IRB Considerations for Investigator-Initiated Research

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About Schulman IRB

- Established in 1983
- Superior audit history with FDA—six consecutive audits with no findings
- 21 CFR Part 11 compliant electronic systems
- Compliant with FDA, OHRP and Health Canada requirements

- Full Board meetings five days a week
- Dedicated daily expedited review of qualifying minimal risk protocols
- Review outcome provided within one business day of new study review
- One business day turnaround for complete new site submissions
About Schulman IRB

- Dedicated streamlined processes tailored to **Phase I timelines**
- **Therapeutically specialized** IRB panels in oncology and neurology with robust understanding of latest techniques, methodologies and discoveries
- Customized services for **institutions**
- **Experienced primary points of contact** for sponsors, CROs, institutions and sites
- **Institutional biosafety committee (IBC) services** for clinical, pre-clinical and non-clinical research
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About Today’s Presenter

Rob Romanchuk, BSHS, CIP, CCRC, CCRCP
Schulman IRB Vice Chairperson

- BSHS, Clinical Research Administration, The George Washington University
- Extensive experience in IRB and research operations, HSP and GCP auditing and training
- Frequent presenter at ACRP, MAGI and other venues
Objectives

- Review the landscape of IIS and industry-sponsored research
- Examine the distinctions between IIS and industry-sponsored studies
- Recognize the common challenges in IIS
- Apply practical strategies for supporting sponsor-investigators
- Provide practical guidance to facilitate IRB review of IIS
Definitions: 21 CFR 312.3

- **Sponsor**: “A person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or a pharmaceutical company, governmental agency, academic institutions, private organization or other organization.”

- **Investigator**: “An individual who actually conducts a clinical investigation (under whose immediate direction the drug is administered or dispensed to the subject).”

**Sponsor-Investigator**: “An individual who both initiates and conducts an investigation…. The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor.”

See: [21 CFR 312.3](#)
IIS Defined

- Investigator-Initiated Studies refer to research for which the investigator also assumes the role of sponsor
  - Alternately characterized as:
    - Investigator Initiated Research (IIR)
    - Investigator Initiated Studies (IIS)
    - Investigator Initiated Trials (IIT)

- Hybrids
  - Investigator-Initiated Sponsored Research (IISR)
Motivation

- **Advance science and/or medical practice**
  - Less than half of all medical treatments delivered are supported by evidence
- **Address unmet medical needs**
  - Targeted populations
  - Innovation in current therapies/treatments
  - New indications for approved drugs
  - “Real World” studies
- **Disease prevention**
- **Population-based**
  - QOL
  - Observational
  - Epidemiological
Support

- **Institutional funding**
  - Least fraught with conflicts
  - May translate into meager resources

- **Cooperative groups**
  - Common in oncology

- **Federal funding**
  - Imposes DHHS regulations

- **Non-profit organizations**
  - Mitigates concerns for COI

- **Industry**
  - Industry provides financial support
  - Caution to avoid suspicion of bias and assure compliance with ICMJE, FCPA, AKS, Sunshine Act
Where You Work Matters

- AMC
  - Significant proportion of your studies are IIS
  - Funding more available
  - Support is extensive

- Community health system
  - Proportion of IIS studies is typically small
  - Infrastructure and support limited
  - Funding is a challenge

- Sponsor/CRO
  - IIS best where the “real world” lies
  - Goal is to make it work in any setting
Regulatory Considerations – INDs
21 CFR 312.50: Responsibilities of Sponsor (INDs)

- Select qualified investigators
  - Includes executed 1572 and financial disclosures from each PI
  - Assure the protection of human subjects
- Provide with information to conduct the investigation properly
- Monitor progress of investigation
- Control and document disposition of investigational drug
Regulatory Specifics – Drugs

21 CFR 312 Responsibilities of Investigator (INDs)

- Ensure that investigation is conducted according to the investigational plan
- Maintain case histories
- Provide reports
  - Progress, safety reports, final reports, financial disclosures
- Protect the rights and safety of subjects under the investigator’s care
  - Obtain informed consent from each subject
- Control the drugs under investigation
- Assure that a responsible compliant IRB and comply with its requirements
- Permit FDA inspections
**IND Considerations**

- IND is required when the study involves a drug that does not have FDA approval.
- For studies involving a marketed drug, an IND not required (i.e. exempt) when:
  - The investigation not intended to be reported to the FDA in support of a new indication or to support a significant change in the labeling of the drug.
  - Is not intended to support a significant change in the advertising of the drug.
  - Does not involve studying a new route of administration, dose, patient population or other factor that significantly increases the risk associated with use of the drug.

