



U.S. Food and Drug Administration

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How to Put Together an IDE Application

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What is an IDE?

- The purpose of an IDE submission
- Different types of IDEs
- What an IDE does/does not permit
- When to seek an IDE
- Clinical Trials Draft Guidance
- Roles of IRBs, investigators and sponsors
- Pre-IDE submissions
- New clinical study requirements for FDAAA

“Investigational Device Exemption”

- An IDE is a **regulatory submission** that permits clinical investigation of devices.
- This investigation is **exempt** from some regulatory requirements.
- The name “Investigational Device Exemption” stems from this description in 21 CFR 812.1:

“An approved investigational device exemption (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device.”

Law ⇒ Regulation

Code of Federal Regulations (21 CFR):

- Part 812 - IDE Regulation
- Part 50 - Protection for Human Subjects, Informed Consent (IC) Regulation
- Part 54 – Financial Disclosure of Investigators
- Part 56 - Institutional Review Boards (IRBs) Regulation

Section 520(g) of the FD&C Act

Purpose of an IDE

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

Purpose of an IDE

An approved Investigational Device Exemption (IDE) allows:

- an investigational device to be used in a clinical study in order to collect **safety and effectiveness** data required to support a Premarket Approval (PMA) application, a Humanitarian Device Exemption (HDE), or a Premarket Notification [510(k)] submission to FDA.
- a device to be **shipped lawfully** for the purpose of conducting investigations

Provisions of the IDE Regulation

- All clinical investigations subject to the regulation must be **approved** before they can begin
- **Assigns responsibilities** to all participants in clinical investigation
- All subjects in the investigation must give **informed consent**

