An Overview of Research Compliance: The IRB & Human Subject Protection

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Topics

• What does the IRB have to do with human subjects protection?

• How to design an effective Clinical Trial Monitoring program?

• Are you ready for an FDA/OHRP audit: What keeps IRB members and Compliance Officers up at night
Who should be responsible for ensuring the safety of Human Subjects in Research

- **Scientists**
  - Scientific Review Boards – Peer Review
  - Biostatistics
  - Medical Licensing, Hippocratic Oath

- **Institutions**
  - IRB - FWA
  - Compliance/Legal
  - Others (IBC, RDRC, IRC, etc.)

- **The Government**
  - OHRP
  - FDA
  - ORI
  - OIG, Attorney General, OCR,

Source: Dunn and Chadwick. Protecting Study Volunteers in Research. Boston: CenterWatch, Inc. 1999
History of Human Subjects Protection

WHY DO WE NEED PROTECTIONS?

- Nuremberg Code (1947 United States v Karl Brandt et al.)
  - voluntary consent
  - freedom from coercion
  - comprehension of risk/benefit ratio
  - qualified investigators
  - ability to withdraw at any time

"responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment"

Declaration of Helsinki - Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964

(Currently includes 32 principles)

Issues addressed:
- Research w/humans should be based on laboratory and animal experimentation
- Experimental protocol should be reviewed by independent committee
- Informed consent/Capacity to consent
- Subjects are minors or those with physical/mental incapacity
- Research conducted by medically/scientifically qualified individuals
- Risks/benefits
- Privacy of the subject/confidentiality of information
- Publication of research results
- Conflict of interest
- Use of placebos
### 1932 - Tuskegee Syphilis Study

- Started as a short study (6-8 months) with 400 syphilitic black males in Macon Co., Al,
- Conducted by the US PHS
- Free medical examinations
- Not told of their disease - Not treated

### 1950s-1961 - Thalidomide Late

- Physicians used ‘samples’ supplied by the manufacturer to study drug safety and efficacy
- Many patients didn't know that they were taking an experimental drug, nor had they given their consent
- Drug had severe teratogenic side effects 1974

### 1974 Congresses Passes the National Research Act

- Informed consent
- IRBs
- 1979: Ethical Principles and Guidelines for the Protection of Human Subjects in Research (Belmont Report)

### Johns Hopkins University: June 2001 -

**It's not the event that shuts down Institutions!**

- FDA Inspection followed report of death of a healthy volunteer who had inhaled hexamethonium
- FDA’s 483 to the IRB (September 2001) cites:
  - failure to obtain effective informed consents: failure to disclose that inhalation administration of the drug was experimental
- Failure of clinical investigator to submit an IND prior to conducting the investigation (3 subjects)
  - changes to IRB approved protocol without notifying the IRB (and without IRB approval)
- Warning Letter Issued **March 31, 2003** to Investigator
  - failure to report an unanticipated AE to the IRB
    - Note: time interval between incidents and Warning Letter – unusual, but not unprecedented.
## The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research

“progress is an optional goal, not an unconditional commitment, and...its tempo...compulsive as it may become, has nothing sacred about it” (Hans Jonas 1969, 245)

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<td>Equitable Burdens and Benefits</td>
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<td>Recruitment</td>
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### Government Shutdowns

- Massachusetts Eye and Ear Infirmary
- UCLA
- VA Health Sys. Greater Los Angeles
- University of Illinois Chicago
- Duke University Med Ctr.
- University of Colorado
- Univ. Texas Medical Branch Galveston
- U Penn
- University of Oklahoma Tulsa
- Johns Hopkins University

- What were factors contributing to shut down?
DHHS Regulations VS. FDA Regulations*

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<th>FDA Regulations*</th>
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<td><strong>Subpart A</strong> – Basic Protections (&quot;Common Rule&quot;)</td>
<td><strong>Informed Consent</strong> - 21 CFR 50</td>
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<td>• IRB Review</td>
<td><strong>IRB Review</strong> - 21 CFR 56</td>
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<td>• 46.111(3) Special protections</td>
<td><strong>Investigational Drugs</strong> - 21 CFR 312</td>
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<td>• Vulnerable populations*</td>
<td>• Marketing Approval - 21 CFR 314</td>
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<td>• Informed Consent</td>
<td><strong>Biologics</strong> - 21 CFR 600</td>
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<tr>
<td>• Institutional &quot;Federalwide Assurance&quot; (FWA)</td>
<td>• Biologics Licensing – 21 CFR 601</td>
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<tr>
<td><strong>Subpart B</strong> - Protections for Pregnant Women, Fetuses, and Neonates</td>
<td><strong>Investigational Devices</strong> - 21 CFR 812</td>
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<td><strong>Subpart C</strong> - Protections for Prisoners</td>
<td>• Pre-Market Approval – 21 CFR 814</td>
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<td><strong>Subpart D</strong> - Protections for Children</td>
<td><strong>Financial Disclosure</strong> – 21 CFR 54</td>
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<td><strong>Electronic Records</strong> – 21 CFR 11</td>
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Definitions: Are you Conducting Research involving Human Subjects? 45 CFR 46.102(d & f)

1. **Research means:**
   - a systematic investigation
   - designed to develop or contribute to generalizable knowledge
2. **Research includes:**
   - research development, testing, evaluation, i.e., pilot studies
3. **“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
4. **“Private Information” means:**
   - Information about behavior in a context in which an individual can reasonably expect that no observation or recording is taking place
   - Information, provided for specific purposes, that the individual can reasonably expect will not be made public (e.g., a medical record)
Definition of Minimal Risk: 45 CFR 46.102(i)

“Minimal Risk” means:

- The probability and magnitude of harm or discomfort;
- Are not greater than those ordinarily encountered in daily life; or
- During the performance of routine physical or psychological examinations or tests.

