Overview of Pre-IDE Submissions and IDE Regulations

Medical Device Technology Innovation Partnerships
The University of Virginia
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Investigational Device Exemption (IDE) and Humanitarian Device Exemption (HDE) Programs
Objectives Today

- **IDEs:** When is an IDE necessary?
- Significant Risk v. Non-Significant Risk
- What is a **Pre-IDE**?
- Sponsor-Investigator Studies
- Stages of Medical Device Trials
- Expanded Access
- Custom Devices
- **HDEs:** Requirements for Humanitarian Device Exemptions (HDEs)
Investigational Device Exemptions (IDEs)
Regulatory Requirements for Clinical Studies of Medical Devices

- Informed Consent and Human Subject Protections (21 CFR Part 50)
- Institutional Review Board oversight (21 CFR Part 56)
- Financial Disclosure (21 CFR Part 54)
- Investigational Device Exemption (IDE) application (21 CFR Part 812)
Investigational Device Exemptions (IDEs)

Purpose:

To encourage discovery and development of useful medical devices for human use, to the extent consistent with the protection of the public health and safety and with ethical standards, while maintaining optimum freedom for scientific investigators in their pursuit of that purpose.
Definitions

Investigational Device

- Is still in the developmental stage
- Object of a clinical investigation is to determine safety and efficacy
- Is not considered to be in commercial distribution

Investigational Use

- Clinical evaluation of an already legally marketed device for a new intended use
Provisions of the IDE Regulation

- All clinical investigations subject to IDE regulations must be approved before they can begin
- Assigns responsibilities to all participants in clinical investigation
- All subjects in the investigation must give written informed consent
Studies Subject to Device Regulation

- If used to support a marketing application: PMA, HDE or 510(k), OR
- Collection of safety and effectiveness information (for a new intended use of a legally marketed device, etc.), OR
- Sponsor-investigator studies of unapproved devices or new intended use of approved device (even if no marketing application planned)
SR, NSR or Exempt?
SR, NSR, or Exempt?

All Device Investigations

Studies Subject to the IDE Regulation

SR Investigations
Full Requirements
21 CFR Part 812

Studies Exempt from the IDE Regulation

NSR Studies
Abbreviated Requirements
21 CFR Part 812.2(b)

21 CFR Part 812.2(c)
Studies **Exempt** from Device Regulation (*no IDE needed*)

- Marketed pre-1976 devices or transitional devices
- 510(k)-cleared and HDE- or PMA-approved devices, if used in accordance with approved label
- Basic physiological research
- *In vitro* diagnostic devices (many)
- Consumer preference testing of marketed device
- Combinations of legally marketed devices
- Custom devices (NARROWLY defined)
- Foreign Studies; Declaration of Helsinki
Pre-1976 or Transitional Devices

- Federal Food, Drug and Cosmetic Act Section 520(l)
- “Transitional Provisions for Devices Considered as New Drugs”
- New versions of these devices are not exempt
Pre-1976 or Transitional Devices

Points to consider:

- Devices may have been reclassified
- If significant risk, IDE would be necessary
- If not significant risk, no IDE but subject to 21 CFR 812, 50 and 56
Pre-1976 or Transitional Devices

- Some were classified:
  - Gauze
  - Adhesive Tape
  - Tampons
  - Dialysis Fluid
  - Denture Cushions
Pre-1976 or Transitional Devices

- Others remain in Class III
  - Injectable Silicone
  - Absorbable Sutures
  - Absorbable Dusting Powders
  - Injectable Teflon
Standard of Care

If a marketed product is used in accordance with approved labeling, no IDE is required.

Off-label use, or practice of medicine, is appropriate when no protocol is involved.
“Practice of Medicine”

“Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship….”

From Section 906 of the FD&C Act
“Practice of Medicine”

- Physician should:
  - Be well informed about the product
- Use firm scientific rationale and sound medical evidence
  - Maintain records on use and effects
- IDE not required; institution may require IRB review/ approval and informed consent
- Other prohibitions still apply
Basic Physiological Research

- Investigating a physiological principle or to expand medical knowledge
- No intent to develop the device for marketing
- Only using the device as a tool to address the research question – not the subject of research
- From preamble to Final Rule in 1980 Federal Register

⇒ No IDE needed; IRB approval and IC should be obtained
If NOT Exempt from Device Regulation, then...