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

Different Types of IDEs

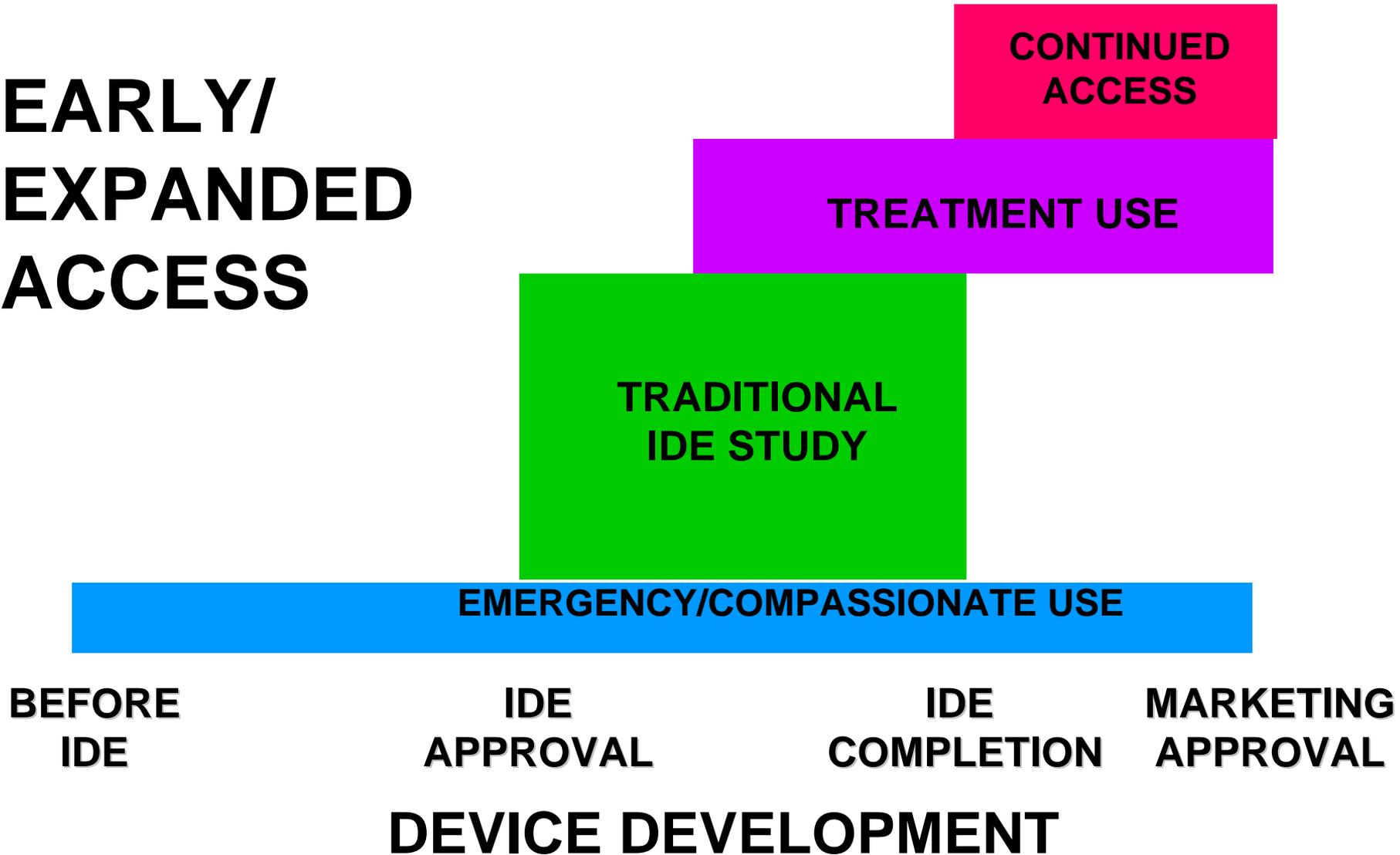
Traditional IDE Study

- **Feasibility** Study (Early or Traditional), including First n Human
- **Pivotal** Study

Expanded Access

- Emergency Use
- Compassionate Use
- Treatment Use
- Continued Access

EARLY/ EXPANDED ACCESS



Approved IDEs are EXEMPT from Regulations Pertaining to:

- Misbranding
- Registration
- Performance Standards
- 510(k)
- PMA
- HDE
- Good Manufacturing Practices (GMPs) except Design Controls
- Color Additive requirements
- Banned Devices
- Restricted Device requirements