* Important to understand as a threshold for Full Board Review vs expedite (or exempt verification)
- All studies have some level of risk or discomfort

Minimal risk

- Observational studies
- Blood draw healthy adults (limits!)
- Studies of perception, views, thoughts
- Study of data already existing and collected for other reasons.

- Existing Samples (Blood, Tissue, Fluids)
- Moderate exercise
- Noninvasive “standard clinical tests” Physical exam, routine psychological exam, MRI, medical history
- Non-invasive Samples (buccal swab, tooth scrapings, saliva, urine)
- Some Phase IV post-market study of drugs/devices
Types of IRB Review (Impact of Minimal Risk Determination)

- Determine if Research involving Human Subjects
  - No IRB Review
- Verification of Exemption (Minimal Risk)
  - 6 Categories - no IRB Oversight
- Expedited Review (Minimal Risk)
  - 9 Categories
- Convened (Full) Review
  - Greater than Minimal Risk
- Continuing Review
  - (Expediteable if now closed to enrollment AND no longer receiving any >Minimal Risk research procedure)
  - At least annual (determined by IRB), Same types of review

NOTE: Initial and Continuing Review Require Vote of the Convened IRB, Meeting All Quorum Requirements, Unless Specific Conditions for Use of Expedited Review are Satisfied

Minimal Risk Determinations: Subpart D - Protections for Children

<table>
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<tr>
<th>Category of Research Involving Children</th>
<th>Requirements</th>
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<tr>
<td>No greater than minimal risk</td>
<td>Assent of child and permission of at least one parent</td>
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<tr>
<td>Greater than minimal risk and</td>
<td>Assent of child and permission of at least one parent</td>
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<tr>
<td>prospect of direct benefit</td>
<td>Anticipated benefit justifies the risk</td>
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<td>Anticipated benefit is at least as favorable as that of alternative approaches</td>
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<tr>
<td>Greater than minimal risk and</td>
<td>Assent of child and permission of both parents</td>
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<tr>
<td>no prospect of direct benefit</td>
<td>Only a minor increase over minimal risk</td>
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<td>Likely to yield generalizable knowledge about the child’s disorder or condition that is of vital importance for the understanding or amelioration of the disorder or condition</td>
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<td>The intervention or procedure presents experiences to the child that are reasonably commensurate with those in the child’s actual or expected medical, dental, or expected medical, dental, psychological, social, or educational situations</td>
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<tr>
<td>Any other research</td>
<td>Assent of child and permission of both parents</td>
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<td>IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children</td>
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<td>The HHS Secretary or the FDA Commissioner approves, after consultation with a panel of experts in pertinent disciplines (e.g. science, medicine, education, ethics, law) and following publication in the Federal Register and public comment</td>
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What are the IRBs?

- Designated by the Institution under federal law to review federally funded research on human subjects (FWA).
- 5 people minimum.
- 1 scientist, 1 nonscientist, 1 nonaffiliated.
- Physicians, Scientists, RNs, Lay members, Clergy, Statistician, Ethicists, Pharmacists, Genetic counselor, Lawyer, HMS.
- Quorum – greater than 50% of membership plus –must be scientist and non-scientist present.
- Institutional Official – Sufficient authority to provide necessary resources

4. Applicability

(a) This Institution assures that whenever it engages in human subjects research conducted or supported by any federal department or agency that has adopted the Federal Policy for the Protection of Human Subjects, known as the Common Rule, the Institution will comply with the Terms of the Federalwide Assurance for Institutions Within the United States (contained in a separate document on the OHRP website), unless the research is otherwise exempt from the requirements of the Common Rule or a department or agency conducting or supporting the research has determined that the research shall be covered by a separate assurance.

