PI & AMC Held INDs/IDEs: Responsibilities & Resources

HCCA
RESEARCH COMPLIANCE CONFERENCE
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AUSTIN, TEXAS

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AGENDA

❖ Why is IND/IDE Topic on the Agenda?
❖ Translational Research & FDA Requirements Overview
❖ PI & AMC Responsibilities
❖ Challenges & Lessons Learned
❖ Suggestions for Best Practices & Resources
❖ How to Inspire Your AMC’s Leadership
❖ Q & A
Q: Why Is IND/IDE Topic On The Agenda?  
A: INDs/IDEs Are Important to AMCs

With the encouragement/seduction of Biotech Industry, AMCs and their faculty are increasingly holding INDs/IDEs

History has demonstrated that AMCs and their faculty:

➢ Do not always identify when an IND/IDE is required
➢ Are not always clear about their responsibilities as IND/IDE holders
➢ Fail to invest in the infrastructure to support the additional responsibilities
➢ Do not always consider the additional liability with sponsor responsibilities
  - Including indemnification for subject injury
➢ Resulting in noncompliance, Warning Letters, harm to research subjects and potential shut down of the research enterprise

Questions for Audience to Consider

➢ Has your institution moved far enough on the compliance continuum, or is your institution a non-compliant outlier?
➢ What steps can you take now to mitigate the risk and how will you inspire leadership to support those efforts?
➢ What risk mitigation tips can we learn from industry’s Quality Systems approach?
➢ If AMCs desire to engage in this work, must (can) AMCs become more like “industry” to better serve the biotech “customer”?
Translational Research & FDA Requirements Overview

FDA is one of 20 agencies under DHHS
- Over 11,000 employees
- 3 FDA Centers for Clinical Research Oversight

FDA is the one of largest consumer protection agencies in the world!

- Center for Drug Evaluation & Research
- Center for Biologics Evaluation & Research
- Center for Devices and Radiological Health
- Office of Combination Products
FDA AUTHORITY BASED ON:

- **LAWS:**
  Passed by Congress; Governs the U.S. Public And FDA
  Federal Food, Drug, and Cosmetic Act of 1938

- **REGULATIONS:**
  Promulgated by FDA to implement the law
  Carries the force of law –
  Code of Federal Regulations (CFR)

- **GUIDANCES:**
  FDA’s current thinking on “Best Practices”
  Alternate methods may be used to meet regulation

FDA Has Regulatory Authority For
Clinical Investigations Of Drugs, Biologics & Devices…

- Regardless of study funding source
- For investigations within the U.S.
- For investigations intended for Commercialization
- For investigations intended to gain scientific knowledge
U. S. STATUTORY REGULATIONS

FDA REGULATED
21 Code of Federal Regulations (CFR)
21 CFR Part 11 – Electronic Records
21 CFR Part 50 – Protection of Human Subjects
21 CFR Part 54 – Financial Disclosures by Clinical Invest.
21 CFR Part 56 – Institutional Review Board
21 CFR Part 58 – Good Laboratory Practices
21 CFR Part 210 – Drug/GMP
21 CFR Part 211 – Drug/GMP
21 CFR Part 820 – Device/cGMP/QSR
21 CFR Part 312 – IND Investigational Drugs/BB
21 CFR Part 314 – NDA / New Drug Application
21 CFR Part 600-680 – Biologics
21 CFR Part 812 – IDE Investigational Device Exemption
21 CFR Part 814 – PMA / Premarket Approval

ICH-GCP – Good Clinical Practice Guidelines

GxP Categories of FDA-Regulated Translational Research: “Bench-to-Bedside”

Key Steps For U.S. Pre-Clinical Medical Device Testing

1. DESIGN & DEVELOP DEVICE:
   - To Compliance with FDA Engineering Design Control Regulations [US FDA 21 CFR 820.30 (A-B)]
   - FREEZE PROTOTYPE DESIGN
   - For Design Verification Design History & Design Control Requirements [US FDA 21 CFR 820.30 (A-B)]
   - APPROVE DEVICE DESIGN: Build Devices For Bench Testing

2. PASS BENCH TESTING
   - QUALIFY GLP VENDOR [US CFR 21 CFR 58]
   - PREP ANIMAL PROTOCOL
     - [Primary Endpoints: Prove Safety/Some Efficacy; 4 Procedures]
   - GAIN ANIMAL STUDY APPROVALS TO BEGIN