Filing an IND

- Contact sponsor to request a letter permitting cross-reference to an existing IND
  - Allows FDA to rely on previous information already submitted data
- Complete FDA form 1571
  - Serves as road map/checklist
- Include FDA form 1572
- Complete [FDA form 3674](https://clinicaltrials.gov) as required (clinicaltrials.gov)
  - FDA provides a [checklist](https://clinicaltrials.gov) to determine an “applicable clinical trial”
IND Submission Content

- Introductory statement and general investigational plan
  - Drug name, active ingredients, structural formula, dosage, route
  - Objectives
  - Summary of human experience (or cross-reference)
  - Protocol summary
- IB: not required for sponsor-investigator studies but may contain important safety information (obtain if possible)
- Protocol
- Chemistry, manufacturing, control information
  - Sponsor-investigator can request a waiver or provide cross-reference letter
- Pharmacology and toxicology
  - Sufficient to demonstrate that the drug is reasonably safe to conduct the proposed trial
- Once submitted: wait 30 calendar days before initiating trial
  - FDA will review, may ask for additional info or issue a hold
Active INDs

- Comply with subpart D of 21 CFR 312 (responsibilities of sponsors and investigators)
- Comply with IND safety reporting requirements (21 CFR 312.32)
- Assure all investigators and FDA are advised of any significant new AEs or risks
- Monitor the study
- Obtain FDA and IRB approval of any protocol amendments prior to implementation
- Notify the FDA of addition of investigators
- File annual reports
Regulatory Considerations – IDEs
21 CFR 812.40 Responsibilities of Sponsor (IDEs)

- Assure IRB and FDA approval prior to initiation
- Select qualified investigators and monitors
  - Includes executed contract
- Provide ICF and protocol to all participating investigators
- Monitor the investigation
- Control the distribution and disposition of devices
- Prohibit promotion of device
- Maintain records
- Submit reports
  - UADEs
  - Annual and final reports
21 CFR 812 Responsibilities of Investigators (IDEs)

- Assure that the investigation is conducted according to:
  - Signed agreement
  - Investigational plan
  - FDA regs

- Protect the rights and welfare of subjects
  - Assure informed consent is obtained from all subjects

- Maintain case histories
- Control devices under investigation
IDE Considerations

- IDE regs describe 3 types of device studies:
  - Significant Risk (SR)
  - Non-Significant Risk (NSR)
  - Exempt studies

- Significant Risk Device
  - Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - 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;
  - 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
  - Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (21 CFR 812.3(m))

- Non-Significant Risk Device
  - Does not meet the above definition
Exempt Studies (21 CFR 812(c)(4))

Exempt studies include:

- Studies of an already marketed device if the device is used in accordance with its approved labeling
- Diagnostic devices, if the testing is:
  - Noninvasive
  - Does not require sampling that presents significant risk
  - Does not introduce energy into the subject
  - Is not used as a diagnostic without confirmation by another, medically established product/procedure

- Exempt studies are otherwise subject to 21 CFR 56 (IRB) and 21 CFR 50 (Informed Consent)

See: 21 CFR 812(c)(4)
SR vs NSR – Who Decides?

