Protecting Human Subjects in Research

Lifespan

Rhode Island Hospital & The Miriam Hospital

September 14 and 15, 2006

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Agenda – Part I

Conducting Research with Human Subjects

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- Types of Research Conducted at Lifespan
- Human Subjects Research Definitions
- The Informed Consent Process
- The Role of the IRB
- The Role of Principal Investigator

Types of Research That May Be Conducted at Lifespan

- Drug Trials under an FDA-Regulated Investigational New Drug Application ("IND")
- Medical Device Studies as part of an Investigational Device Exemption ("IDE")
- Medical or Surgical Intervention Research
- Behavioral and Educational Research
- Tissue Research
- Outcomes Studies
- Surveys and Interviews
- Epidemiologic Studies

Basics of Clinical Trials
Drug Trials

- FDA oversees testing of new drugs in humans
- Before initiating a clinical trial, a sponsor must submit an Investigational New Drug application ("IND"). The IND must contain certain information:
  - Information about the study drug and the proposed investigation, including proposed study protocols
  - An investigative plan, i.e., an explanation of the rationale behind the clinical research, the proposed approach, the types of clinical trials, any significant anticipated risks, etc.
  - A commitment from the sponsor to conduct clinical trials under the supervision of an IRB and to follow all applicable rules

Basics of Clinical Trials
Investigational New Drug Studies

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- Types of new drug studies under an IND
  - Phase I: First stage of testing in humans
  - Phase II: Preliminary safety and efficacy studies
  - Phase III: Expanded large-scale studies
  - Phase IV: Post-marketing studies
- After the research is completed, the sponsor must submit a New Drug Application ("NDA") to the FDA for review and approval

Basics of Clinical Trials
Medical Devices

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- Medical Device - Any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized
- FDA oversees testing and marketing of devices
- Devices are divided into three classes based on safety, effectiveness, and intended use
- Classification identifies the process that must be completed before marketing the product

Medical Device Trials - Investigational Device Exemptions

- Under an Investigational Device Exception ("IDE") manufacturers can ship and use unapproved medical devices for investigational use
- The IDE application is part of the FDA's Pre-Market Approval process for the marketing of new medical devices

Human Subjects Research Federal Regulations

- Definition of Research (Common Rule)
  - A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
    45 CFR 46.102

Human Subjects Research Federal Regulations

- Definition of Clinical Investigation (FDA regulations)
  - Any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the FDA, or is not subject to requirements for prior submission to the FDA, but the results of which are intended to be submitted later to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

    21 CFR 50.3 and 56.102

Human Subjects Research Federal Regulations

- Definition of Human Subject (Common Rule)
  - A living individual about whom an investigator (whether professional or student) conducting research obtains:

    (1) data through intervention or interaction with the individual, or

    (2) identifiable private information.

45 CFR 46.102

Human Subjects Research Federal Regulations

- Definition of Human Subject (FDA Regulations)
  - An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

    21 CFR 50.3 and 56.102

Informed Consent

- "Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied." (The Belmont Report)
- "No investigator may involve a human being as a subject in research … unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative." (Common Rule)

Informed Consent

- A subject's informed consent must be "legally effective informed consent"
  - Consent sought under circumstances that:
    - Provide the prospective subject or subject's representative sufficient opportunity to consider participation, and
    - Minimize the possibility of coercion or undue influence
  - Information is provided to the subject in a clear and understandable language

45 CFR 46.116 and 21 CFR 50.20 & 50.25

The Informed Consent Process

- Informed consent is more than a single document, it a process:
  - Reading and/or reviewing the informed consent document with the subject or subject's legally authorized rep.
  - Question/answer sessions
  - Giving the subject time to think about participation
  - May involve subject taking document home to discuss with family & friends
  - Investigator's measurement of subject's understanding of the study and risks/benefits

The Role of the IRB

- Review proposed and ongoing research studies to ensure compliance with federal regulations and institutional policy regarding the protection of human subjects
- The only review body whose primary responsibility is to apply ethical norms to protect human subjects
  - Primary concern of FDA is scientific validity of studies
  - Primary concern of NIH is advancing medical knowledge

IRB Jurisdiction

- Research involving human subjects is subject to IRB review and approval if:
  - It is conducted, supported or otherwise subject to regulation by any federal department or agency that has adopted the Common Rule (45 CFR Part 46)
  - It involves a test article regulated by the FDA (device, drug, or biologic)
  - An institution has extended the Common Rule to all research conducted by the institution, as Lifespan has
  - The state has mandated IRB review for certain categories of research that otherwise might not be subject to IRB review (e.g., stem cell research)

