

**IDEs and HDEs for IRBs
and Clinical Investigators**

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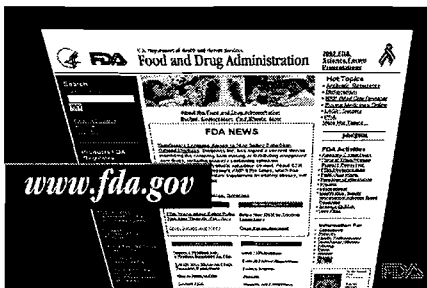
Objectives Today

- Investigational Device Exemptions (IDEs)
- Early/Expanded Access of Investigational Devices
- Humanitarian Device Exemptions (HDEs)
- FDA Amendments Act of 2007

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FDA



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U.S. Food and Drug Administration



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Regulatory Requirements for Clinical Studies of Medical Devices

- Informed Consent and Human Subject Protections
- Institutional Review Board **oversight**
- Financial Disclosure
- Investigational Device Exemption (IDE) application

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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

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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

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Provisions of the IDE Regulation

- All clinical investigations subject to FDA oversight 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

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Studies Subject to Device Regulation

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

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Studies Exempt from Device Regulation (no IDE needed)

- Pre-1976 devices
- 510(k)-cleared and HDE- or PMA-approved devices, *if used in accordance with approved label*
- *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

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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/oc/ohrt/irbs/devices.html#risk>

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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

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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

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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

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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

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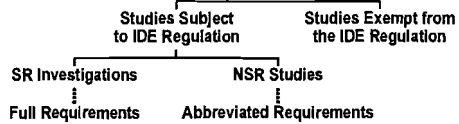
Non-significant Risk Study Examples

- 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

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All Device Investigations



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Study Determination Inquiries

- If an IRB is uncertain whether a study is exempt, significant risk or nonsignificant risk, FDA will make a determination
- E-mail me a draft or outline of the study and a clear description of the devices
- FDAs will issue a letter; the determination is final

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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

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Applicable Regulations

- 21 CFR Part 50:
Informed Consent,
Human Subject Protections
- 21 CFR Part 54:
Financial Disclosure
- 21 CFR Part 56:
Institutional Review Boards
- 21 CFR Part 812:
Investigational Device Exemptions

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SPONSOR Responsibilities

- Ultimately LEGALLY responsible for:
 - IRB approval
 - Conduct and monitoring of study
 - Appropriate reporting to IRB and FDA (*initial, continuing, final unexpected adverse events, 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

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Who can conduct clinical trials?

21 CFR 812.3(e) *Institution* means a person, other than an individual, who engages in the conduct of research on subjects or in the delivery of medical services to individuals as a primary activity or as an adjunct to providing residential or custodial care to humans.

The term includes...hospitals, retirement homes, and physicians' offices. There is no requirement for certification, but they must meet certain standards.

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"A sponsor is responsible for assuring, through personal contact between the monitor and each investigator, that the investigator clearly understands and accepts the obligations incurred in undertaking a clinical investigation."

Monitoring Guidance:

http://www.fda.gov/ora/compliance_ref/bi_mo/clinguid.html

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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

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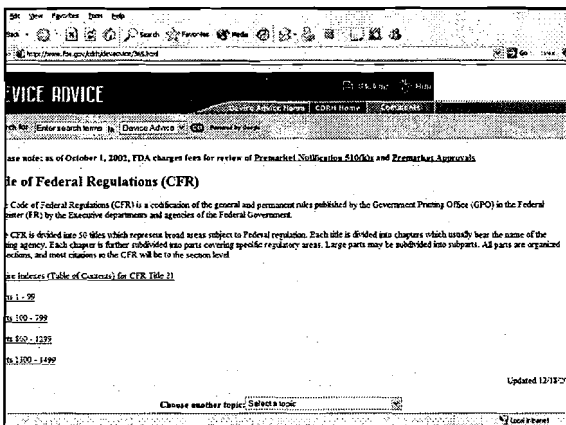
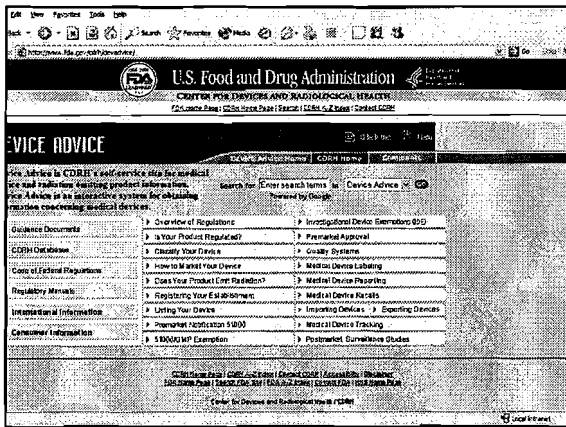
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Investigator Responsibilities

