UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM

Issues in Human Subject Research Compliance:

Improving the Performance of Investigators

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Agenda

- History
- What We Learned . . .
- The Solutions
- Selected Discussion Topics
  - Retrospective Reviews
  - Standard Operating Procedures
  - Monitoring Based on Risk

History

Events at Penn

- Gelsinger death (1999), FDA inspection and suspensions, internal and external committee recommendations
- Initial Response: conduct reviews of faculty “sponsored” trials, develop SOPs for proper conduct
- First instinct - an isolated problem

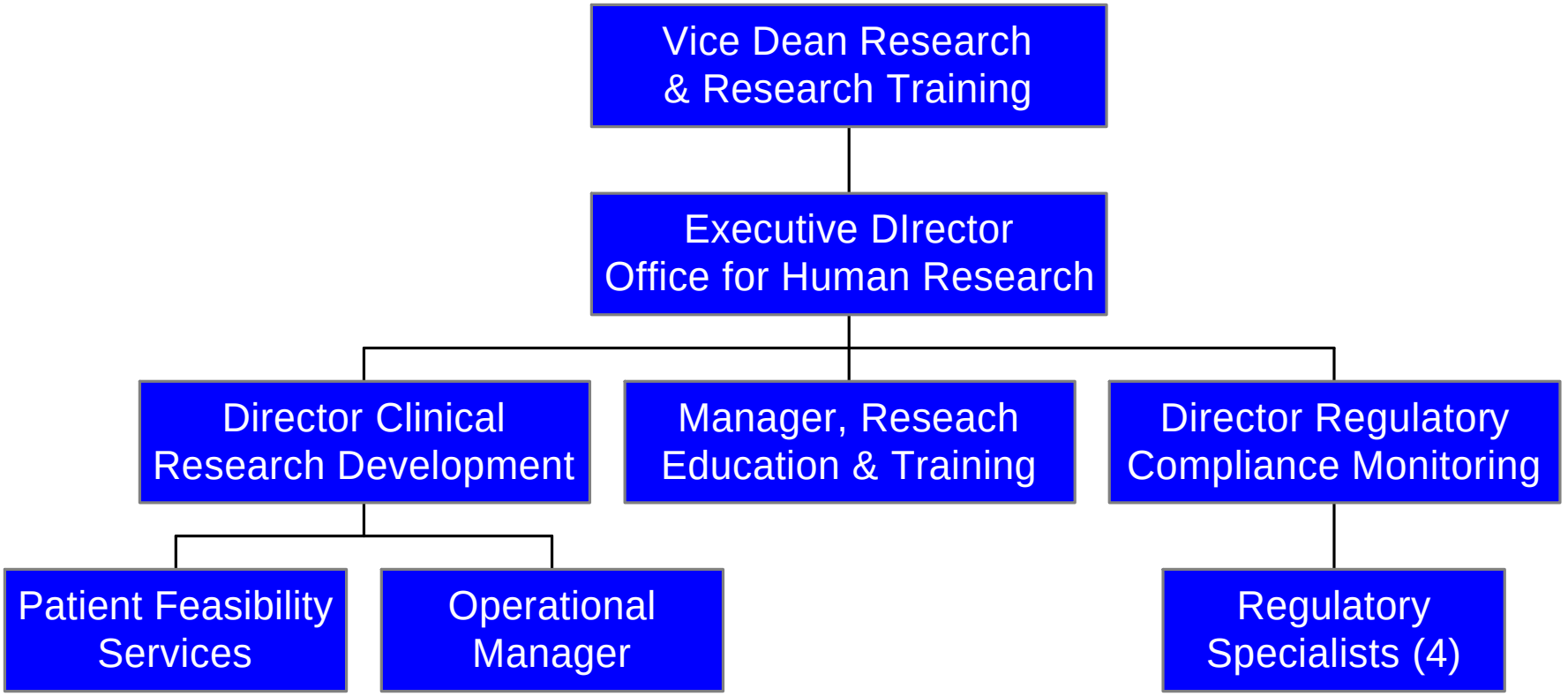
History

- **March 2000 –**Dr. Rodin's charge:
  - Refocus IHGT activities
  - Review existing faculty sponsored trials and develop SOP's
  - Review IRB procedures, develop IRB SOPs and training
  - Review Conflict of Interest Policy in clinical trial conduct
- **August 2000** - the Covalent Group and Center for Clinical Research Practice (CCRP) engaged to conduct reviews and develop SOPs respectively
- **September 2000 –** Administrative Implementation Committee formed to enact recommendations and coordinate activities among offices

History

- **January/February 2001** - SOM Human Research Retreat and "Sponsor" Registration Meeting
- **February/April 2001** - Creation of the Office of Human Research (OHR) and OHR Faculty Advisory Committee
  - To provide planning oversight of the needs, implementation and supervision of human research conduct
  - To guide University policy
  - To provide informed, dedicated service to the faculty e.g., adjudicate Covalent reviews, beta-test SOPs and develop educational programs

Office for Human Research



What We Learned . . .