3. CONDUCT GLP ANIMAL STUDY
   - SUMMARIZE ANIMAL STUDY RESULTS / DATA
   - ADD TO IDE SUBMISSION TO FDA
   - APPROVAL TO START HUMAN TRIALS [US FDA 21 CFR 812]

TO FDA

U. S. FDA Pre-Market Submission Content & Review Process for New Devices

[Diagram showing the process of device submission, review, and approval, including steps for Class I, II, and III devices, and the role of the FDA in each stage.]
Simplified Clinical Research Process

**AN IND / IDE APPLICATION...**

- **Is required when an unapproved drug, device or biologic is used in a clinical investigation**
- **Is required when an approved drug, device or biologic is used in a clinical investigation for an off-label indication**
- **Affirms a body of knowledge about the development, manufacturing, pharmacology, and toxicology of the drug/device to support its use in human testing**
- **Requires that the clinical investigation be conducted in compliance with Good Clinical Practice guidelines and laws**
- **Provides an additional level of patient protection through FDA oversight (as well as IRB oversight)**
- **Data from IND/IDE is utilized to gain FDA NDA / BLA / PMA Approvals**
Example: IND / IDE Submissions: Just a Little Paperwork!

IND/IDE Sponsor-Investigator Responsibilities
**Sponsor-Investigator Definition**

- **21 CFR 312.3 (b)**
- **Sponsor-Investigator** means an *individual* who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. *The term does not include any person other than an individual.* The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

*NOTE:* Corporations, agencies, or other institutions do not qualify as Sponsor - Investigators

**IND/IDE Sponsor-Investigator Responsibilities**

FDA regulations allow CLINICIANS to be *both* study SPONSOR & CLINICAL INVESTIGATOR

The Dilemma:

- Many sponsor-investigators believe that the lack of external monitoring and oversight means that they can perform to a lower standard
- Where a sponsor and an investigator are the same, the number of GCP control points is reduced from four to three

✓ A sponsor-investigator, therefore, needs to be more (not less) informed of responsibilities and more attentive to standards of study conduct and subject protection
Sponsor-Investigators Are Legally Bound...

FDA Form 1571

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

[Form with fields for signature, date, and other information]
FDA Form 1572

✓ IND Sponsors are required to obtain a signed FDA Form 1572 from each Clinical Investigator, containing:

✓ Name and address of CI
✓ Name and code number of any protocol(s)
✓ Name and address of research facility and any clinical labs
✓ Name and address of responsible IRB
✓ Names of sub-investigators
✓ Signed commitment by the investigator

IND/IDE Sponsor-Investigator Responsibilities

☐ Combine ALL Responsibilities of Sponsors AND Investigators...Including:

☐ Good Clinical Practices
  ☐ GCP represent minimum standards for conducting clinical trials outlined through a set of regulations & guidelines
  ☐ Goals:
    ☐ Protect the rights and welfare of subjects
    ☐ Closely monitor the quality and integrity of the data so that FDA's decisions are informed and responsible

☐ Financial disclosure responsibilities & information to be obtained for IND/IDE
IND/IDE Sponsor-Investigator Responsibilities

- Conduct and monitor investigations in compliance with GCP, protocol and applicable IND/IDE regulations
- Obtain and maintain necessary FDA & IRB Approvals
- Ensure adequate medical care for patients involved in study
- Overall responsibility to maintain investigation records, including patient case history records
- Provide written reports to IRB, as required
- Promptly report Serious Adverse Events to the IRB, Sponsor, and FDA
- Maintain investigation related documents for FDA inspections and internal audits

IND/IDE Sponsor-Investigator Responsibilities*

- Selecting Qualified Investigators
  - Providing investigators with information they need to conduct an investigation properly
- Ensuring proper monitoring of the investigation(s)
  - Conduct per protocol
  - Ethical considerations
  - Control of investigational product(s)
- Safety reporting

What About SR vs. NSR Device Studies?