The IRB

- The IRB should consider the following:
  - The sponsor’s description of why the study is not SR
  - Whether the proposed NSR research study meets the definition of “significant risk” (see above)
  - The proposed use of the device as well as any protocol related procedures and tests, not just the device (test article) alone
  - Additional information from the sponsor, if needed

The FDA

- If FDA has already made the risk determination, the IRB does not need to duplicate this effort
SR vs NSR Consequences

NSR devices
- No need for submission of an IDE to the FDA
  - FDA considers an NSR device to have an approved IDE and is thus subject to “abbreviated requirements” of 21 CFR 812.2(b)
    ◊ These address labeling, IRB approval, informed consent, monitoring, records, reports and prohibition against promotion
    ◊ FDA will be unaware of the investigation; IRB acts as surrogate

SR devices
- IDE application must be submitted to the FDA
- Sponsor-investigator may not initiate study until FDA approves the IDE
IRB Considerations

- IRB should consider the following in the NSR/SR determination:
  - What does the sponsor-investigator propose?
  - What is the potential for serious risk/harm?
  - What about the additional procedures required by the investigational plan?

- The determination must be made at a convened meeting
- The determination must be documented in the IRB minutes
- The IRB should have an SOP governing SR/NSR determinations
- The IRB may agree or disagree with the sponsor’s initial NSR assessment
  - The IRB may contact the FDA for assistance
- The IRB may approve a SR study with the condition that it may not be initiated until receipt of IDE letter
Industry Collaborations and IIS
Industry Collaborations

- Advantages
  - Support for protocol design
  - Funding
  - Investigational article

- Risks
  - Confidentiality and publication can become contentious
    - Industry wants to retain data and rights to publish
      - AMCs cannot abdicate their rights to publish without losing their status.
  - Intellectual property
  - Terms usually include provisions to allow institution to own resulting inventions with industry partner an option to negotiate a license for the discoveries at FMV
  - Conflict of Interest
    - Over 30% of investigators have industry interests
  - Compliance with AKS/FCA, Sunshine Act
Managing Risk in Industry Collaboration

- Clarify roles
  - Oversight
  - Safety reporting
  - Monitoring

- Negotiate and execute an agreement
  - Clear terms on publication, intellectual property, etc.

- Carefully negotiate a budget that demonstrates Fair Market Value
Challenges in IRB Oversight
Independent vs Institutional IRB Oversight

- Independent IRB oversight: when local IRB delegates oversight to external, independent IRB
  - Areas of overlap must be clearly defined
  - Institutional oversight of non-IRB issues must be provided
    - Scientific review
    - Budget/contract
    - Compliance with regs outside of IRB/GCP

- Inherent challenges
  - COIs may be more difficult to elucidate
    - Some AMCs use CIRBs to manage studies for which an institutional COI exists
  - Industry-investigator relationship may be unclear
Meeting the challenges of IIS studies starts with consideration of their origin:

- IIS studies are often underfunded/under resources.
  - Can be discerned by details in submission;
    - Who is funding it?
    - What is the setting? AMC? Community hospital? Physician practice?
- Even well funded studies may be deficient
  - Industry wants to demonstrate arms-length relationship
  - Non AMC studies may not be supported with non-monetary resources like statistical expertise, regulatory specialists
- Investigator experience is telling
  - Long CV with extensive research experience and 100+ publications a good sign
  - Short CV with no research experience or publications elicits concern
Support is critical

- If submission indicates investigator has little support, execution is threatened
  - Exposing subjects to risk for a study that is underpowered or may never be successfully executed is unacceptable
- Lack of support is often revealed in the lead up to initial review
  - Responses slow in coming
  - Indicate limited appreciation of critical factors
  - Recommendations can be made regarding what kind of support is needed to provide an ultimately reviewable/approvable study
Protocol Design

- Design may be robust or deficient depending on experience of the investigator and resources available.
  - Inexperienced physician/investigator typically proficient at describing the clinical question but short on research design
    - Clinical equipoise absent or weak
    - Endpoints unclear
    - Inadequate power or statistical plan,
    - Overly optimistic enrollment plan
    - Required elements missing, e.g. monitoring, privacy/confidentiality, safety reporting
- Regulatory status of drugs/devices unclear
  - May be using approved device, but study includes indication not included in its labeling
    - May be unaware of need for SR/NSR determination and its consequences
    - May be naïve regarding need and process of obtaining IDE
Meeting the Challenge: Protocol Design