(b) Optional: This Institution elects to apply the following to all of its human subjects research regardless of the source of support, except for research that is covered by a separate assurance:

[ ] The Common Rule (see section 3 of the Terms of the FWA for Institutions Within the United States for a list of departments and agencies that have adopted the Common Rule and the applicable citations to the Code of Federal Regulations)  [ ] The Common Rule and subparts B, C, and D of the HHS regulations at 45 CFR part 46
Custom Fit IRB to the needs of the Institution

- FWA – Checking or unchecking the Box
- Expertise to fit type of research
- Use of Experienced Investigators
- Compliance/Regulatory experts
- HIPAA
- Tissues/Pathology
- Radiology
- Scientific Review
- Quality and Expertise of Support Staff
  - PhD, PharmD, MD, JD, etc
  - CCRC, RAC, CIP, CIM

IRB Required Determinations

“There now. We get our wish of continuing our work unimpeded, and they get their wish of being in a position of direct oversight at all times.”
### IRB Approval Includes Findings That

- **Review, Approve (§46.111), Exercise Continuing Oversight:**
  1. Risks are minimized through 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

**When Appropriate**
1. Privacy and Confidentiality provisions are adequate
2. Data safety monitoring is adequate
3. Appropriate safeguards are included for vulnerable subjects

### Criteria for IRB Approval

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<td>Qualifications of PI</td>
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IRB Decision Matrix

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RESPECT FOR PERSONS

Informed consent          Privacy & Confidentiality
Surrogate consent         Vulnerable Populations
Assent                    

IRB Oversight Includes...

- Continued ethical evaluation of the research
- Monitoring of the research
- Monitoring of the informed consent process – “Duty to Obtain and Maintain Consent”
- Analysis (as received) of new information, adverse events, and unanticipated problems involving risks to subjects and others
- Formal Continuing Review at intervals appropriate to the degree of risk and no less than annually
Assessment of Risks and Benefits

• “Risk” includes both Magnitude and Probability of Harm

• Risks should be reduced to those necessary to achieve the research objective – Consider Alternatives, Precautions and Safeguards.

• When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk

• When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated.
  – Consider the nature and degree of risk,
  – the condition of the particular population involved,
  – and the nature and level of the anticipated benefits.

• Relevant risks and benefits must be thoroughly arrayed in documents and procedures used in the informed consent process.

• Inform Subjects of “any Reasonably Foreseeable Risks or Discomforts”

Risk of Harm

• Harms commensurate with daily life, requiring no special protection:
  – Inconvenience
• Harms do not have to be Physical
  – Emotional or psychological harm
  – Social harm
  – Physical harm
  – Financial harm
  – Legal harm
  – Moral harm
• Benefits must be reasonably expected
• Examples of things that are not benefits:
  – Payments,
  – extra credit,
  – opportunities for drawings or lotteries,
  – health improvement,
  – and insights in own self.
Risk Benefit Determinations

With both the risk and benefit determination, consider only those potential risks or benefits above and beyond what individuals would receive absent the research - in clinical care.

Confidentiality as a Risk

- Breaches of confidentiality can pose risks to participants of social, psychological, legal, or financial harms
- Regardless of the level of risk, the investigator is obligated to honor the agreement made with the participant, whatever that may be.
- Risk is not fixed; ameliorating conditions or strategies can alter risk level
- Secure data protection plan can reduce risk of confidentiality breaches
- Create sound data protection plan
  - Determine whether identifiers are needed
  - De-identify data (where necessary)
  - Consider storage of data (physical and electronic)
- Destroy, in time, data or identifiers that will not be archived
- If necessary obtain a COC to protect identified data collected on subjects to prevent possible civil/criminal liability, embarrassment etc.
- Obtain a COC for data/tissue banks involving genetic testing/information
Informed Consent Issues - Tampa Tribune 3/11/00

• TAMPA - A lawsuit accusing USF doctors of experimenting on pregnant women without their consent is settled for $3.8 million. The experiment wasn't considered risky and no adverse effects were documented, plaintiffs in the suit agree. However, the failure to inform ... as many as 3,000 ... pregnant women of various experiments conducted between 1986 and 1990 has cost Tampa General Hospital, USF and the state $3.8 million.

• 45 CFR Part 46.116 General requirements for informed consent.
  – “Except as provided elsewhere by this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative.”
Informed Consent

- Legally effective informed consent
  - Legally Authorized Representative (LAR) (see State law)
- No coercion or undue influence (recruitment)
- Obtained by Investigator/Staff trained and authorized by IRB
- Language understandable to the subject
  - Use lowest level vocabulary and syntax.
  - Avoid jargon,
- No exculpatory language – By signing this consent you waive all rights...

Required Consent Elements

1. Statement that study is 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 recommended
8. Statement that participation is voluntary and the subject can withdraw at any time without penalty or loss of benefits to which the subject is otherwise entitled

- Additional elements, as appropriate
  1. Statement that there may be risks which are unforeseeable
  2. Under what circumstances investigator could terminate subject's participation
  3. Additional costs to subject
  4. Consequences of subjects withdrawal from research Statement that will be told of new findings
  5. A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject
  6. Approx. number of subjects in study
Subject selection/enrollment (Discuss Strategy with IRB)

- How are subjects identified?
  - Ads, charts, IST, referrals, own clinic, support groups, public records, Dear Colleague letters, etc.
  
  **Note: FDA Considers Recruitment to be the first step in the Consent Process**

- How, when and by whom are subjects **first contacted** about the study?
  - Letter? In person? By whom? Someone who has reason to know confidential medical info.
  - Letters must be cosigned by MD known to patient.
  - No “cold calls!”

**Tips**
- Familiarize yourself with HIPAA (“preparatory to research” language)
- Develop a recruitment strategy
- Contact population referral groups
- Utilize advertising media (IRB approval needed) – integrate into your budget

Carefully review patient database against the inclusion and exclusion criteria

Is this study compatible with the practice?