*Form FDA 1572: #9. Commitments
Significant Risk vs. Non-Significant Risk IDE Device Studies

21 CFR § 812.3(m): IDE regulations define Significant Risk Device as one that:
1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Significant Risk (SR) vs. Non-Significant Risk (NSR)?
SR = Full IDE for FDA Approval
NSR = Abbreviated IDE for IRB Approval

If Significant Risk (SR)
Submit IDE to FDA for 30-Day Review / Approval
If Non-Significant Risk (NSR)
Initiate Clinical Study After IRB Approval of NSR Under Abbreviated IDE Regulations

Initiate Clinical Study With Appropriate FDA/IRB Approval

Design Device & Manufacture Per FDA QSR/cGMP
Conduct Preclinical Device Testing [Bench & Animal Studies]
Abbreviated IDE Requirements: 21 CFR §812.2(b)

For NSR Devices:
- Label the device in accordance with §812.5
- Present IRB w/ NSR Rationale and Obtain IRB approval
- Investigator must obtain Informed Consent under part 50 and document it
- Monitors Study per §812.46
- Maintains the records required under §812.140(b) (4) and (5) and makes the reports required under §812.150(b) (1) through (3) and (5) through (10);
- Ensures that participating investigators maintain the records required by §812.140(a)(3)(i) and make the reports required under §812.150(a) (1), (2), (5), and (7); and
- Do Not promote device per §812.7

IND/IDE Sponsor-Investigator Responsibilities

Annual Reports: 21 CFR §312.33 (Similar w/ Devices-21 CFR §812)
A sponsor shall within 60 days of the anniversary date the IND went into effect submit a brief report to the progress of the investigation

- Individual Study Information
  - Study Title & Purpose
  - Total Number of Subjects planned for inclusion
  - Brief Description of study results to date
- Summary Info
  - Summary of most frequent / serious adverse event experiences
  - Safety Report Summary
- General Investigational Plan for the coming year
- Description of significant Protocol Changes made during previous year
FDA REGULATED RESEARCH...THE FDA PERSPECTIVE:
CLINICAL RESEARCH BEST PRACTICES = PATIENT SAFETY

- Protocol Design and Protocol Adherence is Key
- Protocol & Informed Consent Approved by FDA/IRB Prior to Study Start
- Clear Inclusion/Exclusion Criteria-Carefully Followed / Documented
- Informed Consent Matches Protocol & Signed & Dated
- CRFs Match Protocol

- Data Integrity (Quality) Achieved by Assuring 2 Key Elements:
  - Accurate CRFs That Capture:
    - Protocol Primary and Secondary Endpoints
    - Key Safety Related Data

How Do We Ensure Best Practices?

Challenges & Lessons Learned
Findings From Recent Warning Letters To Sponsor-Investigators

<table>
<thead>
<tr>
<th>Sponsor Investigator Observations</th>
<th>IDE Study</th>
<th>IND Study</th>
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<tbody>
<tr>
<td>Unaware he/she was Sponsor-Investigator</td>
<td>x x x</td>
<td>x x x</td>
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<tr>
<td>Failure to obtain informed consent</td>
<td>x x x x x x</td>
<td>x x x x x</td>
</tr>
<tr>
<td>Failure to review and evaluate the evidence relating to the safety and effectiveness of the drug as it was obtained from the investigator</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Failure to maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug/device</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Failure to maintain complete and accurate records showing any financial interests of investigators</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Failure to retain records &amp; reports for 2 years after shipment and delivery of the drugs is discontinued and FDA notified</td>
<td>x</td>
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<tr>
<td>Failure to obtain sufficient accurate financial disclosure information from each participating investigator</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Failure to prepare and submit current investigator list to FDA at 6-month intervals</td>
<td>x</td>
<td>x</td>
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Warning Letter
Failure to recognize Sponsor role

Davis, April 2007

“As a sponsor, you are required to obtain a new IDE if a device that is approved for one indication is intended to be used in a clinical study for a new indication”

“Your written response states
• that you were not aware that an IDE was required for an FDA-approved [redacted] to be used off-label,
• that there was no assessment of degree of risk from the IRB and
• that you were not aware that you met the definition of a sponsor-investigator”

Warning Letter
Failure to recognize Sponsor role

Reuter, May 2008

“Your written response states that prior to this work on the [x] device studies, all of the research performed by your office had been done with corporate sponsors who prepared IDE applications and helped you stay on track record-wise”
Warning Letter
Failure to obtain a Signed Investigator Agreement

Davis, April 2007

“You did not obtain signed investigator agreements from any of the twelve physicians who
• implanted investigational devices into subjects or
• provided medical evaluations and/or assessment of subjects enrolled”

Warning Letter
Failure to obtain a Signed Financial Disclosures

Ringel, May 2009

“You failed to obtain financial disclosure information from .... eleven [participating] clinical investigators”
NO MONITORING = No Assurance of Subject Safety!

21 CFR §812.3 (j) Defines “Monitor”

Monitor, when used as a noun, means an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor or a consultant to the sponsor, or an employee of or consultant to a contract research organization.