- Provisions for the inexperienced or under-resourced investigator
  - Guide to writing a protocol supplied to researchers with signals of inexperience
  - Pre-review mechanisms
  - Draft-review provision with expert board consults
  - Well-trained and knowledgeable front line staff
    - Recognize the signs of deficient submissions
    - Work with site/investigator to maximize quality of submission to allow for review
Meeting the Challenge: Initial IRB Review

- Once prepared for Board IIS studies present unique needs
  - Assure expertise represented in members in attendance or
  - Provide expert review consult report
- Assure careful review of scientific merit, study design, statistical plan, subject selection, essential elements
- Assure regulatory status of any drug or device is confirmed and clear
  - Provide approval letters or documentation of any determinations made by regulatory authorities
Meeting the Challenge: Initial IRB Review

- Assure that the PI is aware of the additional responsibilities as sponsor
  - Monitoring the study
  - Reporting IND safety reports and annual reports if under IND/IDE
  - Assuring HSP

- Clarify relationships and resulting potential COIs
  - Is Industry involved and to what extent?
  - Has the PI declared any potential COI?
    ◊ If so, how will it be managed?
IIS Studies and Devices

IIS studies involving devices provide particular challenges

- Is it approved?
  - What is its approved indication?
  - Is it investigational in its use in the study?
- Is the device manufacturer involved?
  - Aware of the research?
  - Providing funding?
  - Extending their IDE to cover the study?
- What documentation is available and included?
  - IFUs, IDE letters, user manuals
    - Prototype studies often have sparse device documentation
  - Exemption letters
- Who is paying for the device and/or study?
  - Is it being provided by the device manufacturer?
  - Is it being charged to the subject?
  - Is it covered by CMS and/or commercial payers?
  - Is this clearly disclosed in the IC?
IIS Studies and INDs

Challenges peculiar to INDs

- Has an IND been filed?
- What is the sponsor-investigator’s position regarding need for an IND?
  - Is the claim “being used as labeled” valid and well documented?
- Is the study scientifically valid?
  - Has it been done before?
  - Risk of “seeding trials”

  ◊ What is the investigator-sponsor/industry relationship?
  ◊ Has the budget been reviewed to demonstrate FMV?
Putting It Together
Scenario #1

- Investigator submits a protocol for IRB review using an approved cardiac stent. The stent will be charged to subjects, and this is clearly explained in the ICF. The sponsor-investigator contends, and the protocol states, that the device is used as labeled and qualifies as an exempt study. Upon preliminary review, it is noted that the protocol includes repeat coronary angiography at 9 months post-implant.
Scenario #1

What valid concerns will the IRB have with this proposal?

1. The study is greater than minimal risk because it includes the 9 month angiogram
2. The stents must be provided without charge to subjects
3. The study does not qualify as exempt because the 9 month angiogram is not standard of care
Scenario #1

What valid concerns will the IRB have with this proposal?

1. The study is greater than minimal risk because it includes the 9 month angiogram
2. The stents must be provided without charge to subjects
3. The study does not qualify as exempt because the 9 month angiogram is not standard of care
A physician would like to study the use of an antibiotic currently approved for skin and soft tissue infections for use in community acquired pneumonia. This use is common off-label, but he would like to collect safety and efficacy data to validate such use.
What would be the best next step for the physician to take?

1. Complete FDA form 1571 and submit an IND application to the FDA
2. Prepare an investigational protocol and submit to the IRB asking for an IND exemption determination
3. Contact the drug manufacturer to determine if they will supply an IND cross-reference letter
Scenario #2

What would be the best next step for the physician to take?

1. Complete FDA form 1571 and submit an IND application to the FDA
2. Prepare an investigational protocol and submit to the IRB asking for an IND exemption determination
3. Contact the drug manufacturer to determine if they will supply an IND cross-reference letter
IIS studies are essential to the progress of science and medicine

Accommodating IIS studies that involve human subjects requires special considerations

Understanding the challenges specific to IIS and their origin is critical in effective IRB review and oversight

Effective oversight of IIS by an independent IRB is meaningful and effective when this understanding is reflected in its culture and related processes
References and Resources

- Understanding FDA Regulatory Requirements for an Investigational Device Exemption (IDE) for Sponsor-Investigators, J. Investig Med 2012, Oct (as accessed at: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3448842/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3448842/))
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