
Human Subject
Protections:
Compliance Issues

The Protection of Human Subjects in Research: Compliance Issues

Pharmaceutical and Regulatory Congress and Best Practices Forum

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Tom Puglisi, PhD

Government Shutdowns
The Compliance Officer's Nightmare !!

Massachusetts Eye and Ear

UCLA

VA Health Sys Greater Los Angeles

Rush Presbyterian St Luke's Med Ctr

University of Illinois Chicago

Duke University Med Ctr

Univ Texas Medical Branch Galveston

University of Oklahoma Tulsa

Johns Hopkins University

Definition of Research

"Research" means

- A systematic investigation
- Designed to develop or contribute to generalizable knowledge
  - Research includes research development, testing, evaluation, pilot studies

Definition of Human Subject

Human subject means

- A living individual about whom an investigator…conducting research obtains
  - Data through intervention or interaction with the individual,

    or
  - Identifiable private information

Definition of Human Subject

"Private Information" means

- Information about behavior where an individual can reasonably expect that no observation or recording is taking place

  or

- Information that an individual can reasonably expect will not be made public (e.g., a medical record)

Federal Oversight of Human Subject Research

- HHS Regulations
  - Revised 1981, 1991
- Federal Policy for the Protection of Human Subjects (Common Rule)
  - Adopted 1991
- FDA Regulations
  - Revised 1981

DHHS Regulations: 45 CFR Part 46

- Subpart A = Core Protections
  - IRB Review
  - Informed Consent
- Subpart B = Additional Protections for
  - Pregnant Women, Fetuses, and Neonates
- Subpart C = Additional Protections for
  - Prisoners
- Subpart D = Additional Protections for
  - Children

Enforcement of DHHS Regulations: Office for Human Research Protections

- Office for Human Research Protections (OHRP) within Office of Public Health and Science (OPHS) within Office of Secretary (OS) of HHS
  - Education
  - Compliance Oversight
  - Administration of Assurances

http://ohrp.osophs.dhhs.gov/

Federal Policy (Common Rule) for the Protection of Human Subjects

- 17 Federal Agencies Adopted **HHS Subpart A**
- Some Agencies Required Additional Protections
  - VA => Compensation for Research - Related Injuries
- Some Agencies Never Adopted the Federal Policy
  - Department of Labor => Miners and Coal Dust
  - Appalachian Regional Commission => Telemedicine
  - Department of Transportation => Sleepy Truck Drivers
- Only Voluntary Protections for Research Not Covered Under HHS Regs, Common Rule, or FDA Regs

Enforcement of Federal Policy

- 17 Federal Agencies Have Authority to Interpret the Policy
- **Human Subjects Research Subcommittee**
  Committee on Science
  National Science and Technology Council

http://ohrp.osophs.dhhs.gov/references/humansubcomrost.htm

Federal Policy (Common Rule): The Assurance Process

- Every Institution "Engaged" in Human Subject Research Supported by a Common Rule Agency Must Provide a Written "Assurance" to Comply with the Federal Policy
- Directly to the Supporting Federal Agency

or

- To the HHS Office of Human Research Protections (OHRP)

Federal Policy (Common Rule): The Assurance Process

- Common Rule Agency Assurances
  - Single Project Assurance (SPA)
  - Multiple Project Assurance (MPA)
- OHRP Assurances
  - Applicable Only to DHHS Research
    => SPA, CPA, NIA, AII
  - Applicable to Common Rule Research
    => MPA, CA, IIA
    => Federalwide Assurance (FWA)

Federal Policy (Common Rule): OHRP Federalwide Assurance (FWA)

- Registration of IRBs (Regardless of Assurance Status)
- 3-Page Assurance Document Covers All Federal Research
  - Reference to Terms of Assurance on OHRP Website
  - Institution Name
  - Institutional Components
  - Reference to Ethical Principles
  - Designation of IRBs
  - Applicability (Optional Extension of HHS Regs or Common Rule to All Institutional Research)
  - Signatures of Responsible Officials
  - Update as Changes Occur or Every 3 Years

DHHS Multiple Project Assurance (MPA) or Federalwide Assurance (FWA)

For Federally-Supported Research

- Common Rule Protections of HHS Subpart A
- IRB Review & Informed Consent

For HHS-Supported Research

- Protections of HHS Subparts A,B,C,D

MPA-FWA Institutions

- Voluntary application of Common Rule or all HHS Subparts to all research, regardless of funding source