Monitor, when used as a verb, means to oversee an investigation.

Warning Letter
Failure to ensure proper Monitoring

Asfora April 2008, Davis April 2007

“As a sponsor, you are responsible for

• submitting written procedures for monitoring the investigation and

• for ensuring proper monitoring of the investigation by adequately qualified and trained monitors.”
Warning Letter
Failure to ensure proper Monitoring

Asfora, April 2008, Davis April 2007

“There are no records to indicate that
• study monitor verified the eligibility of the subjects
• protocol violations were observed by the study monitor
• any actions were taken to correct the observed violation or
• unanticipated adverse events were evaluated”

Warning Letter
Failure to ensure proper Monitoring

Ringel, May 2009

“The monitoring schedule should not be a one-time event but should be an on-going program performed with the frequency necessary to ensure that clinical investigators are complying with
• the signed agreement,
• the investigational plan,
• FDA regulations, and
• any conditions of approval imposed by FDA or the reviewing IRB.”

“Although you may delegated the task of monitoring, as the sponsor you are ultimately responsible for ensuring proper monitoring of the investigation”
Warning Letter
Failure to ensure proper Monitoring

Lin, March 2008

“Our inspection found that you did not monitor any aspect of the study”

“You informed the FDA investigator that the DSMB was to oversee the study and issue reports every 4 months, or sooner if necessary…. [however the supporting documents] indicate only that the DSMB was to monitor adverse events”

Warning Letter
Failure to ensure proper Monitoring

Lin, March 2008

“Your statements to the FDA investigator suggest that you were not aware that you were responsible for monitoring the study until you met with her during the first inspection.

“We remind you that your responsibility as the sponsor was to monitor the overall progress of the investigation, ensure that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND, as well as other FDA regulations”
Warning Letter
Failure to maintain adequate accountability records

Davis, April 2007

“There are no records of the receipt and disposition of the investigational devices which you obtained from various manufacturers throughout the clinical trial.

In addition, there are no records of accountability for the investigational devices you used to treat more than 80 subjects or for at least five of the devices that failed to deploy during the procedure.”

Suggestions for Best Practices & Resources

Where Is Your AMC On The Compliance Continuum?
Compliance Continuum
Where you with Education/Training/Verification?

<table>
<thead>
<tr>
<th>Not So Good Practice Training</th>
<th>Better Practice Training</th>
<th>Best Practice Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No Specific Sponsor-Investigator Training Required</td>
<td>• High level, targeted training on Sponsor Investigator responsibilities</td>
<td>• Just-In-Time, in person, well documented training</td>
</tr>
<tr>
<td>• Click-Through On-Line Slides without Testing</td>
<td>• Documented Training for ALL SIs and their Study Teams including GCP training and training specifics on SI requirements for Drug or Device studies</td>
<td>• On-site review and assessment by Institutional Regulatory Unit</td>
</tr>
<tr>
<td>• No (centralized) retention of documentation of training</td>
<td>• Upstream training of gatekeepers (including IRB staff, departmental research administrators to identify when IND/IDE might be needed)</td>
<td>• Annual Refresher Training</td>
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<td></td>
<td></td>
<td>• Specific “privileges” granted to allow one to be Sponsor Investigator once qualifications demonstrated (e.g. completion of SI training, ACRP Training, CPI Certification)</td>
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</tbody>
</table>

AMC Examples: Education/Training/Verification

<table>
<thead>
<tr>
<th>Institution</th>
<th>Description</th>
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<tbody>
<tr>
<td>University of Miami</td>
<td>Available courses on GCP and Sponsor Investigator Responsibilities</td>
</tr>
<tr>
<td>University of Michigan</td>
<td>Available one-on-one training on Sponsor-Investigator responsibilities</td>
</tr>
<tr>
<td>University of Kentucky</td>
<td>Specific mandatory training modules required of Sponsor – Investigators</td>
</tr>
<tr>
<td>Hopkins</td>
<td>Required site visits: “Compliance monitoring specialist of the OHSR must conduct a site visit with the investigators holding an IDE to determine the PI's understanding of the requirements for sponsors in 21 CFR 812 before initiation of the research. Once an investigator has demonstrated compliance through a site visit, the research may begin. The site visit will be repeated at the time of continuing review.”</td>
</tr>
<tr>
<td>UT Health Science Center San Antonio</td>
<td>Required Discussion of monitoring plan: “All Sponsor-Investigators are required to meet with staff from the Office of Clinical Research to discuss the specific monitoring plan for their Sponsor-Investigator study.”</td>
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</table>
## Compliance Continuum
Where Are You with FDA IND/IDE Submissions?