- Uncertainty over what is standard care vs research
- Uncertainty over whether IND / IDE required
- Poorly written protocols
- Protocol amendments poorly documented
- Informed Consent Form inadequacies
- Study Files incomplete - absent or insufficient documentation
- Case Report Forms did not capture required information
- Study did not have a Research Coordinator
- Study was not monitored

The Solutions

- Define Expectations and Process
  - the SOPs for the IRB, the Clinical Instigator & the Sponsor-Investigator
- Establish an Educational Program
  - Patient Oriented Research Training Program (August 2000)
  - Clinical Research Retreat (Feb. 2001)
  - Sponsor-Investigator Training (Sept. 2001)
  - Research Coordinator Training (Feb. 2002)
- Assess Competencies
  - interactive & educational monitoring program
- Provide Institutional Resources to Facilitate Research,
- Compliance and Good Clinical Practice
  - Establishment of the Office for Human Research

The Solutions

Implementation of School of Medicine Office of Human Research to focus on:

- Proactive Oversight of all Research Initiatives
- Education and Training
- Administrative Re-design
- Retrospective Analysis

The Solutions

Proactive Oversight of all Research Initiatives:

- When is an IND/IDE required?
- IND/IDE protocol/ICF development and internal registration
- Define Risk Assessment standards and evaluate for ALL protocols
- Match monitoring frequency and activity with Risk Assessment
- Define internal standards/practices of DSMB
- Evaluate qualifications of monitoring entity and provide direct assistance when required

The Solutions

Education and Training:

- Dedicated mandatory training for All SOM Sponsor – Investigators on Good Clinical Practice SOP's
- Training/Evaluation of study staff
- Credentialing "Centers" within the SOM to Perform Monitoring

The Solutions

Administrative Re-design:

- Will “Own” the Sponsor-Investigator & Investigator SOP’s
- Develop templates for clinical trial conduct
- Develop budget expectations and models for clinical trials
- Conduct exempted and expedited IRB review
- Interface with contract, Tech Transfer issues

The Solutions

Retrospective Analysis:

- Prioritized assessment of ongoing human research: IND/IDE sponsors, clinical trials not associated with industry sponsor, industry sponsored clinical trials, other human research protocols
- Analysis of “closed” IND/IDE for faculty that have not previously been reviewed

Retrospective Reviews

- Covalent was engaged to conduct detailed reviews of FDA regulated research.
- The reviews would focus on Sponsor – Investigators:
  - Investigational New Drug Applications (IND's) and,
  - Investigational Device Exemptions (IDE's)
- The general concept for the retrospective monitoring activities would be to conduct an FDA-like inspection of the study records to gauge compliance with FDA regulations as described in ICH Good Clinical Practice Guidelines.

Retrospective Reviews

- The scope of this review included a review of:
  - IND / IDE Application (including protocol, Informed Consent, and FDA Forms 1571 & 1572)
  - FDA Communications & Follow-up (including protocol amendments, Annual Reports, and reporting of Adverse Events [AE's] and Serious Adverse Events [SAE's])
  - IRB Communications & Approvals
  - Study Records (including Case Report Forms, Worksheets and Screening Forms)
- We hoped that this type of review would give us sufficient information necessary to make a judgment about whether or not the Investigator had the regulatory "tools" necessary to conduct the trial in a GCP compliant manner.

Sponsor-Investigator SOP's

- SOP Preparation & Maintenance
- Document Development and Change Control
- Sponsor-Investigator Responsibility and Delegation of Responsibility
- Study Team Training
- Prohibition of Financial Conflicts
- Vendor Selection
- Contacts and Submissions for FDA
- Reporting Requirements for FDA
- NIH Requirement for OBA-Reviewed Research
- Clinical Protocol Development, Implementation and Compliance
- Clinical Protocol Amendments
- Developing Documents for Informing Investigators
- Investigator Selection and Qualifications
- Initiation Visit and Site Training
- Communications
- Investigational Product Inventory Management
- Documentation & Record Retention
- Routine Monitoring Visits
- Study Closeout Visits
- Informed Consent
- Participant Recruitment Practices
- Participant Screening and Enrollment
- Specimen Management
- Adverse Event Recognition and Reporting
- Case Report Forms
- Clinical Research Data Management
- Use of Electronic Data Systems
- Quality Assurance Audits
- FDA Inspections