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

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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

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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

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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

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Early/Expanded Access Provisions

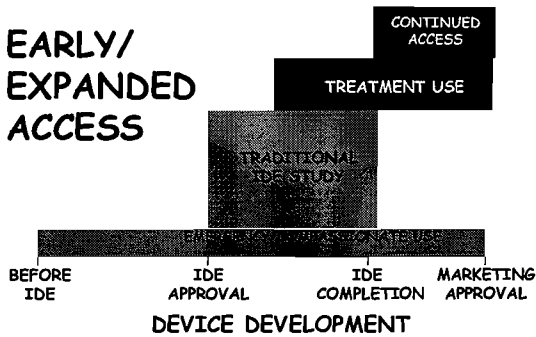
- Emergency Use
- Single Patient/Small Group ("Compassionate Use")
- Treatment Use
- Continued Access

<http://www.fda.gov/cdrh/devadvice/ide/early.shtml>

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EARLY/ EXPANDED ACCESS



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Emergency Use

- **Life-threatening or serious** condition; no alternative
- Before or during an IDE
- Prior FDA approval not required or given – no time (Note that being scheduled for tomorrow does not constitute "emergency")
- **LIMITED** number of patients
- If multiple uses anticipated, prospectively submit IDE or create separate EU arm to existing IDE

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Emergency Use

- Provide documentation to FDA within 5 working days after sponsor learns of use
- Report should include circumstances of case and patient protection measures followed, including:
 - Informed consent
 - Institutional clearance
 - Concurrence of IRB Chairperson
 - Independent assessment from an uninvolved physician
 - Authorization from IDE sponsor if IDE exists, or manufacturer
- Provide monitoring plan and followup information

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Single Patient/Small Group ("Compassionate Use")

- Serious condition; no alternative
- Before or during an IDE
- Prior FDA approval required (30 calendar day review timeframe, usually much less)
- Intended for LIMITED number of patients
- If multiple uses anticipated, prospectively submit IDE or create separate CU arm to existing IDE

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Single Patient/Small Group ("Compassionate Use")

- Request to FDA should include circumstances of case and patient protection measures to be followed, including:
 - Informed consent
 - Institutional clearance
 - Concurrence of IRB Chairperson
 - Independent assessment from an uninvolved physician
 - Authorization from IDE sponsor if IDE exists, or manufacturer
- Provide monitoring plan and followup information

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Treatment Use IDE 21 CFR 812.36

Intended to:

- Facilitate availability of promising new therapeutic devices to patients as early in device development process as possible
- Obtain additional safety and effectiveness data to complement pivotal study dataset

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Treatment Use IDE

- Life-threatening or serious condition
- During or after IDE; no comparable or satisfactory alternative
- Prior FDA approval required
- Wide access
- Flexibility in design, monitoring and followup compared to pivotal trial

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Continued Access

- Intended to:
 - "Extend investigation" while marketing application prepared
 - Allow collection of additional safety and effectiveness data
- IF there is a public health need for device, and preliminary evidence that device is likely to be effective and no significant safety concerns identified

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Continued Access

- Starts after the pivotal IDE study is complete and marketing application is being prepared/reviewed
- Prior FDA approval required
- Controlled access (same investigators and enrollment rate as in pivotal trial)