<table>
<thead>
<tr>
<th>&quot;Not So Good&quot; Practices</th>
<th>Better Practices</th>
<th>Best Practices</th>
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<tbody>
<tr>
<td>IND/IDE Submissions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No to minimal</td>
<td>• Institution</td>
<td>• Means to</td>
</tr>
<tr>
<td>Investigator Awareness</td>
<td>Requires Notice</td>
<td>capture &amp;</td>
</tr>
<tr>
<td>of Need for IND / IDE</td>
<td>of IND / IDE</td>
<td>identify PI</td>
</tr>
<tr>
<td>Submission</td>
<td>Submission</td>
<td>role</td>
</tr>
<tr>
<td>• No Institutional</td>
<td>(Registration)</td>
<td>• Smart IRB</td>
</tr>
<tr>
<td>Awareness / Support of</td>
<td></td>
<td>application</td>
</tr>
<tr>
<td>IND / IDE Submissions</td>
<td></td>
<td>prompts to</td>
</tr>
<tr>
<td>• No Tracking of IND/IDE</td>
<td></td>
<td>make accurate</td>
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<tr>
<td>Studies</td>
<td></td>
<td>assessments</td>
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### AMC Examples
IND/IDE Submissions

<table>
<thead>
<tr>
<th>Institution</th>
<th>Description</th>
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<tbody>
<tr>
<td>Duke</td>
<td>All faculty and staff members who file IND/IDE must register the IND/IDE with the DUHS HRPP by submitting all documents relevant to the IND/IDE to the Duke Translational Medicine Institute (DTMI) Regulatory Affairs Office and completing the DTMI regulatory Affairs Office</td>
</tr>
<tr>
<td>Hopkins</td>
<td>The eIRB application must include all supporting FDA documentation</td>
</tr>
<tr>
<td>Mayo</td>
<td>Consultative submission writing assistance available</td>
</tr>
<tr>
<td>Michigan</td>
<td>Consultative submission prep and submittal services available (MICHRA-MIAP)</td>
</tr>
<tr>
<td>Minn.</td>
<td>&quot;All University faculty members who file an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) with the Food and Drug Administration (FDA) as a sponsor-investigator must submit all documents relevant to the IND/IDE to a University documentation unit (a central file). Documents will be used to remind and assist sponsor-investigators of their reporting obligations to the FDA and to track reports and communications with the FDA</td>
</tr>
<tr>
<td>Oregon</td>
<td>Consultative writing assistance available: &quot;Investigator Support &amp; Integration Services&quot; program</td>
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<tr>
<td>Partners</td>
<td>Consultative submission writing assistance available</td>
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<tr>
<td>Penn</td>
<td>Mandatory assistance</td>
</tr>
<tr>
<td>Pitt</td>
<td>Mandatory central registration and assistance</td>
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<tr>
<td>Vanderbilt</td>
<td>Consultative submission writing assistance available</td>
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</table>
The Compliance Continuum
Where Are You with IRB Oversight?

"Not So Good" Practices
IRB
- No Special IRB Staff or Reviewer Training on IND/IDE Requirements
- IRB Does Not Require Copy of FDA IND/IDE Approval Letter
- Uninformed Assessment of SI Qualifications
- IDE SR vs. NSR Misunderstandings
- No verification of PI’s on-determination so if in error, needed IND/IDEs missed--IRB Does Not Check FDA approved labeling

Better Practices
IRB
- IRB educated on IND/IDEs
- IRB has means and time to review FDA approved labeling
- IRB appropriately identifies need for IND/IDE
- IRB documents SR vs. NSR determinations
- IRB relies of SI certification/attestation that he/she understands SI responsibilities

Best Practices
IRB
- IRB Staff & Members Trained On IND/IDE Requirements
- IRB verifies if use represented as on-label
- Built-In IND/IDE Smart Logic w/Hard Stops: Can’t Go Forward Without …
- IRB receives documentation demonstrating SI understands responsibilities
- Expanded SCR checklist to ensure SCR Includes review of IND/IDE Annual Report and monitoring reports