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Informing Consent *

- Informed consent is a process, not a signed document.
- Informed consent results when full disclosure of role, benefits, risks, choices, and outcomes are explained in understandable ways.
- Voluntary informed consent cannot be realized when differentials of power, class, economics, desperation, and other possible sources of coercion are not considered and addressed.

- Do you advise subjects of primary and all secondary goals of the study?
Informed Consent Generally

- **There is no such thing as “passive consent”**
  - consent is required unless formally waived
  - documentation is required unless formally waived

- **There is no such thing as a “secondary subject”**
  - if an investigator obtains “identifiable private information” about a living individual, the individual is a human subject, regardless of the source

- **Deception Research**
  - Requires a formal waiver of consent
  - Documentation of Waiver required in minutes or review documents:
    - If Consent is altered or waived
    - If Consent Document is altered or waived
    - Document Consent waiver and waiver of HIPAA Authorization separately

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Topics

- **What does the IRB have to do with human subjects protection?**

- **How to design an effective Clinical Trial Monitoring program?**

- Are you ready for an FDA/OHRP audit:
  What keeps IRB members and Compliance Officers up at night
PHS regulation 42 CFR Part 50(a)

“Each institution that applies for or receives assistance under the Act for any project or program which involves the conduct of biomedical or behavioral research must have an assurance satisfactory to the Secretary that the applicant:

1) Has established an administrative process that meets the requirements of this subpart, for reviewing, investigating and reporting allegations of misconduct in science in connection with PHS sponsored biomedical and behavioral research conducted at the applicant institution or sponsored by the applicant; and

2) will comply with its own administrative process and requirement of this subpart.”

Scientific Misconduct, Investigator Non-Compliance
What Are They Complaining About?

- Failure to follow the protocol (70)
- Falsification (67)
- Informed Consent Issues (55)
- Failure to report adverse events (40)
- Qualifications of persons performing physicals (27)
- Inadequate Records (25)
- Failure to get IRB approval, report changes in research (20)

- Failure to follow FDA regulations (13)
- Charging for the test article (9)
- Drug accountability (7)
- No active IND (7)
- Violations of GLP regs (7)
- Misleading advertisements (5)
- Blinding (3)
- No 1572 (2)
- Monitoring practices (2)
- IRB shopping (1)

Stan W. Woollen and Antoine El Hage, PhD
Office of Good Clinical Practice
“Scientific Misconduct - The ‘F’ word”
October 2001
Audit Programs - What the Institution Must Do

- Clarify Applicability of Program to Type of Research
- Definite Scope (Assess resources)
- Mechanism of reporting allegations to
  - PI/Research Team
  - IRB
  - Institution
  - Federal Agencies
- Inquiries
- Investigations – For Cause
- Documentation sequestration
  - If Research Integrity Issues

Additional Suggestions for Institutional Prevention

Standard Operation Procedures (SOPs)

- Create institutional SOPs and guidance documents defining how day-to-day research should be conducted
  - Research informed consent process
  - Adherence to Protocol
  - Consent Process
  - Data Validation
  - Serious Adverse Event reporting
  - Drug accountability

- Make SOPs and guidance documents easily accessible to research staff
  - Departmental Binders
  - Open network access
  - Intranet Website
Additional Suggestions for Institutional Prevention

Audit Program

- Establish an internal research auditing program*
  - Institutional Level
  - Departmental Level
- Encouraged by the FDA but not mandatory
- Caution: New business plan (where no prior audit program in place) should not assess staffing based on intended randomization of studies to be reviewed per year
  - Corrective action plans and re-audits could overwhelm a new program

Audit Program (Institutional Level)

Create a central Research Compliance or Quality Assurance group
- Reporting to “appropriate”
  - Officials (Research IO/Integrity Officer) or
  - Boards (IRB/Research Oversight)
- Appropriate = Authority to Act

Staff the group with experienced individuals
- History of hands on protocol management (regulatory and conducting trials)
- Well versed regarding ICH/GCPs and federal regulations
- Understand IRB Regulations
Additional Suggestions for Institutional Prevention

Audit Program (Institutional Level)

• Develop SOPs for conducting audits
  – Who comprises the audit team?
    » Qualifications, experience, training,
  – Which protocols are eligible to be audited?
  – How are trials chosen for audit?
    » IND/IDE, Multi-Center, Random, Other -NCI
  – How are research teams notified?
    » How much time before audit
  – What items are reviewed during the audit?
  – What do you do with audit Reports
    » Establishment of QIOC or similar committee

Additional Suggestions for Institutional Prevention

Develop SOPs for conducting audits (con’t)

What needs to be reviewed:
• Activation/Continuing Review Information
• Informed Consent
• Eligibility
• Protocol Compliance
• Treatment
• Toxicity/Adverse Event Reporting
• Response/Disease Outcome
• General Data Quality
Additional Suggestions for Institutional Prevention

Develop SOPs for conducting audits (con’t)