IRB Review

- Examples of IRB Submissions
  - Application for initial review
  - Application for continuing review
  - Amendments or modifications
  - Reports (e.g., adverse events)
  - Application for emergency review
- Possible IRB Responses to New Protocols
  - Approval
  - Conditional Approval
  - Deferral
  - Disapproval

IRB Authority

- Authority of IRBs
  - Require modifications in protocol as condition of approval
  - Require modifications in language of consent form as condition of approval
  - Require interim reports from PI on subject safety as condition for initiation of further procedures
  - Appoint person to monitor the consent process
  - Suspend ongoing research
    - As to enrollment of new subjects
    - As to further interventions performed on subjects already enrolled
  - Terminate ongoing research

Criteria for IRB Approval

- To approve a research study, an IRB must determine that all the following requirements are satisfied:
  - Risks to subjects are minimized
  - Risks to subjects are reasonable in relation to anticipated benefits to subjects, if any, and the importance of knowledge that may reasonably result from the study
  - Selection of subjects is equitable
  - Informed consent will be sought from each prospective subject or his/her legally authorized representative
  - Informed consent will be appropriately documented

Roles of a Principal Investigator in a Clinical Trial

- Evaluate potential subjects for inclusion in clinical trials
- Obtain and document informed consent for each subject
- Ensure that research subjects understand the difference in goals and expected benefits between *research* and *treatment*
- Follow ethical guidelines that govern research with human subjects at Lifespan

Roles of a Principal Investigator in a Clinical Trial

- Report to IRB as required by federal regulations and institutional policy
  - Continuing review applications
  - Any modifications to protocols
  - Adverse Events
- *Primary responsibility* for the administrative management, scientific data integrity, conduct of the trial
- *Ultimate responsibility* for the safety of each research subject

Questions?

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Agenda – Part II
Adverse Event Reporting

- Why Does Adverse Event Reporting Matter?
- What is an Adverse Event?
- What Needs to be Reported?
- Who Submits and Receives Reports?
- Government Enforcement: Recent Cases
- Lifespan Adverse Event Reporting Policies
- Examples

Why Does Adverse Event Reporting Matter?

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Why Does Adverse Event Reporting Matter?

- Allows for on-going assessment of risk and ensures the protection of subject safety and subject choice
- Collects data from multi-site clinical trials to determine significance of observed events
- In an FDA-regulated drug or device trial, helps to determine:
  - the risks and benefits of a new drug or device
  - the drug or device's safety in the target population
  - accurate and appropriate information for package inserts if the drug or device is approved and marketed

Why Does Adverse Event Reporting Matter?

"[In clinical research] [d]octors must give fair warnings of risks that are known or that reasonably should have been known by them."

Goodman v. U.S. (Ninth Circuit, 2002)

What is an Adverse Event?

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What is an Adverse Event?

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- Adverse event reporting is governed by many different regulations and sources
- Regulations do not clearly define what specific types of events would be reportable
- Much debate over what the regulations actually require, and how best to comply

What is an Adverse Event?

- Definition depends (in part) on:
  - Applicable regulations
    - HHS Regulations ("Common Rule")
    - FDA Regulations
  - Definition of adverse event in IRB Policies and Procedures, and in specific protocol approvals
  - Sponsor's definition of adverse event in specific protocols

What is an Adverse Event?

- Factors considered in defining adverse events (not all necessarily required to trigger various reporting requirements):
  - Expectation (was the event identified in IRB submission?)
  - Severity (even if expected)
  - Frequency (even if expected)
  - Relation (to participation in study, and to drug)

What is an Adverse Event?

- Frequency of adverse event is not expressly discussed in the regulatory definitions
- However, if an expected non-serious event that is related to participation in the research occurs for longer duration than expected, or occurs more frequently than expected, should be reported to IRB (new trend)

Which Rules Apply?