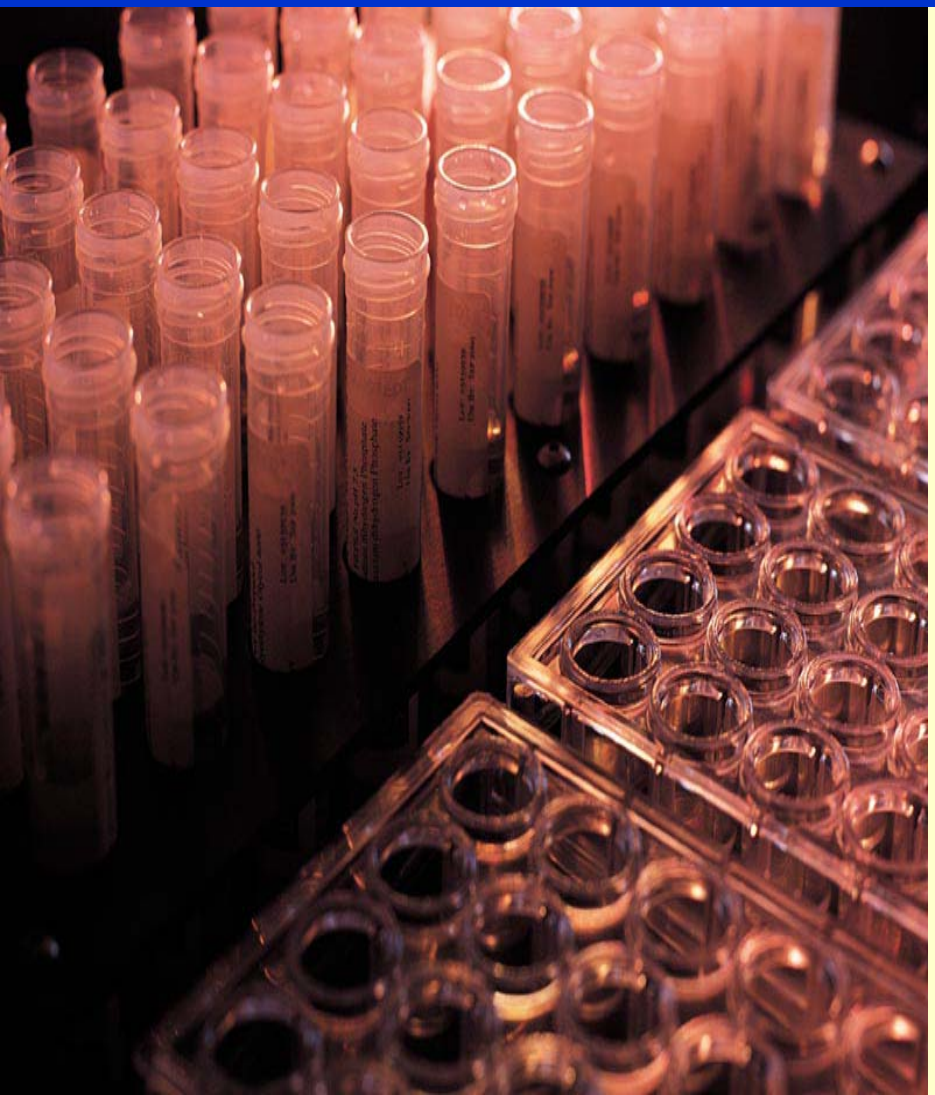
Institutional Responsibility for Protecting Human Subjects

- Institutional Commitment & Infrastructure
- Authorized Institutional Official
- IRB Chair, IRB Members, IRB Staff
- Other Institutional Committees
- Research Investigators and Co-Investigators
- Study Coordinators and Research Staff
- Everyone Else Involved in the Research Enterprise

Roles and Responsibilities: Authorized Institutional Official

- Legal Signatory for Institution (e.g. Assurance)
- Overall Organizational Responsibility
- Ensure Adequate Placement of IRB within Institutional Structure
- Ensure Adequate resources for IRB (staff, computers, office space, etc.)
- Inspire and Enforce Institutional Culture of Respect and Compliance
- eg: Oversight and Monitoring of Research