• How are results to the research team communicated?
• How does investigator respond to findings?
• To whom is the final report addressed?
  – MDACC – Quality Improvement Oversight Committee
    • Determines if acceptable, Recommends CAP
  – Report directly to IRB if:
    » If clearly Unacceptable Audit,
    » Unanticipated Problem resulting in risk to subjects or others, or
    » Serious act of non-compliance

Audit Program (Institutional Level)

Process should be:
Proactive, Collegial, Relationship Building Approach

• Not punitive, move toward less harsh terms
  – Quality Improvement Review,
• Educational focused
  – Prevent repeat of deviations/errors
• Evaluated regularly
  – Establish Performance Metrics and Best Practices
Additional Suggestions for Institutional Prevention

Audit Program (Departmental Level)

- Could be specialized to meet each departments needs,
- Research teams should be involved in developing program in order to promote ‘by in’,
- Department staff should be mentored by institutional auditors team on performing audits,
- Good idea to have departmental audit rotate team members

Monitoring Program - Preferred approach for high risk trials (ie Investigator held INDs, high-risk trials, new investigator trials)

- Prospective rather than retrospective
- More pro-active
- Allows for additional central control over the conduct of trial
- Requires additional staff
- Very time consuming
Additional Suggestions for Institutional Prevention

Require Education for Investigators and Research Staff

- Essential step
- Research nurse and coordinator training
- Existing and new faculty training
- Ensure system in place to identify faculty/staff who do not comply with required training
- Use Education to Rehabilitate non-compliant Investigators
- Continuing education/Re-certification (CITI)

Think Human Subject Protection Program Not IRB: An HSPP is Collaborative approach to Human Subject Protection
What is Your Organizational Plan

• Education (For and By):
  – Investigators and Research Teams
  – IRB
  – Monitors

• Review - Ongoing
  – Scientific Review
  – IRB
  – DSMB/DMC
  – Monitors/Auditors (Internal & External) also use Self Audits

• Document
  – By all to demonstrate quality/compliance
  – Used by all to assess quality/assurance (make sure you know what is going on)

• Communicate
  – How/with Whom – often and with everyone (PI, IRB, IO, Sponsor, Feds)
  – What – Minutes, Suspensions, Terminations, Monitoring/Auditing Reports, Non-Compliance, Unanticipated Problems, DSMB Reports

Topics

• What does the IRB have to do with human subjects protection?

• How to design an effective Clinical Trial Monitoring program?

• Are you ready for an FDA/OHRP audit: What keeps IRB members and Compliance Officers up at night
Lessons Learned from FDA and OPRR/OHRP Closures

- Are you properly documenting what you are doing
- Are you doing what your documents say
- When is the last time you assess your Policies and SOP’s

Assess your audit Readiness

- What Needs to be done
  - Review IRB P & P – measure compliance – assess usefulness
    - Review every six months
    - Are you following your policies and Procedures – Update/remove
    - Are they in line with current guidance (AE/Unanticipated problems)
    - Do you perform Quality Audits – do the auditors know IRBs
    - Survey Investigators for Quality Improvement Issues
      - Use Research Quality Oversight Committee
    - How do you communicate concerns to IO/Institution
Use Self Assessment Tools

• FDA checklist
• OHRP Checklist
• AAHRPP Standards
• See Web sites for Shared SOP’s
• Use IRBForum as a resource
• Call other Institutions and Administrators

Assess your audit Readiness

– Make sure IRB Membership lists are up to date (Result = Quorum issues)
  • Confirm required membership and appropriate expertise
  • CV’s on file

– Review IRB Minutes
  • Required Approval determinations
    – Criteria for IRB Approval (46.111)
  • Quorum issues – People coming and going, COI, “Majority”
Meeting Minutes

- **Minimum Documents needed each Initial Review:**
  - Principal Investigator, Protocol Title
  - Protocol/Protocol Summary
  - Grant
  - Contract? AAHRPP accreditation requires contract review
  - Investigator Brochure or package insert (if the drug/device is investigational, an investigator brochure is required. If the drug/device is approved, a package insert is required.
  - Advertisements
  - Consents/Translations
  - Include Other Reviews whenever possible
    - SRB
    - IBC, RDRC, IRC etc.

Minutes Documentation (not all inclusive)

- **Discussion:** Summary of any controverted issues and their resolution. Include information on the following: Don’t be afraid to document that 1 or more members disagree with the approval.
  - Scientific Design issues
  - Risk/Benefits (document the risk level assigned)
  - Is it Minimal risk or Greater than minimal risk
  - Document in the minutes when an IND/IDE is necessary and who is holding the IND/IDE.
  - Is it an off label use of an approved drug (does it qualify for IND exemption)
  - Trials involving devices (document risk level assigned)
  - Document in the minutes if it is a significant risk device or a non-significant risk device.
  - Document if any other approvals are necessary. For example approval by the Scientific Review Board (CRC), Biosafety, RDRC or Radiation Safety Committee for isotopes, etc.
  - Document how risks to subjects have been minimized. Include the discussion of safety considerations of any washout period/rescue medications, method of reaching maximum tolerated dose.
  - Include a statement of whether any payment to subjects was deemed acceptable by the Board.
  - Justification for use of placebo (is SOC effective in this condition)
Minutes