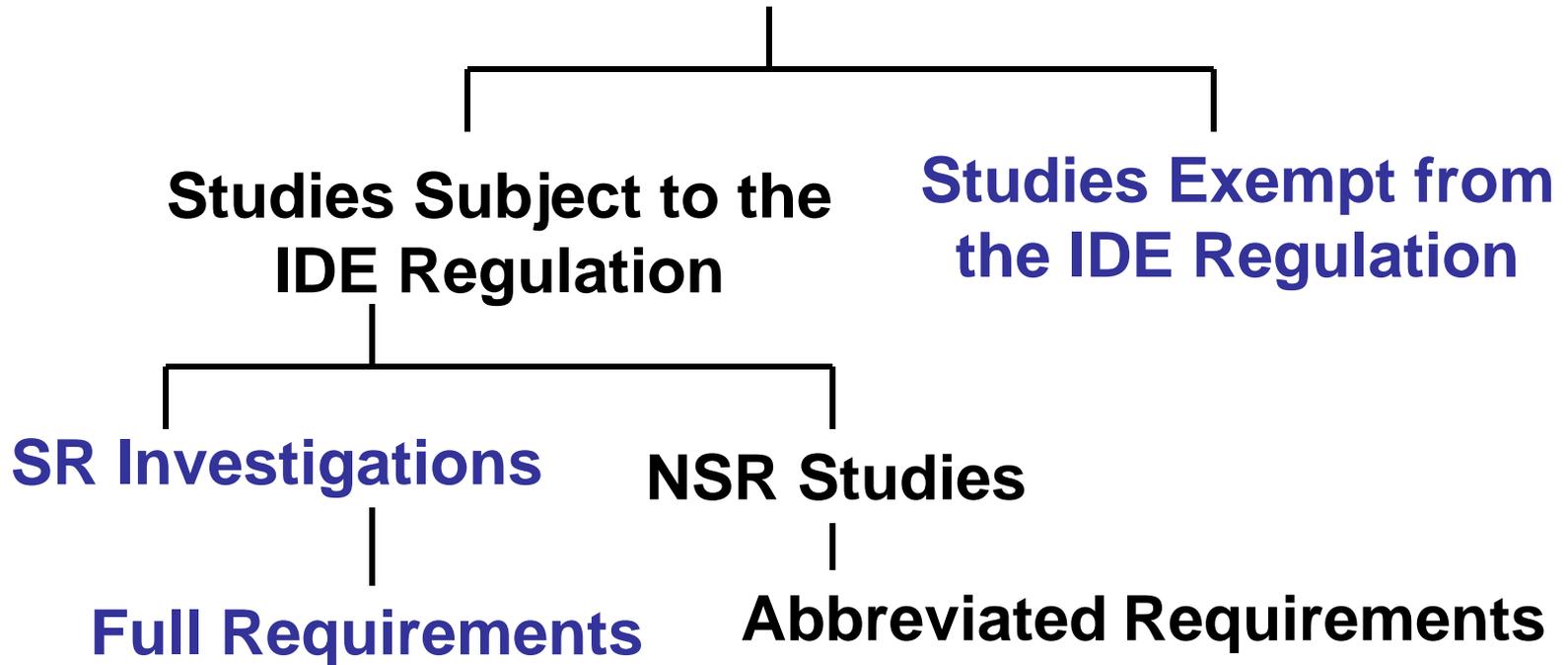
Approved IDEs are NOT EXEMPT from Regulations Pertaining to:

- Adulteration
- Labeling
- Prohibition on: promotion and/or marketing, commercialization, prolonging the investigation, representing the device as safe and effective
- Import/Export

Studies Subject to the Regulation

- To support marketing application [PMA, HDE or 510(k)]
- Collection of safety and effectiveness information (e.g., for a new intended use of a legally marketed device)
- Sponsor-investigator studies of unapproved devices or new intended use of approved device (even if no marketing application planned)

All Device Investigations



Studies Exempt from Need for IDE

- Preamendments (pre-1976) devices
- 510(k)-cleared or PMA-approved devices, if used in accordance with approved labeling
- ***In vitro*** diagnostic devices (most of the time)
- Consumer preference testing
- Combinations of legally marketed devices
- Custom devices (NARROWLY defined)

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
 - No intent to develop the device for marketing
 - Only using the device to address the research question
- ⇒ **No IDE needed**; IRB approval and informed consent 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
- See IRB Information Sheet on SR/NSR:
<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/UCM118082.pdf>

Risk Determinations Can Be Challenging



Based on risk of use of the device in the study

“Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors
Significant Risk and Nonsignificant Risk Medical Device Studies”

Significant Risk (SR) Study

Presents a **potentially 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
- Extended wear contact lenses

Significant Risk IDEs

- Sponsor submits IDE application to FDA
- FDA **approves, approves with conditions 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 (daily wear only)

IDEs for In Vitro Diagnostics (IVDs)

- When an IDE is required for IVD studies, same principles of SR versus NSR apply
- Use of marker(s) to stratify different study arms may result in either SR or NSR
- Correlation studies where marker(s) do not impact patient management in studies
- IVD tests (any combination of equipment, disposables, software, procedure, algorithms) used in clinical trials outside their cleared/approved intended uses are investigational devices

Companion Diagnostics: IDEs and INDs

- May submit an IDE to OIVD or device validation information in an IND to CDER (no need for both since CDER will consult OIVD when appropriate)
- Study may be IND-exempt but still require an IDE