AMC Examples: IRB Oversight

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<tr>
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<tr>
<td>Stanford</td>
<td>Prior to approving a protocol that involves a sponsor-investigator, the IRB must be satisfied that the sponsor-investigator is knowledgeable about his/her responsibilities and has adequate policies and procedures in place to comply with the FDA regulatory requirements.</td>
</tr>
<tr>
<td></td>
<td>• IRB may rely on feedback from the STANFORD entity providing the education in its determination of proficiency.</td>
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<tr>
<td></td>
<td>• IRB may also contact or site visit the sponsor-investigator as deemed necessary.</td>
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<td></td>
<td>• An on-site compliance audit, designed to evaluate compliance with the FDA regulatory requirements, will be conducted on at least an annual basis and is a condition of continuing review approval by the IRB.</td>
</tr>
<tr>
<td>Duke</td>
<td>If an investigator in the proposed research project is also the IND/IDE holder and/or is otherwise subject to FDA regulations related to duties as a sponsor/investigator, the IRB in conjunction with others within the DUHS Human Research Protection Program (HRPP) will:</td>
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<tr>
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<td>• evaluate whether the investigator is knowledgeable about the additional regulatory requirements of sponsors and</td>
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<td></td>
<td>• follow them while conducting the study.</td>
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<tr>
<td>Utah</td>
<td>IRB requires that sponsor-investigators submit with their IRB application a monitoring plan or standard operating procedures describing how they will fulfill all the additional requirements of sponsors.</td>
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</table>
### The Compliance Continuum
**Where Are You with On-going Study Activities?**

#### (Institution Perspective)

<table>
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<td><strong>Institutional Perspective</strong></td>
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</tr>
<tr>
<td>• Limited to No Institutional Resources for Monitoring / Auditing of IND/IDE Studies</td>
<td>• Some staffing to support for-cause audits of SI studies</td>
<td>• Institution supports Quality System for Clinical Research</td>
</tr>
<tr>
<td>• No central SOP samples available to SIs</td>
<td>• Some staffing for sample of random not for cause audits</td>
<td>• Institution requires &amp; approves SI SOPs</td>
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<tr>
<td></td>
<td>• Makes some sample SOPs available</td>
<td>• Institution supports and sometimes requires centralized monitoring function for all SI studies</td>
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<td></td>
<td>• Makes some tools available to SI</td>
<td>• Issues identified are promptly discussed with SI, reported to IRB and escalated for corrective action as appropriate</td>
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<td></td>
<td>• Some effort to share &quot;lessons learned&quot;</td>
<td>• Institution requires annual audits of all SI IND/IDE Studies w/Results Reported to IRB for SCR</td>
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<tr>
<td></td>
<td>• Advises SI of available monitoring resources (in-house and through third party CROs)</td>
<td>• Institution supports &quot;SWAT&quot; Remediation Team to promptly address any studies with major Audit Findings</td>
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<td></td>
<td></td>
<td>• Institution ensures timely Institutional Reports for FWA Compliance</td>
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### The Compliance Continuum
**Where Are You with On-going Study Activities?**

#### (Study Team Perspective)

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<td><strong>Study Team Perspective</strong></td>
</tr>
<tr>
<td>• Unclear about SI responsibilities</td>
<td>• Takes advantage of some of the institutional tools and SOPs made available for SIs</td>
<td>• Highly qualified study team that embraces continuous quality improvement systems</td>
</tr>
<tr>
<td>• Little or poor use of clear delegation logs</td>
<td>• Basic understanding of SI responsibilities</td>
<td>• Appropriate delegations of tasks</td>
</tr>
<tr>
<td>• PI is very busy and travels frequently so has limited time to supervise team or other clinical investigators</td>
<td>• Completes monitoring responsibilities</td>
<td>• Timely, engaged supervision of delegated tasks</td>
</tr>
<tr>
<td>• Annual reports late, if done at all</td>
<td>• Completes annual reports</td>
<td>• Timely completion of SI responsibilities</td>
</tr>
<tr>
<td></td>
<td>• FDA Readiness Drills</td>
<td>• Timely implementation and documentation of any necessary corrective action plans</td>
</tr>
</tbody>
</table>
The Compliance Continuum
Where Are You with Post-Study Activities?