- Common Rule applies to all research under Lifespan's Federalwide Assurance
- FDA Regulations apply to all research involving a device regulated by the FDA *in addition to* Common Rule requirements
- Lifespan Reporting Requirements apply to all research at Lifespan
- Sponsor Rules apply as explained in specific protocols

The Common Rule

- Common Rule addresses "unanticipated problems involving risks to subjects or others" 45 CFR 46.103(b)(5)
  - Little guidance regarding scope of this category
  - Not necessarily co-extensive with an adverse event
  - No minimum risk threshold (but usually interpreted to be something serious and/or significant)
  - Actual harm not required -- risk of harm reportable
  - Example: theft of a research computer with confidential patient information stored on it, even if it was returned the next day with no evidence that the data had been accessed

The Common Rule: Requirements for Research

- Institutions must have written procedures for ensuring prompt reporting to IRB, institutional officials, agencies of events referenced in 45 CFR 46.103(b)(5)
- For research covered by FWA, institutions must promptly report events referenced in 45 CFR 46.103(b)(5) to OHRP
- IRB must determine that risks to subjects are minimized and reasonable in relation to benefits to subjects, importance of knowledge gained

The Common Rule: Requirements for Research (cont.)

- IRB must ensure, when appropriate, that "the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects" 45 CFR 46.111(a)(6)
- IRB must conduct continuing review of research at least annually
- IRB must have authority to investigate possible non-compliance or suspend or terminate research

FDA Regulations

- FDA Regulations address several types of adverse events for drugs:
  - Unanticipated problems involving risks to subjects or others in drug trials (applies to reports from investigator to IRB)
  - Adverse effects that may reasonably be regarded as caused by or probably caused by the drug (applies to reports from investigator to sponsor)
- A similar reporting scheme exists for medical devices

Regulatory Reporting Obligations

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Regulatory Reporting Obligations

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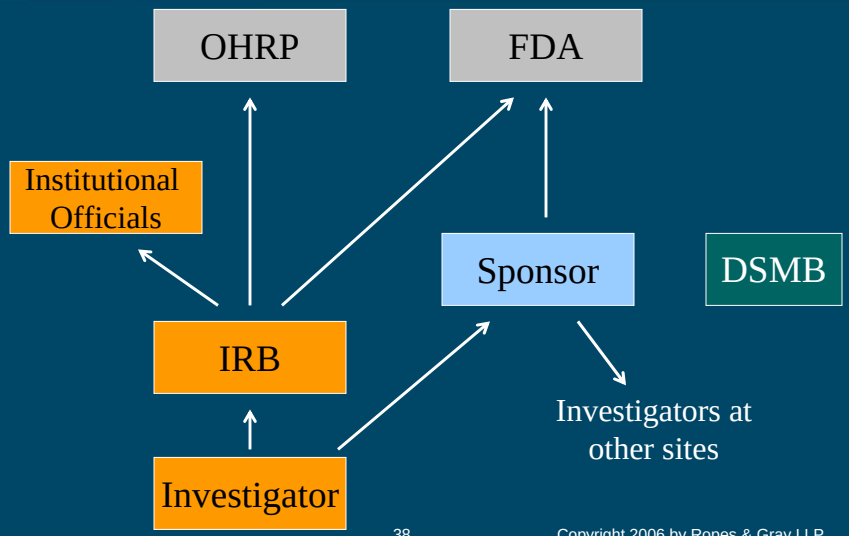

Regulatory Reporting Obligations: Investigator to IRB

- Unanticipated problems involving risks to subjects or others (promptly) (Common Rule)
- Summary of adverse events and any unanticipated problems involving risks to subjects or others (at continuing review)
- Any information about risks associated with the research (at continuing review)

Regulatory Reporting Obligations: Investigator to Sponsor

- Adverse events that may be reasonably regarded as caused by or probably caused by the drug (promptly, unless the event is alarming, in which case immediately) (FDA)
  - Note that there is no severity or expectation threshold to trigger investigator's responsibility to report adverse events related to the drug to sponsor
    - Sponsor, however, only required to report serious, unexpected and related adverse experiences to FDA

Regulatory Reporting Obligations: Sponsor to FDA – Drug Trials

- Adverse experiences associated with the use of the drug both serious and unexpected (within 15 calendar days after receipt of information)
- Finding from tests of drug in laboratory animals suggesting a significant risk to human subjects (no later than 15 calendar days after receipt of information)

Regulatory Reporting Obligations: Sponsor to FDA – Drug Trials

- Unexpected fatal or life-threatening experience associated with use of the drug (by telephone or fax no later than 7 calendar days after sponsor's receipt of the information)
- Post-drug approval: must still report any adverse drug experience both serious and unexpected whether domestic or foreign (within 15 working days of receipt of information)

Regulatory Reporting Obligations: Sponsor to Other Investigators

- Sponsor required to report much of the same information to all other investigators:
  - Adverse events that are serious/unexpected/associated with drug
  - Tests on animals indicating significant risk to humans
  - Any new observations discovered by or reported to the sponsor about the drug or device (other than the other safety information) as investigation proceeds

Regulatory Reporting Obligations (cont.)