Example

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

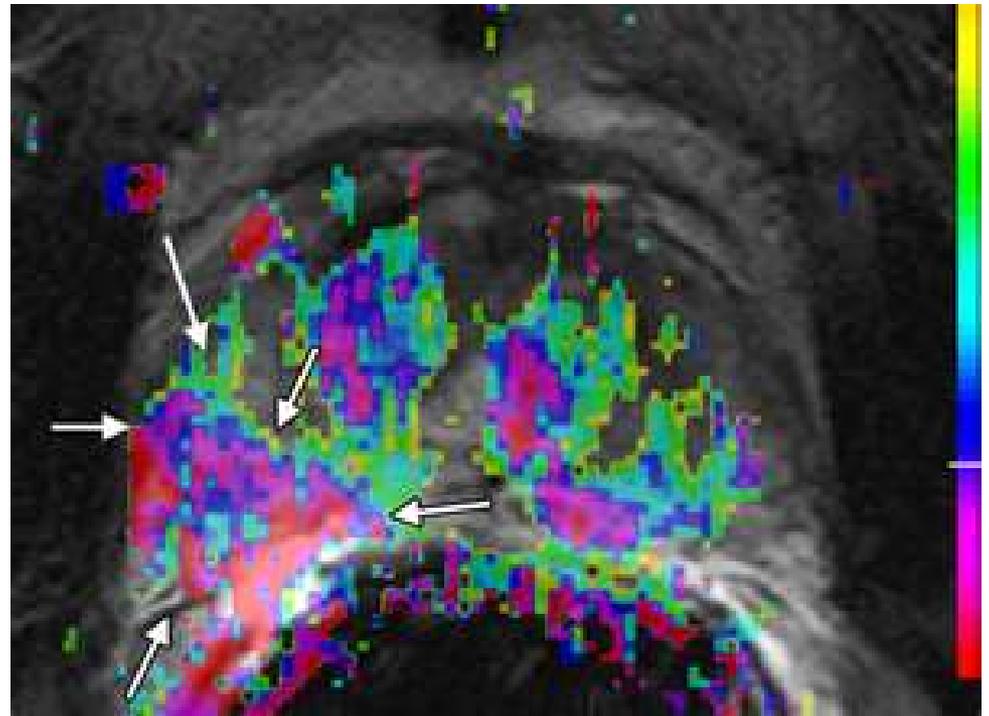
A study is proposed looking at the safety and effectiveness of a cleared daily wear lens to be used as extended wear lens. The lens has undergone some design changes.

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



Study Determination Inquiries

- If an IRB is uncertain whether a study is exempt, significant risk or nonsignificant risk, FDA will make a determination
- Submit an outline/draft protocol and details about the device(s) that are being investigated as a “Pre-IDE” submission.
- FDAs will issue a letter; the determination is binding on the study sponsor and IRBs.

Content of IDE Application

- **U.S. Sponsor** (manufacturer or investigator)
- Prior Investigations
- Investigational Plan
- Manufacturing Information
- Investigator and IRB Information
- Sales Information
- Labeling
- Informed Consent



