About Schulman IRB

- Established in 1983
- Superior audit history with FDA—five 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
About Schulman IRB

- Review outcome provided within **one business day** of new study review
- **One business day** turnaround for complete new site submissions
- Dedicated streamlined processes tailored to **Phase I timelines**
- **Expert oncology Board members** experienced in all phases of oncology research
- Customized services for **institutions**
- **Experienced primary points of contact** for sponsors, CROs, institutions and sites
About Schulman IRB

- Clinical Quality Assurance (CQA) and Human Research Protection (HRP) consulting services provided by Provision Research Compliance Services

Provision is a joint venture between Schulman IRB and Falcon Consulting Group

www.provisionrcs.com
The industry’s choice for central and local IRB services.
About Today’s Presenter

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

- BSHS, Clinical Research Administration, The George Washington University
- Extensive experience and IRB and research operations, HSP and GCP auditing and training
- ACRP Chapter Chair 2011-2014
- Frequent presenter at ACRP, MAGI and other venues
Objectives

- Outline a brief history of medical devices and related regs
- Describe important differences between drug and device studies
- Analyze common challenges presented to each party
- Identify best practices in device studies
- Demonstrate concepts through interactive case studies
Drugs and Devices: Twin Sons of Different Mothers

- Different in Nature
  - **Drug**: “primary intended use achieved through chemical action or by being metabolized by the body”
  - **Device**: “is intended to affect the structure or any function of the body…and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.”*

*FDA: “Is the Product a Medical Device?” [webpage](http://example.com)
Drugs and Devices: Reared in Different Environments

Seeking an identity
- Pure Food and Drug Act of 1906 failed to address devices
- FD&C act of 1838 defined devices
  - FDA enforcement focused on removing fraudulent devices from the market in cooperation with the FTC and USPS

Regulatory history marked by disparate events
- **Drugs**: thalidomide tragedy, etc.
  - Response: Kefauver-Harris Amendments of 1962
- **Devices**: Dalkon Shield tragedy
  - Response: Medical Device Amendments of 1976
The Medical Device Amendments of 1976

- Marketing approval now required proof of effectiveness and safety
- Devices assigned to one of 3 levels of risk
  - Levels of “controls” applied for each category
- Two routes to approval
  - **510K**: allows notification to FDA of intent to market a device that is “substantially equivalent” to marketed device
  - **Premarket Approval (PMA)**: required of new Class III investigational devices
    - Must be assigned an IDE number (Investigational Device Exemption) to begin shipping for clinical trials
Further Tragedy

- The Bjork-Shiley Heart Valve, approved under the MDA in 1979 was implanted in 86,000 patients worldwide
  - Later experienced fractures that led to 300 deaths, 196 in US
- Legislative attention led to the Safe Medical Device Act (SMDA) of 1990
The Safe Medical Devices Act

- Expanded FDA authority to include pre-production design, validation of GMP, safety reporting, tracking, recall authority and mechanism for civil penalties against violators
  - By 1982, PHS Bureau of Radiological Health transformed into the Center for Devices and Radiological Health (CDRH) under auspices of FDA
The Medical Device User Fee and Modernization Act (MDUFMA)

- Signed into law, October 26, 2002
  - Institutes user fees for PMAs and 510(k)s
  - Sets performance goals for premarket reviews
  - Allows for 3rd party inspections by accredited persons
Device Classifications

- **Class I**
  - Examples: bandages, exam gloves
  - Subject to “general controls”

- **Class II**
  - Examples: powered wheelchairs, infusion pumps
  - Subject to “special controls”

- **Class III**
  - Life-sustaining, substantial importance in preventing disability and death
**510(K) Process**

- A submission to FDA for marketing clearance
  - Allows FDA to classify a device as “substantially equivalent” to a legally marketed device (“predicate device”)

- Required when:
  - Introducing device for first time
  - Changing an indication for a previously cleared device
  - Making significant modifications to a cleared device

- In 2014: 1,712 510(k)s received
- About 10% of 510(K)s require clinical data which are collected under IDE regulations
- About 4% are found NSE: require a PMA
PMA Process

For:

- All Class III devices
- Class II device with new intended use, indication or technological characteristics
- High risk devices
- NSE to pre-amendment Class I or II devices
  - In 2014, 19 PMAs were received
Other Pathways and Hybrids

- **Modular PMA**
  - Allows PMA to be submitted, reviewed and conducted in modules

- **Streamlined PMA**
  - Applies to Clinical Lab Devices when technology is well known

- **Product Development Protocol (PDP)**
  - Investigation of the device and development of information necessary for approval are merged.
  - Essentially a contract with milestones that allows period reporting
  - A completed PDP is equivalent to a PMA

- **De Novo Petition**
  - Novel and low risk devices that do not have a predicate for 510(k)
  - Avoids PMA
Protocol Design Differences

- Smaller population: 100s vs. 1000s
- No phases
  - Feasibility study – evaluate safety
  - Pilot study – effectiveness, optimize protocol
  - Pivotal study – intended population
  - Often employ “roll-ins”
- Controls problematic
  - May use sham procedure/device
  - Use historical control
Devices: A Different Animal