- Remember!!
  - If you have initiated the research and are a "sponsor-investigator" under FDA Regulations, you must meet the AE reporting requirements for both sponsors and investigators

Regulatory Reporting Obligations: IRB to Institutional Officers/OHRP/FDA

- Both Common Rule and FDA Regulations require IRB policies ensuring prompt reporting to IRB, institutional officials, Office for Human Research Protections (OHRP) and/or FDA of any unanticipated problems involving risks to subjects or others
- Remember: Investigator has responsibility under FDA Regulations to report unanticipated problems involving risks to IRB

Trends in Adverse Event Reporting

- OHRP Draft Guidance on Reporting Adverse Events and Unanticipated Risks
  - Guidance issued October 11, 2005
  - Defines adverse events and unanticipated problems
  - States appropriate timeframes for reporting
  - Suggests considerations and written procedures for IRBs
  - Used to revise adverse event reporting policy at Lifespan

Government Enforcement: Recent Cases

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Government Enforcement: Focus on Adverse Event Reporting

- OHRP and FDA have focused heavily on deficient adverse event reporting
- Evidence of an investigator's failure to minimize risks to subjects
- Failure to follow protocol's definition of adverse events leads to warnings and sanctions
- Directly related to investigator's responsibility to submit relevant material to IRB for continuing review

Government Enforcement: Recent Cases

- Several recent cases are particularly illustrative:
  - University of Pennsylvania (FDA Letter 2000)
  - Johns Hopkins (OHRP Letter 2001, FDA Letter 2003)
  - Lutheran General (FDA Letter 2004)

University of Pennsylvania
FDA Warning Letter, November 30, 2000

- Death of 18 year old Jesse Gelsinger (enrolled in gene therapy study)
- Investigator failed to report certain adverse events to IRB as defined and required by protocol
- Adverse event reporting that occurred had inaccurate and misleading statements
- Resulted in significant malpractice action (substantial settlement reached)

Johns Hopkins University
OHRP Letter, July 19, 2001

- Hexamethonium study resulting in pulmonary complications and death of healthy volunteer
- Principal investigators failed to report prior adverse event in this study involving another healthy subject
- Investigators failed to promptly report cough, shortness of breath, and decrease in pulmonary function experienced for 8 days by first subject

Johns Hopkins University
OHRP Letter, July 19, 2001 (cont.)

- OHRP particularly concerned that investigators continued to expose additional subjects to inhaled hexamethonium before resolving symptoms of first subject and reporting event to IRB
- **This, and other deficiencies, resulted in temporary suspension of Johns Hopkins' ability to initiate new research projects and restrictions on all ongoing research**

Johns Hopkins University
FDA Warning Letter, March 31, 2003

- FDA noted multiple violations for the same study including failures to submit an IND for the study, to provide FDA with supporting data, to obtain proper informed consent, and to report adverse events to IRB
- Investigators failed to follow protocol regarding unexpected events, delivery rates and systems for hexamethonium bromide
- **On June 2, 2003, the PI was placed on a restricted list by the FDA**
  - May not serve as principal clinical investigator for more than one FDA regulated clinical study per year for three years

Lutheran General Cancer Center
FDA Warning Letter, October 4, 2004

- Subjects remained in IND study after reports of disease progression, violating protocol
- Adverse events in medical charts were not added to case report forms
- **Investigator failed to inform IRB of report from Sponsor that serious, unexpected adverse event had occurred at another study site**

Lifespan Adverse Event Reporting Policies

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IRB Policies on Adverse Event Reporting

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- IRB policies and procedures often include:
  - Specific definitions of adverse and serious adverse events
  - Required time-frame for reporting to IRB
  - Specific forms on which to report
- IRB terms of approval may also include protocol-specific reporting requirements and time-frame

IRB Policies on Adverse Event Reporting (cont.)