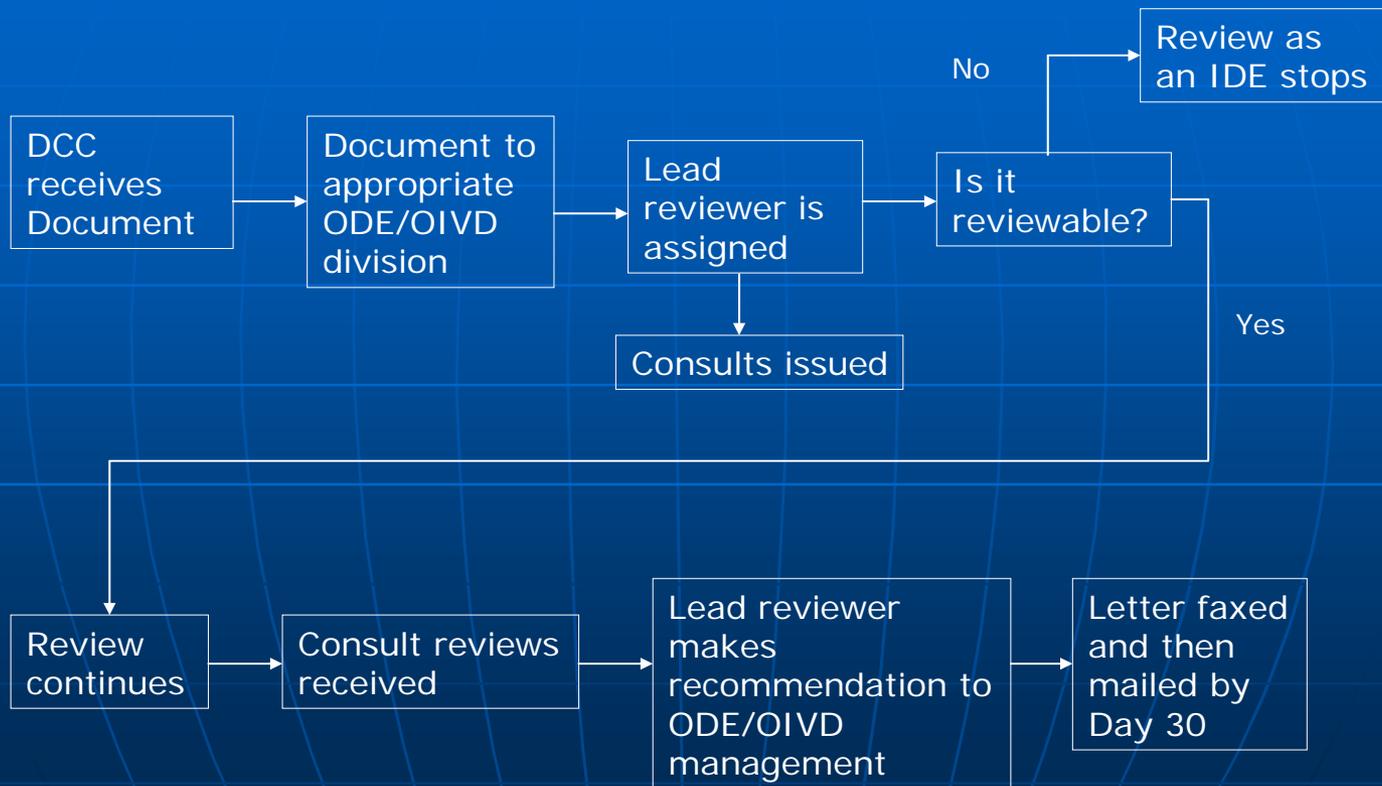
FY2009 IDE Review Decisions

- 222 Original IDEs + 4,503 IDE Supplements out of 9,655 CDRH Submissions means **49% of all CDRH submissions** are IDE-related
- **Approved or Approved with Conditions 56%**
- Disapproved 44%

Reasons for Disapproval

- **Safety**
- **Study Design**

IDE Document Flow



Clinical Trials Draft Guidance

“Design Considerations for Pivotal Clinical Investigations for Medical Devices”

- Issued August 15, 2011
- Deadline for public comment – November 14, 2011
- Intended to help manufacturers and researchers design clinical investigations to satisfy premarket clinical data requirements
- To facilitate design of studies that represent practical investments of time, effort, and resources
- <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm265553.htm>

Stages of Medical Device Studies

- **Exploratory Stage** – first in human and feasibility/pilot studies, iterative learning and product development
- **Pivotal Stage** – definitive study to support the safety and effectiveness evaluation of the medical device for its intended use
- **Postmarket Stage** – includes studies intended to better understand the long-term effectiveness and safety of the device, including rare adverse events

Least Burdensome

- “Least Burdensome” requirements apply for both PMA and 510(k) clinical investigations
- Conducting appropriate studies that satisfy regulatory requirements in an efficient, appropriate and scientifically sound manner provides the least burdensome pathway forward to providing evidence to reasonably assure safety and effectiveness for a given device