- Need to assess whether proposed study of device is considered **SIGNIFICANT RISK (SR)**, or **NONSIGNIFICANT RISK (NSR)**
- IRBs can and do make this assessment most of the time
- FDA can assist IRBs and/or investigators by making risk determinations; this determination is final
Significant Risk (SR) Study

Presents a **potential serious risk** to the health, safety, and welfare of a subject and is:

- an implant; or
- used in supporting or sustaining human life; or
- of substantial importance in diagnosing, curing, mitigating, or treating disease or preventing impairment of human health
Significant Risk (SR) Study Examples

- Evaluation of a marketed biliary stent for use in the peripheral vasculature
- Evaluation of unapproved radiofrequency ablation device for treatment of primary hepatic neoplasia
Significant Risk IDEs

- Sponsor submits application to FDA
- FDA approves, conditionally approves or disapproves IDE within 30 calendar days
- Sponsor obtains IRB approval
- After both FDA and IRB approve the investigation, study can begin
Non-Significant Risk IDEs

- Sponsor presents protocol to IRB and a statement why investigation does not pose significant risk
- If IRB approves the investigation as NSR, it can begin
- Abbreviated IDE requirements (labeling, IRB, consent, monitoring, reporting, prohibition on promotion)
- **No** IDE submission to FDA needed
Non-Significant Risk Study
Examples

- Most functional MRI studies
- Study of non-invasive blood pressure measuring device
- Electroencephalography studies
- Studies of wound dressings
- Contact lens studies
- Studies of conventional laparoscopes
A study is being performed to assess the tolerability of "electropulsation". Electrical pulses with increasing intensity will be applied to human nail until the subject feels mild discomfort.

Answer: NSR
Example

A study is proposed looking at the safety and effectiveness of an cleared daily wear lens to be used as extended wear lens. The lens has undergone some design changes.

Answer: SR
Example

A study is proposed to determine the safety and effectiveness of a prostate tissue diagnostic test obtained by a prostate biopsy to diagnose prostate cancer

Answer: SR
Example

A study looking at patient preference of color of a legally marketed tongue depressor- red, yellow, or white

*Neither SR or NSR*

*Answer: Exempt*
Pre-IDE or Study Determination Inquiry

- If an IRB is uncertain whether a study is exempt, significant risk or non-significant risk, FDA will make a determination
- Brief protocol, device description, and a description of intended population
- FDA will issue a letter; the determination is final
Pre-IDE or Study Determination Inquiry

- Appropriate review division
- 60-day turnaround time
- Also appropriate for OUS studies even if no IDE is planned
What do **ALL** clinical studies of unapproved or investigational medical devices conducted in U.S. have in common?

Same basic applicable regulations REGARDLESS of whether sponsor is a manufacturer or clinical investigator
Sponsor-Investigator

Dual Role: An individual who both initiates and actually conducts the study

Dual Responsibilities: Sponsor and Investigator
Sponsor Responsibilities

- Ultimately LEGALLY responsible for:
  - IRB approval
  - Conduct and monitoring of study
  - Appropriate reporting to IRB and FDA
  - Device disposition
  - Investigator agreements
  - Informing other investigators as needed
  - Adequate record-keeping
  - Labeling
  - Prohibition of promotion/marketing
Investigator Responsibilities

- Sign Investigator Agreement and Commit to:
  - Follow protocol, FDA regs, and IRB/FDA conditions of approval
  - Provide financial disclosure or certification to sponsor initially and updates
- Obtain IRB Approval
  - Initial, for study changes, & at least annually
Investigator Responsibilities

812.140(a)(2) Investigator is responsible for:

(2) Records of receipt, use or disposition of a device that relate to:

(i) The type and quantity of the device, the dates of its receipt, and the batch number or code mark.

(ii) The names of all persons who received, used, or disposed of each device.

(iii) Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.
Investigator Responsibilities

- Conduct Study:
  - Obtain informed consent from subjects
  - Enroll subjects, follow protocol, collect data (fill out CRFs)
  - Submit required reports to IRB and sponsor
Monitoring

- The act of overseeing the progress of a clinical trial and ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and applicable requirements
- Ongoing continuous process
DSMB v. Monitoring

Data Safety Monitoring Board (DSMB)

Monitoring is a different process than oversight of a Data Safety Monitoring Board
Data Safety Monitoring Board (DSMB)

- A group that reviews data from a trial
- They advise the sponsor regarding the continuing safety of trial subjects
- Evaluate data for continuing validity and scientific merit
Monitor

- An individual designated by a sponsor or contract research organization to oversee the progress of an investigation
  - Must be qualified by training and experience to monitor the investigation
  - 21 CFR 812.3(j) & 21 CFR 812.43(d)
Purpose of Monitoring

- Protect human subjects
- Ensure reliability of the data
Monitors Inspect

- IRB approvals
- Informed Consent Documents
- Case Report Forms (CRF)
- Source documents
Monitoring