- Different Regulations
  - Drugs: 21 CFR 312
  - Devices: 21 CFR 812

- Different Regulatory Agencies
  - Drugs: CDER
  - Devices: CDRH
21 CFR 812 Notable Points

- **Sponsor** must:
  - Get a risk determination from an IRB
  - Get an IDE* for SR devices before starting study
  - Comply with prohibitions against commercialization of investigational devices
    - May not charge in excess of recovery for manufacture, research, development and handling
  - Obtain a signed agreement with each investigator before shipping devices

* In 2014, 120 IDEs were received by the CDRH
21 CFR 812 Notable Points

- IRB must:
  - Make a risk determination
    - SR devices will require IDE
    - May disagree with sponsor
    - FDA may make final determination
  - Otherwise follow requirements of 21 CFR 56
- Caution: Previously NSR devices or 510(K) exempt devices may be SR in the investigational application
Risk Determination

Significant Risk Device:

- Intended as an implant
- Used in supporting or sustaining human life
- Is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health;
- Otherwise presents potential for serious risk to health, safety or welfare of subject
## Regulatory Differences

<table>
<thead>
<tr>
<th></th>
<th>IND (Drug)</th>
<th>IDE (Device)</th>
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<tbody>
<tr>
<td><strong>Startup</strong></td>
<td>1572 must be executed prior to study start</td>
<td>CTA must be executed prior to device shipment</td>
</tr>
<tr>
<td><strong>Startup</strong></td>
<td>CMS approval not required</td>
<td>CMS approval must be granted prior to study start if CMS contractors will be billed</td>
</tr>
<tr>
<td><strong>IRB Responsibilities</strong></td>
<td>No risk determination is made by IRB for IND studies</td>
<td>IRB must make risk determination before study can proceed—nonsignificant risk devices do not require an IDE (812.66)</td>
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Protocol may be submitted to the IRB before IDE approval is granted but study may not begin until IDE is granted

# Regulatory Differences

<table>
<thead>
<tr>
<th>Adverse Event Definition</th>
<th>Drug</th>
<th>Device</th>
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<tbody>
<tr>
<td>IND reports for “any untoward medical occurrence associated with the use of the drug, whether or not considered drug related”</td>
<td>UADEs means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified (812.46)</td>
<td></td>
</tr>
<tr>
<td>AE Reporting</td>
<td>IND reports within 15 days Unexpected fatal or life-threatening adverse events within 7 days</td>
<td>UADEs reported to FDA and all reviewing IRBs within 10 days</td>
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<tr>
<td>Investigational Article</td>
<td>Drug provided at no charge – pharmacy often manages receipt, storage and dispensing</td>
<td>Devices often require purchase agreements and must be priced to avoid “commercial distribution,” e.g. charge only what will recover “costs of manufacture, research, development and handling” (812.7)</td>
</tr>
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</table>
Device Sponsor Responsibilities

- **Regulatory Responsibilities**
  - Selecting investigators
  - Providing investigators with necessary information to conduct the investigation
  - Ensuring proper monitoring of the investigation
  - Ensuring that the IRB review and approval are obtained
  - Submitting an IDE application to FDA
  - Ensuring that any reviewing IRB and FDA are promptly informed of any significant new information about an investigation
    - Sponsors must also comply with the labeling, reporting, and record-keeping requirements established in 21 C.F.R. Part 812 AND
    - Refrain from engaging in promotional activities and the other prohibited activities enumerated in 21 C.F.R. §812.7
Device Sponsor Characteristics

- Medical Engineering vs. Pharmaceutical background in R&D
- Often startups or spinoffs that have only one product
  - Goal may be to develop device and attract large device company
  - Once device is developed, may be bought by large company with subsequent upheaval in personnel
- Field team may have mixed level of experience with device studies
- Different mix of professionals
  - e.g.: monitors, clinical device specialists
  - More hands-on, may be present for each deployment
- May have mixed experience with payor coverage, charging, billing, coding and other facility considerations related to devices studies
Device Investigator Responsibilities

- **Regulatory Responsibilities**
  - Ensuring that an investigation is conducted in accordance with a signed agreement, the investigational plan, and FDA regulations
  - Protecting the rights, safety, and welfare of subjects under the investigator’s care
  - Controlling devices under the investigation
  - Disclosing financial interest
  - Ensuring that informed consent is obtained from subjects
    - Investigators, like sponsors, are also subject to certain record-keeping and reporting requirements
Device Investigator Characteristics

- Procedure focused
  - Device-specific training often required
  - Skill level can impact outcomes and AE rates
- Accustomed to limited follow-up visits
- Hospital/facility-based
  - Implants/deployments often require special procedural facilities
  - Special imaging requirements
Device Study Facilities

- Hospital or specialized facilities
- Highly technical setting
  - Specialized clinicians
  - May or may not have research background
- Procedure driven
  - Throughput critical
Hotspots and Challenges
IRB Hotspots

IRB:
- Must understand responsibility in risk determination
- Must adequately document decision-making process
- Must not confuse nonsignificant risk determination with “minimal risk” determination
  - Use of HUDs can be especially challenging
  - IDE regs confused with HUD regs
Sponsor/CRO Hotspots