FDA Regulations



- **Informed Consent - 21 CFR 50**
- **IRB Review - 21 CFR 56**
- **Investigational Drugs - 21 CFR 31**
- **Marketing Approval - 21 CFR 314**
- **Biologics - 21 CFR 600**
- **Biologics Licensing – 21 CFR 601**
- **Investigational Devices - 21 CFR 812**
- **Pre-Market Approval – 21 CFR 814**
- **Financial Disclosure – 21 CFR 54**
- **Electronic Records – 21 CFR 11**

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

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

Drugs and Biologics

- Investigational New Drug Application (IND)
- 21 CFR Part 312

Devices

- Investigational Device Exemption (IDE)
- 21 CFR Part 812

FDA Regulations: Responsibilities of Investigators

- Ensuring Conduct of the Research per the Investigator Agreement, Investigational Plan, and All Applicable Regulations
- Protecting the Rights, Safety, and Welfare of the Research Subjects
- Controlling access to and use of the test article (drug/biologic/device)
- Monitoring and Reporting Adverse Events
- Maintaining and Retaining Accurate Records

FDA Regulations: Responsibilities of Sponsors

- Maintaining the IND
- Obtaining Qualified Investigators and Monitors
- Providing Necessary Information / Training for Investigators
- Monitoring the Investigation
- Reporting Significant Adverse Events to FDA and to Investigators
- Maintaining and Retaining Accurate Records

FDA Reporting Requirements: 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 (21 CFR 312.64)
- **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 (21 CFR 312.32)
  - Unexpected Drug Experience = any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure or IND application (21 CFR 312.32)

FDA Reporting Requirements: 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)

Requirements for Reporting to the IRB

- Required by HHS Human Subject Regs [46.103(b)(5)] and FDA IRB Regs [21 CFR 56.108(b), 312.66]
  - Unanticipated problems involving risks to subjects or others
  - Serious or continuing noncompliance with Regs or IRB
- Adverse Events (Required by FDA for devices only)
  - Local IRB Policy Determines Requirements
  - (i) Any serious adverse events experienced by subjects
  - (ii) Any adverse events reported to the study sponsor

FDA Regulation Exceptions and Exemptions: 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
- **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

Enforcement of FDA Regulations

- Office of Good Clinical Practice
  - Within Office of Science Coordination & Communication
  - Within Office of Commissioner

    http://www.fda.gov/oc/gcp
- Bioresearch Monitoring Program
  - Within Office of Regulatory Affairs
- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiologic Health (CDRH)

Accreditation of Institutional Human Research Protection Programs

- **Mandatory Accreditation:** Department of Veterans Affairs Medical Centers
  - National Committee for Quality Assurance (NCQA)
- **Voluntary Accreditation**
  - Association for the Accreditation of Human Research Protection Programs (AAHRPP)

Accreditation of Institutional Human Research Protection Programs

National Committee for Quality Assurance (NCQA)

- Six Domains => 130 Elements => 100 Point Scoring System
  - Institutional Requirements
  - IRB Structure and Function
  - Consideration of Risks and Benefits
  - Recruitment and Subject Selection
  - Privacy and Confidentiality
  - Informed Consent

http://www.ncqa.org

Accreditation of Institutional Human Research Protection Programs

Associations for the Accreditation of Human Research Protection Programs (AAHRPP)

- Five Domains => 21 Standards => 60 Elements
  - Organization
  - Research Review Unit
  - Investigator
  - Sponsor
  - Participant
- Institutional Self Assessment
- On-Site Evaluation
- Determination by Council on Accreditation

http://www.aahrpp.org

Top Ten Compliance Concerns

Top Ten Concerns:
1. Inadequate Resources

- Ultimate Source of Almost All Recent Shutdowns
- 45 CFR 46.103(b)(2) requires “meeting space and sufficient staff to support the IRB’s review and record keeping duties.”
- Reflects Institutional Commitment to Human Subject Protection Responsibilities

Top Ten Concerns:
2. Inadequate Training

- Initial and Continuing Training of:
  - IRB Chair
  - IRB Members
  - IRB Staff
  - Research Investigators
  - Research Staff
- Required vs Optional
- Resources
  - Books (Dunn & Chadwick, Amdur & Bankert)
  - Web-based Modules (OHRP, NIH, NCI, Commercial Products)
  - Workshops (OHRP/FDA, Commercial Products)
  - Conferences (PRIM&R / ARENA, Medical Research Summit

Top Ten Concerns:
3. Inadequate Initial Review

IRB Approval Includes Findings That . . .