Device Categories

- **Therapeutic Devices** – Intended to treat a specific condition or disease
- **Aesthetic Devices** – Provide a desired change in a subject's appearance through physical modification of the structure of the body
- **Diagnostic Devices** – Provides information when used alone or in the context of other information to help assess a subject's condition

Pivotal Study Categories

- **Clinical Outcome Studies** – subjects are assigned to an intervention and then observed or tested at planned intervals using validated assessment tools to assess clinical outcome parameters or their surrogates to determine the safety and effectiveness of the intervention (typically therapeutic/aesthetic devices)
- **Diagnostic Clinical Performance Studies** – determine how well the diagnostic device output agrees with the true target condition (typically diagnostic devices)

Types of Study Designs

- In general, double-masked (blinded), randomized, controlled, multi-center clinical studies are the “gold standard”
- Such studies may not be necessary or feasible in certain situations
- Manufacturers should provide information to advocate for any proposed study design

Pivotal Device Study Review by FDA and Risk to Subjects

- FDA expects that pivotal clinical studies to be scientifically rigorous and to yield robust data regardless of whether the study is a significant risk device study.
- Device manufacturers are encouraged to obtain FDA feedback on study design for pivotal trials. Such advice is available for both significant risk device studies and nonsignificant risk device studies.

Benefit-Risk Determination Draft Guidance

“Draft Guidance for Industry and Food and Drug Administration Staff - Factors to Consider when Making Benefit-Risk Determinations in Medical Device Premarket Review”

- Issued August 15, 2011
- Deadline for public comment – November 14, 2011
- Intended to improve predictability, consistency, and transparency of premarket review decision making
- <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm267829.htm>

How to Comment on Proposed Regulations

- Announcement in Federal Register when comment period begins (90 days, but may be 10 days to 9 months)
- Go to fda.gov home page; guidance document; or to regulations.gov
- Close November 14, 2011 at midnight
- <http://www.fda.gov/RegulatoryInformation/Dockets/Comments/default.htm>

Sponsor Responsibilities

- Ultimately LEGALLY responsible for:
 - IRB approval
 - Conduct and monitoring of study
 - Reporting to IRB and FDA (initial, continuing, final, unexpected AEs, study suspension, device recall, emergency use, IRB withdrawal, etc.)
 - Device disposition
 - Investigator agreements
 - Informing other investigators as needed
 - Adequate record-keeping
 - Labeling
 - Prohibition of promotion/marketing

Investigator Responsibilities

- Sign Investigator Agreement-- 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

- Conduct Study:
 - Obtain informed consent from subjects (note: subjects are considered enrolled in the study when they sign the IC)
 - 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
- New Draft Guidance: “Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring” issued 8/24/2011 – comment until 11/24/11

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf>

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

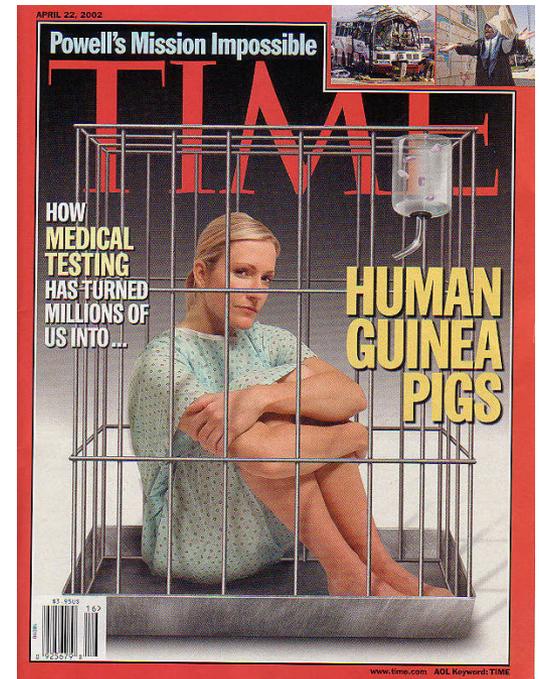
- Assures that appropriate steps are taken to protect the rights, safety and welfare of humans participating as subjects in the research.
- Group process to review research protocols
- FDA requires IRB registration (if they review FDA-regulated studies)
- Many institutions have their own IRB; there are also independent/contract IRBs
- An IRB must comply with all applicable requirements of the IRB regulation (Part 56) and the IDE regulation (Part 812)
- FDA does periodic inspections of the IRB's records and procedures to determine compliance with the regulations.