- If the research involves pregnant women, human fetuses or neonates, document Subpart B (Additional protections for pregnant Women, Human Fetuses and Neonates)
- If the research involves prisoners, document Subpart C (Additional Protections pertaining to Prisoners in Research)
- Document any privacy and confidentiality issues. (For example, the consent contains the appropriate HIPAA language, samples are de-identified, etc.)
- Document that the consent contains all the required elements
- Document if consent monitoring is required
- Document waiver/alteration of consent
- Document and number any stipulations the board has required prior to approval
- Document the decision and the vote (State how many members present, how many voted for, against and how many abstained. State if any members recused themselves from the discussion and vote)
- If the protocol is approved with stipulations, the minutes must state whether the stipulations are to be reviewed by the Chair, by a subcommittee, or by the full IRB

Assess your audit Readiness

- First Priority - What is not being done
  - Required determinations
    - Vulnerable populations (pediatric, Pregnant women/neonates prisoners (prisoner rep), Wards of state (advocate) etc.)
    - FDA (IND - new drug/herbal/off label use, IDE - SR/NSR, HDE)
    - DOD Studies
  - Required Reporting
    - Prompt reporting = 30 days
    - Unanticipated problems involving risks to subjects or others
    - IRB approval suspension
    - Serious or continuing non-compliance (IRB Determination)
      - Hold on enrollment may equal suspension
**IRB Post Assessment Action Plan – Report to IO**

- **Focus on prospective corrective action plan**
  - What resources are needed to implement

- **What is being done poorly**
  - Inconsistent documentation
  - Poorly Documented

- **What responsibilities are understaffed**
  - Failure to review in a timely manner – may result in risk to subjects
  - Reviews are performed in haste
  - Issues are overlooked or Determinations not Made

**Does your Institution have Multiple IRBs**

- How do you assess, maintain, and validate, quality review standards
- How do Maintain Consistency and Individual IRB Autonomy
- How do You avoid IRB shopping
- Do you have an appeal process
- Do you Have an Executive IRB?
  - Set Standards/policy
  - Made up of Chairs/Vice Chairs and experienced members of other IRBs
What keeps you awake at Night

1. Multi-center Studies – Data Quality Monitoring
   1. Data Monitoring Plans
2. International Research
3. Studies needing an IND or IDE
   - PI Initiated IND/IDE studies
      - Monitoring/Reporting
      - Off Label Use
      - IND/IDE Exemptions
      - GMP Issues
4. CLIA Issues
5. Embryonic Stem Cell Use
6. ClinicalTrials.gov
7. Billing
8. Tissue Banks
9. AE/Unanticipated Event Reporting –to IRB & Feds
10. Staffing
    - Timely Reviews
    - Quality of Reviews
    - Quality of documentation
      - Minutes - completion
      - Reviewer worksheets
      - Required determinations
      - Unreported events

Is PI Engaged in Research at Other Institutions

➢ List all performance sites
   - IRB approval needed for all sites “engaged in research”
   - Do other sites have an IRB
   - Check your FWA – Have other Institutions named you as their IRB of Record without permission (OHRP just started notifying)
   - Enter into formal agreement and submit to OHRP
     - Unaffiliated Investigator Agreement/ IRB Authorization agreement
     - Performance Site Specific Information Form
     » Assess site for capacity to conduct research
   - See OHRP Guidance on “engagement in research”
     http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm
     - Providers of identifiable private information
     - Employees or agents of institutions not selected as research sites administering certain clinical trial related medical services
Regulatory Basis of Multicenter Review

“In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With [approval], an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.”

Is your PI the lead PI in a multi-center Study*

• Do you have a data monitoring plan (DMP)
• Is the study properly funded to allow for monitoring
• Has the IRB approved the DMP

— *Caution- watch out for amendments that keep adding sites
  » Who is responsible for data quality/data management
### International Research

- An IRB must review and approve all international research involving human subjects. An international institution or site considered engaged in research must obtain IRB approval from an institution that holds a Federalwide Assurance in the country where the research is taking place (if the research is supported by federal funding).
- What should be the “standard of care” in research conducted in countries that vary widely in wealth and income?
  - “Local Standard”: The prevailing standard at the site, i.e., the kind of care that people usually get and would get if the study were not conducted
  - “Universal Standard”: The standard of care of the wealthiest countries – usually this is the standard prevailing in the sponsors’ countries
- What are the standards that are applied in that country
  - [http://www.hhs.gov/ohrp/international/HSPCompilation.pdf](http://www.hhs.gov/ohrp/international/HSPCompilation.pdf)

### International Research

- What is the capacity for conducting and overseeing research
  - Foreign Investigator’s qualifications, ICH/GCP training
  - Research Team – Human Subject Training, ICH/GCP training
  - Site specific issues – SOC, Insurance, quality of care, resources
  - IRB/IEC – Standards, experience
- What are the standards that are applied in that country
  - [http://www.hhs.gov/ohrp/international/HSPCompilation.pdf](http://www.hhs.gov/ohrp/international/HSPCompilation.pdf)
- What is your IRB’s knowledge of local context
  - Social, Cultural, Religious
  - Is there a local IRB
  - Have you consulted with a local expert

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*Source: [www.hcca-info.org](http://www.hcca-info.org) | 888-580-6373*
IND/IDE Requirements and Off Label Use

- The FDA approves a marketing claim (label) about the use of a drug or product not the drug or product specifically
- “Off label” prescription practices
  - Common physician practice
  - Not FDA-approved
  - Not included on package insert

When Does the FDA Regulate Drugs and Devices?