- IRB policy or approval terms may be *stricter* or more *specific* than regulations (shorter time-frame for reporting)
- **Remember**
  - **You must follow the IRB-imposed reporting requirements, even if stricter than regulatory requirements**

Lifespan Adverse Event Reporting Policy: Investigator's Duties

- Report Certain Events to the IRB
  - Serious, unexpected, and related to the research activity
  - Unexpected adverse events, regardless of severity, that may alter the IRB's analysis of risk versus potential benefit of the research and warrant consideration of substantive changes to the protocol and/or informed consent must also be reported to the IRB
  - Expected adverse events that are occurring at a rate greater than anticipated

Lifespan Adverse Event Reporting Policy: Recent Changes

- The revised reporting policy does not change the type of adverse events that are to be reported to the IRB
- Policy clarifies the types of events *not* reportable to the IRB:
  - Adverse events that are unrelated to the research activities
  - Adverse events for studies that are not being conducted at Lifespan

Lifespan Adverse Event Reporting Policy: Reporting Forms

- Single Adverse Event
  - For one event, local or at another site
  - Existed Previously
- Multiple Adverse Events
  - Allows grouping of events
- Fatality (*new*)
- Sponsor-required reporting (*new*)
  - For adverse events that do not meet the policy's criteria for reportable events but must be reported according to the study sponsor

Lifespan Adverse Event Reporting Policy: Next Steps

- Currently, new procedures, reporting forms, and instructions are being finalized
- Once complete, a selected group of investigators will use the revised
- After initial test and any subsequent revision, institution-wide training will begin
- At completion of training, new reporting forms and procedures will be mandatory

The Bottom Line

- Investigators Must:
  - Fully describe expected adverse reactions in protocol
  - Adhere to Lifespan reporting policies
  - Adhere to reporting requirements and approval requirements by IRB for specific protocol
  - Adhere to protocol regarding reporting to sponsor
  - Provide IRB with IND Safety Reports from sponsor and DSMB summaries as required
  - Summarize all relevant adverse events, from all sites, at time of continuing review

The Bottom Line

- IRBs Must:
  - Examine and approve plan for monitoring at time of initial consideration; require definitions of expected adverse reactions
  - Assure that investigators understand and adhere to reporting requirements
  - Adequately consider adverse events at continuing review and as reported individually
  - Demand meaningful information from PI, sponsor, and DSMB, especially in multi-site studies

Examples

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Example #1

- A subject enrolled in a phase III, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of a new investigational anti-inflammatory agent for management of osteoarthritis develops severe abdominal pain and nausea one month after randomization.
- Subsequent medical evaluation reveals gastric ulcers. The investigator breaks the blind on the subject's study group assignment and learns that the subject was assigned to receive the active investigational agent.

Example #1 (continued)

- The protocol and informed consent document for the study indicated that the there was a 10% chance of developing mild to moderate gastritis and a 2% chance of developing gastric ulcers for subjects assigned to the active investigational agent.
- The investigator concludes that the subject's gastric ulcers resulted from the research intervention and withdraws the subject from the study. A review of data on all subjects enrolled so far reveals that the incidence of gastritis and gastric ulcer are within the expected frequency.

Example #1

- Is this an “unanticipated event involving risks to subjects or others”?
- If so, to whom should it be reported?
- Is this an adverse event that should be reported to the sponsor?
- Does this investigator have any other reporting duties?

Example #2

- Subjects in a clinical trial studying post-operative treatment for hip replacement are randomized into one of two groups. The experimental group receives an interventional regimen of Physical Therapy. This regimen is not currently practiced in standard of care. Subjects in the control group receive standard of care treatment for post-operative hip replacement therapy. All subjects receive follow-up phone calls at 30 and 60 days, during which time they are administered a questionnaire and asked about any healthcare utilization in the previous 30 days.

Example #2 (cont.)

1. A subject enrolled in the experimental group falls during the physical therapy, breaking her wrist.
2. A subject enrolled in the experimental arm reports during the 30 day follow-up call that she had been admitted to a local hospital for pneumonia 10 days ago.
3. A subject in the control arm of the study reports during the 60 day follow up that he was in a car accident and was seen in the emergency room for a severely bruised hip.
4. A subject in the experimental arm complains of soreness in the surgical hip during the 30 day follow-up phone call.

Example #2

- Which of these are “unanticipated events involving risks to subjects or others”?
- Which are adverse events that should be reported to the sponsor?
- What are the investigators’ other reporting duties?
- Do the answers to these questions change if the control group had received a new drug instead of physical therapy?

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