- Does the sponsor-investigator need to ensure adequate monitoring of the investigation at his/her own site?
Required Elements of an IDE

- **U.S. Sponsor** (manufacturer or investigator)
- Prior Investigations
- Investigational Plan
- Manufacturing Information
- Investigator and IRB Information
- Sales Information
- Labeling
- Informed Consent
- 21 CFR 812.20
21 CFR Part 56: IRBs

- **Extremely important** role in the protection of rights, safety and welfare of human research subjects
- Study risk determinations
- Specific constitution of diverse members (scientists, physicians, clergy, laypeople, attorneys)
- Review protocols, adverse events
- Lots of guidance from FDA and HHS
IRB Responsibilities

- Determine jurisdiction
  - FDA, NIH, “basic physiologic research”

- Determine the risk
  - Minimal risk (expedited IRB procedures)
  - NSR or SR (unless FDA has already decided)

- Review study
  - Approve, approve w/modifications, table pending additional information, disapprove
IRB Responsibilities

- Review informed consent
  - For SR device trials, FDA has reviewed for compliance w/section 50.25
- Review study changes & adverse events; do continuing review
- Submit reports to sponsor & FDA
Custom vs. IDE Device

- **Custom device:**
  - One device which deviates from devices generally available or from premarket approval requirements to comply with requirements of an individual physician for a specific patient.

- **IDE device:**
  - Investigational or experimental
  - May be *customized* to fit an individual patient.
Custom vs. IDE Device

- Custom device:
  - Is not generally available to or generally used by other physicians – one device
  - Made for a specific use in a specific situation
  - Many devices are routinely sized for individual patients; however, they are not custom devices

- IDE device:
  - Available in a clinical trial setting for multiple subjects
  - May be customized to fit a specific patient (e.g., dental devices, orthopedic devices)
Custom vs. IDE device

- **Very few** devices/situations meet the definition of custom!

- Questions: Check with CDRH Office of Compliance or Office of Device Evaluation (IDE/HDE Staff)
Valid Scientific Evidence

Valid scientific evidence is defined in 21 CFR 860.7 as evidence from "well-controlled investigations, partially controlled studies, studies, and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device."

This evidence can come from a variety of sources which range considerably in the quality and level of clinical evidence of safety and effectiveness.
Stages of Medical Device Studies

1) **Exploratory** Stage – first in human and feasibility/pilot studies, iterative learning and product development

2) **Pivotal** Stage – definitive study to support the safety and effectiveness evaluation of the medical device for its intended use

3) **Postmarket** Stage – includes studies intended to better understand the long-term effectiveness and safety of the device, including rare adverse events

- Draft Guidance: “Design Considerations for Pivotal Clinical Investigations for Medical Devices”
  
Early/Expanded Access

- Continued Access
- Treatment Use
- Traditional IDE Study
- Emergency/Compassionate Use

Device Development:

Before IDE
IDE Approval
IDE Completion
Marketing Approval

The University of Virginia
Humanitarian Use Devices (HUDs) and Humanitarian Device Exemptions (HDEs)
Section 520(m) of the Food, Drug and Cosmetic Act

“... to encourage the discovery and use of devices intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals in the United States.” [yearly]
Intent of HDE Provisions

Provide incentive for development of devices intended for treatment or diagnosis, in small patient populations where otherwise a device manufacturer’s R&D costs could exceed market returns.
Statutory Conditions

- Device not otherwise available (through a 510(k) or PMA)

- No comparable device available (through a 510(k) or PMA)

- Device:
  - Does not pose unreasonable risk of illness or injury [i.e., safety is demonstrated], AND
  - Probable benefit outweighs the risk (i.e., exempt from effectiveness requirements of a PMA)
Statutory Conditions

- Approval (HDE) authorizes **marketing** of HUD
- IRB approval required before the device is used
- Local IRB may approve or defer
- Labeling must clearly identify device as HUD, and that effectiveness for that indication has not been demonstrated
- Amount charged cannot exceed cost of research, development, manufacturing and distribution, except for devices with pediatric indications (FDAAA 9/2007)
FDA Approval Threshold

Device does not expose patients to unreasonable risk of illness or injury, AND probable benefit outweighs the risks of using the device, taking into account the probable risks and benefits of alternative therapies.
Examples: Two Fetal Bladder Stents (Double pigtail stent with trocar & guidewire)

Used in fetal urinary tract decompression following the diagnosis of fetal post-vesiculocystic obstructive uropathy in fetuses of 18 to 32 weeks gestational age.