<table>
<thead>
<tr>
<th>&quot;Not So Good&quot; Practices Post-Study</th>
<th>Better Practices Post-Study</th>
<th>Best Practices Post-Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Failure to budget for document retention</td>
<td>• Study Records Retained, Somewhere?</td>
<td>• Institutional data retention policy</td>
</tr>
<tr>
<td>• Failure to Retain Study Records</td>
<td>• PI &amp; Staff Education on FDA Inspections</td>
<td>• Secure data retention systems</td>
</tr>
<tr>
<td>• No Investigator /Faculty Exit Strategy from Institution</td>
<td>• FDA Readiness Drills</td>
<td>• Effectively communicate timing and expectations of FDA inspections</td>
</tr>
<tr>
<td>• No transition plan</td>
<td></td>
<td>• Conduct Periodic Mock BIMO Inspections</td>
</tr>
</tbody>
</table>

Clinical Research Quality ... . . . Assurance

✓ Build Quality in Upfront

✓ Assure High Quality Throughout

✓ Develop Continuous Quality Improvement Now & In the Future
How Does Biotech Industry Ensure High Quality Clinical Research?

GxP Quality System Requirements

- OPERATING PROCEDURES
  - Process Flows
  - Good Documentation Practices
  - Documented Evidence
  - Work Instructions
  - Job Aids

- RESPONSIBILITY & TRAINING
  - ORG Chart
  - SOP Training (Read & Understand)
  - Skills Training (How To)
  - Train the Trainer

- TOOLS
  - Tools Necessary to Execute Procedures & Perform Functions Effectively

CLINICAL RESEARCH MANAGEMENT OVERVIEW

REGULATORY AGENCIES
BEST CLINICAL RESEARCH PRACTICES
"FDA GOLD STANDARD"

Standardized Clinical Research Templates & Forms & Document Control

Clinical Research Standard Operating Procedures (SOPs)

CLINICAL RESEARCH QUALITY MANUAL (CROM)

CLINICAL RESEARCH ENTERPRISE EXECUTIVE LEADERSHIP

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Quality Process Approach & Deliverables

Procedure & Practice
- Compliant & Efficient
- Aligned w/Scientific / Research Goals
- Easy to Understand
- Easy to Use

Skills & Techniques
- Develop Skilled Team
- Targeted Materials
- Internal Trainers / External Trainers
- Internal Audits
- Training: SI & Research Team
- FDA Readiness Drills / Mock FDA Inspections

Tools & Templates
- Clinical Research Quality Manual
- SOPs
- Templates

EXECUTIVE RESPONSIBILITY
CLINICAL RESEARCH MANAGEMENT & OVERSIGHT

METRICS, ANALYSIS & CONTINUOUS IMPROVEMENT

Clinical Research Activities / Process

INPUT | Process | OUTPUT

Corrective Action & Preventive Action (CAPA Management)

Based on ISO 9001/13485
Conduct Periodic Internal Regulatory Audits

REGULATORY BINDER AUDIT CHECKLIST

Section 3 Study-Specific Documents

<table>
<thead>
<tr>
<th>Audit Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process Audit</td>
</tr>
<tr>
<td>Case Report</td>
</tr>
<tr>
<td>Informed Consent Documents</td>
</tr>
<tr>
<td>Study Procedure Manual</td>
</tr>
</tbody>
</table>

Conduct Periodic Internal Regulatory Audits
Good Documentation Practice TIPS

- DOCUMENTS EXPLAIN:
  - WHAT WILL OCCUR [SOPs & PROTOCOLS]
  - WHAT SHALL OCCUR [INFORMED CONSENT]
  - WHAT HAS OCCURRED [VALIDATION TEST REPORT]

- IN THE U.S.A., ESSENTIALLY ALL MEDICAL PRODUCT DESIGN & DEVELOPMENT DOCUMENTS, INCLUDING CLINICAL TRIAL RELATED DOCUMENTS, ARE LEGAL DOCUMENTS: TREAT THEM AS VERY IMPORTANT-EVIDENCE THAT DEVELOPMENT ACTIVITIES WERE CONDUCTED AND CONDUCTED CORRECTLY

- TIPS FOR BEST DOCUMENTATION PRACTICES:
  - STANDARDIZE A VERSION CONTROL SCHEMA: AND REQUIRE THAT EVERYONE USE IT!!
  - APPROVE FINAL VERSION DOCUMENTS: MAKE SURE THE CORRECT FOLKS SIGN AND DATE THE FINAL VERSION [NOT THE DRAFT VERSION]
  - IF AN APPROVED VERSION DOCUMENTS IS REVISED, ROUTE THE DRAFT REVISION FOR REVIEW AND FINAL APPROVAL, AND MAKE SURE THE REV NUMBER IS UPDATED

- IF A RECORDING ERROR OCCURS, CROSS-OUT THE MISTAKE WITH ONE LINE, INITIAL AND DATE – ALWAYS USE INK & DO NOT USE WHITE OUT OR BACK-DATE: EVER!
Standardized IND / IDE Study Tracking & Planning