1. Risks are minimized thru sound research design
2. Risks are reasonable relative to anticipated benefits
3. Selection of subjects is equitable
4. Informed Consent will be obtained
5. Informed Consent will be documented
6. Data Safety Monitoring is adequate
7. Privacy and Confidentiality provisions are adequate
8. Appropriate safeguards are included for vulnerable subjects

Top Ten Concerns:
4. Inappropriate "Conditional Approval"

- Conditions for Approval Specified by IRB and Verified by IRB Chair or Designated IRB Member
- Required Conditions Must Be:
  - Stated in Specific Detail
  - Amenable to Objective Verification
- Required Conditions May Not Involve:
  - Non-Directive Requests for Clarification
  - Substantive Revision or Re-Write of Protocol or Informed Consent Document

Top Ten Concerns:
5. Inadequate Continuing Review

- **All IRB members should at least receive and review**
  - the current informed consent document
  - protocol summary
  - status report on the progress of the research
  - the number of subjects enrolled
  - description of any adverse events or unanticipated problems
  - any withdrawal of subjects from the research
  - complaints about the research
  - a summary of any recent literature
  - findings obtained thus far
  - amendments or modifications since the last review
  - reports on multi-center trials
  - any other relevant information

Top Ten Concerns:
6. Informed Consent Deficiencies

Informed Consent Must:

- Be Legally Effective
  - Federal Regulations
  - Applicable State Law (who is legally authorized representative)
- Be In Language Understandable to the Subject
- Be Free of Coercion or Undue Influence
- Be Free of Exculpatory Language (broadly defined)
- Include Eight required elements
- Include Six additional elements

Top Ten Concerns:
6. Informed Consent Deficiencies

Required Elements

1. Statement that study involves research and information on purposes/duration/ procedures/experimental procedures
2. Reasonably foreseeable risks or discomforts
3. Benefits which may be reasonably expected
4. Alternative procedures
5. How confidentiality will be maintained
6. For more than minimal risk, information on compensation for injuries
7. Contact names -- at least one not associated with the research
8. Participation is voluntary and Subject can withdraw at any time without penalty or loss of benefits to which the subject is otherwise entitled

Top Ten Concerns:
7. Inadequate Documentation

- Incomplete Files
- Inadequate Meeting Minutes
  - Controverted Issues
  - Reasons for Requested Changes/Disapprovals
  - Separate Vote on Each Action
  - Quorum and Recusals
- Inadequate Documentation of Required Determinations
  - Findings/Justification for Waiver of Informed Consent
  - Findings/Justification for Waiver of Documentation of Consent
  - Categories/Justification for Research Involving Children
  - Categories/Justification for Research Involving Prisoners
  - Categories/Justification for Research Involving Pregnant Women, Fetuses, and Neonates

Top Ten Concerns:
8. Inappropriate Expedited Review or Exemptions

- Expedited Review
  - Minimal Risk and Satisfying 1 of 9 Categories
  - Minor Changes in Previously Approved Research within the Current Approval Period
- Exemptions
  - Satisfies 1 of 6 Categories
  - Verified by Official Other Than Investigator

Top Ten Concerns:
9. Late Continuing Review

- Approval Period May Not Exceed One Year
- No Grace Period
  - No Enrollment of New Subjects
  - Continued Involvement of Previously Enrolled Subjects Only for Subject's Best Interests
- Continuing Review May Occur Up to 30 Days Prior to the End of the Approval Period

Top Ten Concerns:
10. Failure to Maintain Written Policies/Procedures

- Regulations Require Procedures for:
  - Initial and Continuing Review
  - Reporting Determinations to Investigator & Institution
  - Determining Which Projects Need
    - Review More Often Than Annually
    - Verification from Sources Other than Investigator
  - Ensuring That Changes Are Not Implemented without IRB Approval
  - Ensuring Prompt Reporting of
    - Proposed Changes
    - Unanticipated Problems Involving Risks to Subjects or Others
    - Serious or Continuing Noncompliance
    - Suspension or Termination of IRB Approval
- OHRP Guidance 04/02/2002


Your worlds
Our people