- Alternative Therapies
  - Repeated needle aspirations of fetal bladder
  - Open fetal surgery
Example: Heart Valve
(Surgically implanted bovine jugular vein with a competent tri-leaflet venous valve)

- Indicated for correction or reconstruction of the Right Ventricular Outflow Tract (RVOT) in patients aged less than 18 years with congenital heart malformations such as pulmonary stenosis and Transposition with Ventricular Septal Defect (VSD)

- Alternative Therapies
  - Homografts
  - Polyester conduits
Example: Gastric Stimulator

- Indication
  - Chronic, intractable nausea and/or vomiting secondary to gastroparesis

- Alternative Therapies
  - Drugs
Medically Plausible Subset

If the disease or conditions occurs in >4,000 patients per year, the device could be used in a subset of the disease or condition AS LONG AS sponsor shows the subset is medically plausible (NOT just "readily identifiable").
Medically Plausible Subset

A medically plausible subset is one in which use of the device is limited to that subset because of some inherent property of the device and/or the disease. That is, the sponsor must explain why the device couldn't also be used in all patients with disease or condition.
HUD Designation
(21 CFR 814 Subpart H)

- Request submitted to FDA’s Office of Orphan Products (not CDRH)
- Designates the intended population for the device
  - Must be <4000/year in the U.S.
  - If subset of a larger population, must be “medically plausible” subset
- 45 day review
HDE Review by CDRH

- Ensure HUD designation has first been granted from Office of Orphan Products
- Explanation why device would not otherwise be available
- Statement that no comparable device exists
- Amount charged (can recover R&D, manufacturing and distribution)
- Device description
- No user (MDUFMA) fee
- 75 days
HDE Review by CDRH

- Bench and animal testing
- Clinical experience: data, literature, investigation(s), marketing experience
- Manufacturing information: QSR applies (unless elements waived)
- Labeling (physician and patient), including HUD statement (that no effectiveness demonstrated)
Points of Confusion

- HDE devices are **marketed, NOT investigational**, devices
- Informed consent is not an FDA requirement, but can be (and often is) a state, local, institutional or IRB requirement
- A clinical trial for a new indication requires an IDE for SR devices (so far, all HDEs are SR)
HDEs

- 52 approved HDEs since 1996
- List of approved HDEs and their Summaries of Safety and Probable Benefit (SSPB) available at:

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm
Please Note

- Use of HDE device once approved is not necessarily limited to the HDE indication (IRB can approve “off-label” use)

- Device may also have other different HDE- or PMA-approved indications

- Can have multiple HDEs for the same indication, but once any device is PMA-approved for same indication, FDA may rescind HDEs (due to comparable device)
Off-label Use of HDE-Approved Products

- Individual IRBs may:
  - Disapprove any use of the HDE
  - Approve only on a case by case basis
  - Approve only for “on-label” use
  - Approve for “on-label” use and case by case for “off-label” use
  - Approve for ANY use, on- or off-label
Responsibilities for HDE Holders

- Maintain records of names and addresses of facilities to which HUD is shipped, correspondence with IRBs, and any other information required by reviewing IRB or FDA
Key Points

- HDE is marketing approval
- IRB approval required
- Informed Consent not required by FDA
- No requirement to submit PMA
- Can have multiple HDEs for same indication from different sponsors
HDE vs. PMA

- Both marketing approvals
- Approval thresholds differ:
  - PMA: safety and **effectiveness**
  - HDE: safety and **probable benefit**
- **IRB approval required for using HDE**
- Profit not allowed for HDE, except pediatric indication (can recover costs of R&D, manufacturing and handling)
- No MDUFMA user fees for HDE application
- Both subject to post-market Medical Device Reporting (MDR) requirements
Off-label or Compassionate Use

- HDEs are marketed products
  - Section 906 of the FD&C Act states: “Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship...”
Off-label or Compassionate Use

- Prior FDA approval is not needed for off-label use of a HUD if it is being used in the practice of medicine and not for investigational use.

- IRBs need to determine whether or not they will approve off-label use of HUDs in their facility.
Off-label or Compassionate Use

- If data will be collected on the “off-label” use for research, publication, etc., it is considered an investigational use, and requires an IDE
  - To date, all approved HDEs have been significant risk devices
FDAAA and IRBs

Section 303c:
FDA will issue guidance for institutional review committees on how to evaluate requests for approval for devices for which a humanitarian device exemption has been granted

HDE Guidance 2010:
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm
Resources

- Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors
  - Frequently Asked Questions About Medical Devices
  - Significant Risk and Nonsignificant Risk Medical Device Studies
- Device Advice: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm
Questions/Comments

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