protections
- Food and Drug Administration

Issues in Research Involving Human Subjects

Definition of Human Subject

- Human subject means a living individual about whom an investigator…conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

Six Exemptions

- Research conducted in established or commonly accepted educational settings…
- Research involving the use of educational tests, **survey procedures, etc….**
- Public Official/Federal Statute
- Existing data, documents…
- Research and demonstration projects…
- Taste and food quality evaluation...

Informed Consent

- Legally effective informed consent
- No coercion or undue influence (recruitment)
- Language understandable to the subject
- No exculpatory language
- Eight required elements
- Six additional elements

Eight Required Elements

- Statement that study is research and information on purposes/duration/procedures/experimental procedures
- Reasonably foreseeable risks or discomforts
- Benefits which may be reasonably expected
- Alternative procedures
- How confidentiality will be maintained
- For more than minimal risk, information on compensation for injuries

Eight Required Elements (cont.)

- Contact names
- Statement that participation is voluntary and can withdraw at any time (conflicts with research like xenotransplantation which requires lifelong follow-up)

Six Additional Elements

- Statement that there may be risks which are unforeseeable
- Under what circumstances investigator could terminate subject's participation
- Additional costs to subject
- Consequences of subjects withdrawal from research
- Statement that will be told of new findings
- Approximate number of subjects in study

Informed Consent Generally

- There is no such thing as passive consent
- There is no such thing as secondary subjects

Risks to Subjects

- A risk is unanticipated if it is not in the consent form.
- Questions raised as a result of an unanticipated risk:
- Does the informed consent form need to be amended?
- Do previously enrolled subjects need to be reconsented?
- Does any report need to be made to any government office?

Waiver of Informed Consent

- Minimal risk research
- Waiver or alteration will not adversely affect the rights and welfare of the subjects
- Research could not practicably be carried out without the waiver or alteration
- Subjects will be provided with additional pertinent information

Documentation of Informed Consent

- Written consent form
- Signed by subject or subject's LAR
- Copy SHALL be given to subject
- Opportunity to read before signing
- Short form written consent document requires oral presentation and witness to oral presentation (requires signatures from witness and person actually obtaining consent)

Research involving Pregnant Women and Fetuses

- Subpart B
- Revised Subpart B – 12/13/01
- Activities directed toward pregnant women as subjects
- Activities directed toward fetuses in utero
- Activities directed toward fetuses ex utero

Research involving Prisoners

- Subpart C
- Prisoner representative on OHRP approved roster
- Additional duties under 305
- Finding of permissible category under 306
- Certification to OHRP
- Concurrence from OHRP

Research involving Children

- Subpart D
- Not greater than minimal risk research
- Greater than minimal risk but presenting the prospect of direct benefit
- Greater than minimal risk and no prospect of direct benefit
- Research not otherwise approvable
- Assent and consent

OHRP Compliance Investigations

- 74 findings
- Failure to make findings and determinations required by the regulations
- Failure to conduct continuing review
- Failure of institution to adequately support IRB
- Conflicts of interest
- Inadequate consent forms and process

Consequences of Non-Compliance

- Restrictions on Assurance
- Suspension of Assurance
- Negative Publicity
- Warning Letters
- Loss of public confidence in research

Other Issues

- Conflict of Interest
- Accreditation Efforts

Conclusion