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 with modifications, table pending additional information, disapprove

IRB Responsibilities

- Review informed consent
 - For SR device trials, FDA has reviewed for compliance with section 50.25
- Review study changes and adverse events; do continuing review
- Submit reports to sponsor and FDA



The IDE Pre-Submission Program

1999 Guidance:

- Goal is to benefit the sponsor
- Not a pre-requisite for an IDE
- Single cycle

Pre-IDE is appropriate:

- During testing or protocol development
- For NSR study protocols
- To determine whether a significant or non-significant risk device study
- For *in vitro* diagnostic device study protocols
- Study protocols to be conducted outside U.S. (OUS)

The IDE Pre-Submission Program

Pre-IDE is not appropriate:

- If device or indications for use are not well characterized
- For an in-depth review of data
- To determine regulatory path [510(k) vs. PMA]
- To determine jurisdiction for combination products
- To determine the device classification

Food and Drug Administration Amendments Act (FDAAA) TITLE VIII – CLINICAL TRIAL DATABASES

- Expands ClinicalTrials.gov clinical trial registry to include devices, and adds results database
- Primarily responsibility of NIH to implement
- Expanded Results Database – 9/28/2010
- Information on how to register is available on the National Library of Medicine (NLM) Protocol Registration System (PRS) website (<http://prsinfo.clinicaltrials.gov/>)
- NIH Fact Sheet on Registration:
<http://prsinfo.clinicaltrials.gov/s801-fact-sheet.pdf>

Resources

- Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm>

- Frequently Asked Questions About Medical Devices
- Significant Risk and Nonsignificant Risk Medical Device Studies

- Device Advice:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm>

- CDRH Learn:

<http://www.fda.gov/Training/CDRHLearn/default.htm>

Science & Research

Science and Research Special Topics

Running Clinical Trials

Guidances, Information Sheets, and Notices

Resources for You

- Federal Register Notice: Protection of Human Subjects
- A Self-evaluation Checklist for IRBs

Information Sheet Guidances Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors

Background

Through FDA's new Information Sheet Guidance Initiative, these Information Sheets will be revised and updated as needed. The date of the most recent revision is listed next to the title. [Learn more about this initiative.](#)

General

- [Frequently Asked Questions \(1998\)](#)
- [IRB Information Sheets--Research and Review \(Updated 9/98\) -- Cooperative Research \(1998\)](#)
- [Non-Local IRB Review \(1998\)](#)
- [IRB Information Sheets--Research and Review \(Updated 9/98\) \(1998\)](#)
- [Sponsor-Investigator-IRB Interrelationship](#)

Medical Devices

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Postmarket Requirements (Medical Devices)
Compliance Activities (Medical Devices)
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Information for regulated industry on determining how to comply with the federal laws and regulations governing medical devices.

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CDRH Learn

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CDRH Learn is our latest innovative educational tool. It consists of a series of training modules describing many aspects of medical device and radiological health regulation, covering both premarket and postmarket issues. This tool is intended to provide the medical device and radiological health industry with an information resource that is comprehensive, interactive, and easily accessible.

Disclosure:

The presenters are FDA/CDRH staff and therefore, as employees, have claimed no interests, financial or otherwise, with medical device or radiation-emitting products that may be shown in any of the presentations.

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