- Is the article regulated by FDA?
  - Intent of the distributor generally determines whether it’s regulated
  - Nature of the article generally determines whether it’s regulated as a drug, device, biologic, or combination

If the article is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, then it is regulated by FDA.
When Does the FDA Regulate Drugs and Devices?

- How is the article regulated?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Operates through metabolism, chemical reactions, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device</td>
<td>Is not metabolized</td>
</tr>
<tr>
<td>Biologic</td>
<td>Cells, vaccines, etc. (it is or was alive, or came from something that is or was alive)</td>
</tr>
<tr>
<td>Combination</td>
<td>Some combination, e.g., HIV test kit</td>
</tr>
</tbody>
</table>

Examples

- A software program system designed to provide greater resolution in digital photo images is normally not regulated by FDA; that same system if sold to a hospital for use in MRI image analysis is a medical device.

- A chemical sold for industrial uses is not regulated by FDA. That same chemical when used by a hospital to facilitate diagnosis or treat an ailment would be drug.
Do You Need an IND?

• IND – Investigational New Drug [Application]
• New (unapproved) drugs
  – (Almost) always require an IND prior to initiation of human subjects research
• When the principal intent of the investigational use of a test article is to develop information about the product’s SAFETY or EFFICACY, submission of an IND may be required.
  - Investigational use suggests the use of an approved product in the context of a clinical study protocol
• Approved drugs
  – Physicians may prescribe lawfully marketed products off-label for clinical purposes
  – An IND is needed to do research unless a regulatory exemption applies
• Caution: Regarding PI initiated studies - GMP issues arise whether your institution is manufacturing the product or subcontracting the manufacturing process. How do you validate the quality before administering to humans?

Emergency/Compassionate Use

• Conditions
  – Life-threatening/severely debilitating condition
  – No standard acceptable treatment is available
  – No time to obtain IRB approval
  – Single use (subsequent uses require prospective IRB review and approval)

• IND is required for emergency use of unapproved investigational drugs or biologics or with FDA’s authorization in advance of IND submission
Do You Need an IDE?

- IDE – Investigational Device Exemption
- Significant risk device
  - Full IDE requirements
  - Approved by FDA
- Non-significant risk (NSR) device
  - “Abbreviated” IDE requirements
  - Approved by IRB

Do You Need an IDE?

- **Exemption:** In vitro diagnostic device studies:
  - Testing is non-invasive; and
  - Study does not require invasive sampling presenting significant risk; and
  - Energy is not introduced into a subject; and
  - Information gained from the study is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic device or procedure.

- **Early/expanded access**
  - Emergency use
  - Compassionate use
  - Treatment use
  - Continued access
### Emergency Use

- **Conditions**
  - Life-threatening or serious disease or condition that requires immediate treatment
  - No available, generally accepted alternatives for treatment
  - No time to use existing procedures to obtain FDA approval
  - Unforeseeable (emergency is foreseeable if the device may be used in emergencies)
- May occur before IDE is approved, but FDA must be notified immediately after shipment and there are special subject protection requirements for the administering physician

### Who is holding the IND: Sponsor Obligations

(Regulatory Sponsor = Holder of IND/IDE)

- Select investigators
- Select monitors
- Provide training
- Monitor investigations
- Provide information
Provide Information

- Drugs, biologics
  - Investigator's Brochure
- Devices
  - Report of Prior Investigations
  - Describes the investigational device and details of the study

Sponsor Obligations

- Drug studies: IND Application
- Devices studies: IDE application
- Allows shipment of drugs/devices for clinical research purposes
- Sponsor must maintain effective application
  - Ensure compliance with GCPs
  - In effect 30 days after receipt unless FDA notifies sponsor otherwise
- Control shipments investigational agents
- Obtain 1572 or Investigator’s Agreement
1572 Vs. Investigator’s Agreement

- **FDA Form 1572**
  - Personally conduct/supervise
  - IND must use this form
  - Overview of regulations

- **Investigator’s Agreement**
  - Supervise testing
  - Devise individual form
  - Explanation for terminated research

Sponsor Obligations

- Review data to assure continued safety
- Inform FDA & investigators adverse events
  - IND Safety Reports
  - Serious
  - Unexpected
CLIA Issues in Clinical Trials

- Laboratory tests/biomarkers (DNA, RNA, protein) that are used as criteria for enrollment, dosing or treatment decisions are required to be performed in a CLIA-approved clinical laboratory.
- Correlative science not directly influencing treatment can be done in a non-CLIA-approved laboratory setting.
- Protocols proposing use of biomarkers in treatment management should be discussed with the Molecular Targets and Markers Testing Facility (MTMTF) prior to protocol submission.
- **Core Question:** Does this protocol propose using biomarkers to influence enrollment, dosing or treatment decisions?
  - If yes, the following questions should be clarified:
    - How will the biomarker be used (enrollment criteria, treatment decision, etc)?
    - Specify the marker(s) to be used.
    - Specify the assay proposed (i.e. immunostain, serum marker, transcript level, mutation analysis).
    - Is the assay currently being offered as routine laboratory test at MDACC?
    - Specify the material to be tested (blood, fresh tissue, fixed tissue).
    - Will the proposed assay require additional tissues to be collected? What type?
    - Has a CLIA-certified laboratory been identified for this testing?
    - How many patients are expected to be enrolled?
    - When/how often would the proposed testing be performed?
    - What is the required turn-around time for results?