Investigator SOP's

- SOP Preparation & Maintenance
- Investigator Responsibility and Delegation of Responsibility
- Study Team Training
- Prohibition of Financial Conflicts
- Assessing Protocol Feasibility
- Pre-Study Site Visit
- Initiation Visit
- Communications
- Investigational Product Inventory Management
- Documentation & Record Retention
- Routine Monitoring Visits
- Study Closeout Visits
- Informed Consent
- Participant Recruitment Practices
- Participant Screening and Enrollment
- Specimen Management
- Adverse Event Recognition and Reporting
- Clinical Research Data Management
- Use of Electronic Data Systems
- Quality Assurance Audits
- FDA Inspections

IRB SOP's

- General Administration
  - Statement of Authority and Purpose
  - Activities Requiring IRB Review
  - Policies & Procedures Maintenance
  - Training & Education
  - Management of IRB Personnel
  - Conflicts of Interest
  - Signatory Authority
- IRB Organization
  - Composition of the Board
  - Management of the Board
  - Duties of IRB Members
- Functions & Operations
  - Research Submission Requirements
  - Research Exempt from IRB Review
  - IRB Meeting Administration
  - Administrative Review and Distribution of Materials
  - Documentation and Document Management
- Review of Research
  - Expedited Review
  - Initial Review Criteria for IRB Approval
  - Continuing Review
  - Criteria for Renewal
  - Study Completion
  - Categories of Action
- Reviews Requiring Special Consideration
  - Vulnerable Populations
  - Categories of Research
- Communication & Notification
  - Investigative Staff
  - Other Entities
- Informed Consent
  - General Requirements & Documentation
  - Exemptions
  - Assent
- Responsibilities of Investigators
- Quality Assurance
  - QA / QC Program
  - Audits by Regulatory Agencies

Monitoring Based On Risk

- Develop a baseline Standard Monitoring Plans based on Patient Safety Risk
  - the higher the risk the more intensely the study is monitored
- Allow the PI to Self-assess the project's safety level
  - this will allow the PI to budget appropriately required monitoring activities
- The IRB is the final decision point of the assigned risk level
  - every study is independently assigned a risk level by the IRB.
- OHR can customize the monitoring plan based on the unique circumstances of the project

Risk Assessment

- **MINIMAL Risk**: Studies "that the probability and magnitude of harm or discomfort anticipated in the research are not greater than in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests." {CFR 45 Part 46.102(i)}. These studies, qualify for IRB expedited review. Examples of Minimal Risk studies may include but are not limited to: Survey research, venipuncture (with small amounts of blood), taste & observation studies, MRI studies, and studies which utilize non-invasive procedures which pose no more risk to a patient than would be experienced in ordinary life. These also include all studies qualifying for expedited IRB review as allowed in 45 CFR 46.

Risk Assessment

- **LOW Risk**: Studies that represent "a minor increase over minimal risk" (CFR 45 Part 46.406(a)). "The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, physiological, social or educational situations {CFR 45 Part 46.406(b)} . These studies would not qualify for expedited review. Studies, which might meet the requirements for minimal review but which include special populations (children, mentally disabled or prisoners) and/or invasive procedures fall into this category. Most Phase IV studies involving the expanded application of a marketed drug or device may fall into this category. Examples of study activities that may qualify for this level of risk assessment include studies that involve: Biopsies, catheter placement, pharmacokinetic studies, and pharmacodynamic studies, and pharmacoeconomic studies with approved compounds.

Risk Assessment

- **MODERATE Risk**: Studies that involve increased risk due to the nature of the research or the population being evaluated. "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of knowledge that may reasonably be expected to result {CFR 45 Part 46.111(a)(2)}. Examples may include: HIV/AID's and Hepatitis C studies (because of the potential impact to employability and insurance coverage), cancer studies and some studies that include a "Washout" period or placebo use in an otherwise treatable disease.

Risk Assessment

- **HIGH Risk**: Studies "involving greater than minimal risk and no prospect of direct benefit to the individual subjects but likely to yield generalized knowledge about the subjects disorder or condition" {CFR 45 Part 46.406}. Examples may include:, studies involving any investigational drug or device that utilizes a significant invasive investigational procedure, new chemical entities or class of test article having a high expectation of toxicity, gene transfer, emergency studies with waiver of informed consent, and xenotransplantation.

Risk Assessment

- Other Considerations Beyond Patient Safety
  - Is this a Penn Sponsored Study?
  - Is this a multi-site trial?
  - Did Penn manufacture the test article (ie. GMP issues)?
  - Does the investigator have a financial Conflict of Interest?
  - Is the Investigator new to Clinical Research?
  - Etc.
- OHR would develop a “menu”of procedures that could be added to the standard monitoring plans to address these issues.

QUESTIONS?