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Custom vs. IDE device

- Custom device:
 - 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

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Custom vs. IDE device

- Custom device:
 - Is not generally available to or generally used by other physicians
 - Made for a specific use in a specific situation
 - Many devices are routinely sized for individual patients, however, they are not custom devices
- IDE devices
 - Available in a clinical trial setting for multiple subjects
 - May be customized to fit a specific patient (e.g., dental devices, orthopedic devices)

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Custom vs. IDE device

- **VERY VERY FEW** devices/situations meet the definition of custom!
- Questions: Check with CDRH Office of Compliance or Office of Device Evaluation (IDE/HDE Staff)

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Humanitarian Use Devices (HUDs) and Humanitarian Device Exemptions (HDEs)

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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]

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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**

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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)

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Statutory Conditions

- Approval (HDE) authorizes **marketing** of HUD
- IRB approval required before the device is shipped and 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)

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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

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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

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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)

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- ~43 approved HDEs since 1996
- List of approved HDEs and their Summaries of Safety and Probable Benefit (SSPB) available at:

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2>

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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)

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Off-label use of HDE-approved products

- FDA does not regulate the practice of medicine (i.e., "off-label" use): see Section 906 of FD&C Act
- Each IRB approval **MAY or MAY NOT** allow for use of HDE-approved product outside approved indication (i.e. "compassionate use")
 - Each IRB approval needs to be very specific and detailed as to what it is approving with respect to use of the product at its own institution

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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

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Off-label ("compassionate") use of HDE-approved devices

- FDA recommends (but cannot **require**) that off-label ("compassionate") use follow same patient protection guidelines as for investigational/unapproved products and submit to Agency for FDA written concurrence prior to use

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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

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Responsibilities for **Users** of HUDs

- Obtain IRB (initial full and continuing (may be expedited)) approval **before** HUD is used in patient as IRB sees fit (e.g., individual approvals, use under specific protocol, or no further restrictions)
- Emergency off-label use provision
 - Yes, but strongly recommend following certain patient protection measures (IRB chair's concurrence, informed consent, independent assessment by uninvolved physician, authorization from HDE holder, followup report to HDE holder (who sends to FDA))
- Compassionate Use provision
 - Yes, but strongly recommend following above patient protection measures **before** use of device and prior FDA concurrence, including description of circumstances and why alternative therapies unsatisfactory

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Responsibilities for **Users** of HUDs

- Use of a HUD for treatment of individual patients does not constitute research; **however**, if data being collected on a **new** indication, this is research and requires an IDE (if significant risk)
- FDA does not require Informed Consent in this circumstance (since not research), but this does not preclude state, institution or IRB from requiring prospective informed consent (HDE Patient Labeling also useful)
- No IDE required for research to collect safety and effectiveness data to support a PMA or 510(k) **IF done in accordance with approved labeling**, but IRB approval and informed consent are still required (21 CFR Parts 50 and 56)

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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

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HDE vs. PMA

- Both marketing approvals
- Approval thresholds differ:
 - PMA: safety and **effectiveness**
 - HDE: safety and **probable benefit**
- **IRB approval required for shipping of 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

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Points of confusion

- HDE devices are **marketed, NOT investigational**, devices
- FDA does not recommend a CMS category for HDE devices (as for IDE studies)
- 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)

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Resources

- Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors
 - Frequently Asked Questions About Medical Devices
 - Significant Risk and Nonsignificant Risk Medical Device Studies
- Guidance: Humanitarian Device Exemption (HDE) Regulation: Questions and Answers
- Device Advice:
<http://www.fda.gov/cdrh/devadvice/>

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FDA

- FDA Amendments Act (FDAAA) of 2007
- Pediatric Device Safety and Improvement Act of 2007
 - Profit on new HDEs intended for use in a pediatric population
 - Guidance to IRBs on the review of HDEs
- Clinical Trials Databases
 - Mandatory reporting of certain device clinical trials on ClinicalTrials.gov
 - Initial reporting of protocol information on ongoing trials
 - Expanded later to include detailed results

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Questions/Comments

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