ClinicalTrials.gov – New FDA Requirements

- Expands registration requirements to most trials of drugs, devices and biologics under FDA jurisdiction
- In devices, requirement extends to devices approved under 510(k), PMA, HDE
- Includes pediatric post-marketing device trials
- Excludes small device trials to determine feasibility where primary outcome is not health outcome
- Phase I drug trials excluded
- Works through existing NIH mechanism
- Preempts all state laws in this area
ClinicalTrials.gov – New FDA Requirements

- Applies to trials conducted outside the U.S. “on products with or seeking FDA approval”
- Registry data requirements expanded
- Also includes research facility name and location/contact information; expanded access status of drug; IND/IDE number
- Must be available via internet
- Registry must be searchable by disease, drug or device name, location of trial, age group, study phase, sponsor
- “Responsible party” for registration may be sponsor or PI, if PI has access to all data and right to publish data

ClinicalTrials.gov – New FDA Requirements – Implementation Time

- Registration must occur for all “applicable clinical trials” that are initiated after Sept 27, 2007 or ongoing as of Dec. 26, 2007, by later of: Dec. 26, 2007 or 21 days after first subject is enrolled
- Trials ongoing as of Sept. 27, 2007 and that do NOT involve a serious or life-threatening disease must be registered by Sept. 27, 2008
- Trials ongoing as of Sept. 27, 2007 and do NOT involve serious or life-threatening condition and are completed by Dec. 26, 2007 are not subject to new requirements (but may be subject to previous FDA 1997 requirements)
FDA Amendments of 2007: Results Database

- By no later than Sept. 26, 2010, HHS must issue regulations relating to reporting of results for drugs and devices, approved or unapproved, cleared or uncleared

- Institutions must clarify in CTA
  - Who is responsible party
  - If it is sponsor then reserve right to submit if not done in timely manner

- Much of this detail will be defined in regulations over the next three years

**Penalties**

- $10,000 for violation by any person adjudicated in one proceeding
- $10,000 per day if not corrected within 30 day period after notice
- Grant applications to PHS and other federal agencies must include certification of compliance: False Claims Act risk here

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FDA Amendments of 2007: Adverse Events

- By March 26, 2009, HHS must determine “best method for including in registry and results databank …information on serious and frequent adverse events for drugs”

- IF HHS fails to do this, then Act requires registry and results databank to include
  - table of anticipated and unanticipated serious adverse events grouped by organ system
  - table of all adverse events that exceed a frequency of 5 percent within any arm of a trial
Good News:
New Guidance on Reporting to OHRP

- The following events need to be reported to the IRB:
  - Any unanticipated problems involving risks to subjects or others.
  - Any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB.
  - Any suspension or termination of IRB approval. [45 CFR 46.103(b)(5)]

Good News:
New Guidance on Reporting to OHRP

What is the Timeframe for
- Reporting to the IRB?
  - Regulations state “prompt”
  - Depends on nature of incident
    - Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.
    - Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
What is an Unanticipated Problem?

- Any incident, experience, or outcome that meets all of the following criteria:
  - unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents; and (b) the characteristics of the subject population being studied;
  - related or possibly related to participation in the research; and
  - suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem

1. Is the adverse event unexpected in nature, severity, or frequency? NO
2. Is the adverse event related or possibly related to participation in the research? NO
   - YES
3. Does the adverse event suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized? NO
   - YES

Report the adverse event as an unanticipated problem under 45 CFR part 46

The adverse event is not an unanticipated problem and need not be reported under 45 CFR part 46
Billing Issues - January 18, 2008 Coding Changes

- On January 18, 2008 CMS issued transmittals eliminating the QV, QA and QR modifier – retroactive to January 1, 2008.

- New modifiers to be placed on out-patient billing forms CMS-1450/CMS-1500:
  - Q0: “investigational clinical service”
  - Q1: “routine clinical service”

- V70.7 ICD-9 code required as secondary diagnosis on forms

Billing – Long Term Concerns regarding Changes

- Encourages providers to place clinical trial number on claim; this is voluntary for providers…..for now

- Requires Medicare contractors to accommodate receiving clinical trial number

- Data Mining Potential
  - Requires CMS Common Working File to “generate one monthly report…to CMS data center” that identifies:
  - use of the clinical trial numbers
  - use of the new modifiers
  - number of clinical trial claims
  - number of patients

- **Do your Study documents support your billing determinations?**
  - Protocol, Consent, CTA,
  - Budget and Billing Event Matrix