Simplified Clinical Research Documentation Flow
SIMPLIFIED GCP PROCESS FLOW

STEP 1
Pre-Study Activities

STEP 2
Study Approval

STEP 3
Ongoing Study

STEP 4
Adoption to Clinical Practice

INPUT

PROCESS

OUTPUT

DOCUMENTATION

DOCUMENTATION

DOCUMENTATION

DOCUMENTATION
**STEP 1**
PRE-STUDY ACTIVITIES

**INPUT**
- Study Design
- Protocol Prep
- CRF Prep
- Biostats
- Determine Database Needs
- CMS Billing
- IP / Contracts
- Draft IND / IDE

**PROCESS**

**OUTPUT**
(Deliverables)

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**STEP 2**
STUDY APPROVAL ACTIVITIES

**INPUT**
- Contracts / IP
- &
- IRB Approvals
- FDA
- IND / IDE
- Approvals

**PROCESS**

**OUTPUT**
(Deliverables)

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STEP 3
ON-GOING STUDY ACTIVITIES

INPUT

PROCESS

OUTPUT (Deliverables)

Database Initiation
Study Initiation
Enrollment
SAE/Safety Reporting
DSMB Review
Protocol Amend
FDA/IRB Annual Reports
Monitoring
Database Lock
Close Out
Final Reports

STEP 4
PRE-STUDY ACTIVITIES

INPUT

PROCESS

OUTPUT (Deliverables)

Journal Publications
FDA NDA / PMA / BLA
Reviews
BIMO Inspections
FDA Approvals
Market Launch
On-going
Safety Monitoring
How to Inspire Your AMC’s Leadership...
How to Inspire Your AMC’s Leadership…

- FDA Enforcement Actions Have Inspired Institutions—CIA

- OR...should we inspire AMC Leadership BEFORE the Perfect Storm...

- Where Patients Die and AMC is Forced to Comply?

Sponsor-Investigator Non-Compliance? …There Are Consequences!

FDA Form 483 Inspection Citations…
Can lead to Warning Letters…
Univ. of Pennsylvania’s Response: Part 1: Mandatory Education

- Required advanced-level course in Good Clinical Practices which includes the following:
  - Introduction to Good Clinical Practices (GCP)
  - FDA Regulations for Clinical Research (IND/IDE)
  - Informed Consent
  - Adverse Events
  - Data and Safety Monitoring
  - FDA Audits

- Penn IRB will not review a protocol application from the School of Medicine, or one which involves federal funding, absent certification demonstrating completion of training.

Univ. of Pennsylvania’s Response: Part 2: External Regulatory Review

- Hired an independent CRO to conduct a regulatory review of faculty who serve as sponsor/investigators

- Communicated findings to both the central University Oversight Committee and a School of Medicine Advisory Committee.

- Reviewed findings with individual investigators, documented the necessary responses and tracked completion of these responses.
University of Pennsylvania’s Response: Part 3: On-going Quality Assurance

- Implemented on-going Quality Assurance / Quality Improvement program
- Implemented formal process of risk assessment to determine studies requiring oversight by groups independent of the principal investigator
- Developed SOPs to
  - Address specific roles and responsibilities of Sponsor-Investigators (including SI SOP Manual)
  - Provide detailed guidance and policies for conducting GCP-compliant research
- Developed a Human Research Forms, Tools & Templates Library

Spectrum of “Behavior”

- Human Errors
  - Carelessness
  - Short cuts
  - Exaggeration
  - Deliberate Invention / Falsification

- NEGLIGENCE
- FRAUD
Recent Example From FDA Office of Criminal Investigation (OCI)

- Clinical Investigator Fraud: An investigation by OCI and the Veterans Affairs (VA) Office of Inspector General resulted in the conviction of a VA physician:
  - Who falsified documentation of a clinical drug study and recklessly enrolled patients who did not qualify under the study protocol.
  - The physician's criminal negligence caused the death of one patient by falsely documenting the results of blood chemistry analysis.
  - The physician was prosecuted and sentenced to 71 months federal incarceration.
Other Legal Issues for SI Studies…

- Determine if institution or funding agency will provide indemnification for clinical investigation
  - Typically, very little indemnification, if any, is able to be secured
  - Limited Indemnification: donation of study drug and agreement to indemnify the sponsor-investigator only for manufacturing defects

Clinical Research Quality: The Prize!
Q & A

THANK YOU!

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UMHS

KAY FULLER, RAC
MDRS, LLC