Sponsor/CRO

- Understanding of device study nuances may be mixed
  - Pricing
  - CMS approval process
  - Billing for IDEs
    - Prequalification of subjects
  - Credentialing requirements for clinical specialists and other personnel
Investigator Hotspots

**Investigator/Research Staff**
- Clinical expertise often critical
- Training requirements must be met
- Device accountability may be challenging
- UADE reporting is less burdensome, but:
  - Sponsor and/or IRB may request more than regs require
  - May request specific range of AEs
Facility Hotspots

Facility

- Local IRBs may pose a challenge in multisite trials, e.g. device determinations
- Presence of clinical device specialists entails credentialing procedures or other access requirements
- CMS submissions included in startup process
- Contractual landmines
  - Risk of Stark, AKS, FCA violations
- More is required of coding, billing, purchasing/procurement personnel
  - Billing errors may occur without robust CT billing process
Patient/Subject Hotspots

Devices are not drugs

- Usually a one-time (permanent implant)
- Pay particular attention to special considerations in device studies during the consent discussion
  - Implants may be permanent
    - Discuss how battery changes will be covered
    - Is explant possible? If so, under what circumstances?
  - Device approval
    - What if it is approved? What are the costs of “maintenance”?
    - What if it is not approved? Are they willing to live with it indefinitely?
  - Often newer models are developed over the course of the study
Case Exercise 1: Identify the Hotspots

Local physician investigator wants to participate in an industry-sponsored study of an investigational implant of IDE pain pump at a community hospital.

- Local IRB will review the protocol
- Physician negotiates and executes CTA directly with sponsor
- Physician is credentialed to implant but not employed by the hospital
- Research coordinators are employees of physician
- Facility personnel assist during implant
- Facility charges for implant procedure
- Device has a battery
Identify the Hotspots

“Local IRB will review…”

- Which of the following items will the IRB want to consider?
  1. How much is the sponsor charging for the device?
  2. Is the physician trained in the use of the device?
  3. Is the device greater than minimal risk?
Identify the Hotspots

“Local IRB will review…”

- Which of the following items will the IRB want to consider?
  1. How much is the sponsor charging for the device?
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Identify the Hotspots

“Physician/PI negotiates directly with sponsor…”

- What contract/budget information will the facility need access to?
  1. List of budget items proposed as “standard of care”
  2. Investigator fees
  3. Record retention terms
  4. Subject injury terms
Identify the Hotspots

“Physician/PI negotiates directly with sponsor…”

- What contract/budget information will the facility need access to?
  1. List of budget items proposed as “standard of care”
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Identify the Hotspots

“The device has a battery….”

- How should this be accommodated?
  1. Dispense extra batteries to the subject
  2. Include replacement costs and charges in the budget/contract negotiation
  3. Include details regarding replacement and cost in the informed consent
  4. Pre-qualify subjects prior to implant
Identify the Hotspots

“The device has a battery….”

How should this be accommodated?

1. Dispense extra batteries to the subject
2. Include replacement costs and charges in the budget/contract negotiation
3. Include details regarding replacement and cost in the informed consent
4. Pre-qualify subjects prior to implant
Case Exercise 2: Identify the Hotspots

An investigator would like to conduct a study of a marketed device for a new expanded application and publish his findings. A colleague at another AMC will participate.

- The manufacturer is willing to provide the devices and some funding, but has declined further involvement.
Identify the Hotspots

“Marketed device…new indication”

What are the implications during IRB review?

1. It’s marketed, so it doesn’t need an IDE
2. A risk determination is unnecessary
3. It must be provided free of charge by the sponsor
4. Animal testing will be needed
Identify the Hotspots

“Marketed device…new indication”

What are the implications during IRB review?

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4. Animal testing will be needed
Identify the Hotspots

“The manufacturer is willing to provide the devices and some funding, but has declined further involvement”

- What does this mean for the physician investigator?
  1. He cannot do the study
  2. He has assumed the sponsor role
  3. He can charge for the devices and thus add to the funding
  4. He must decline the funding
Identify the Hotspots

“The manufacturer is willing to provide the devices and some funding, but has declined further involvement”

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Identify the Hotspots

“A colleague at another AMC will participate…”

What will this require of the sponsor-investigator?

1. He will need to check his CV for appropriate training and expertise
2. He will need to arrange for independent monitoring of the colleague’s records
3. He will have to provide and document training
4. He cannot pay the colleague
Identify the Hotspots

“A colleague at another AMC will participate…”

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Hot Topics

- **Combination products**
  - Possibilities expanding: drug-device, device-biologic, drug-device-biologic
  - Office of Combination Products assigns FDA center for primary jurisdiction

- **Medical apps**
  - Challenges in privacy protections
  - Challenges in assuring adequate consent

- **Connected devices**
  - “Hackability” a concern
  - Privacy a challenge
Conclusion

- Investigational device studies differ from drug studies in important ways.
- Understanding the challenges faced by each of the parties engaged in the process assures success for all.
- All of the challenges related to device studies are surmountable with forethought and good planning.
Meeting the Challenge of Device Studies

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