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Clinical Investigations:

Investigational Device Exemption (IDE), Institutional Review Boards (IRBs) and Informed Consent

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November 16, 2021

Purpose of an IDE

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- An approved Investigational Device Exemption (IDE) allows:
  - An investigational device to be used in a clinical study in order to collect safety and efficacy 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
- Failure to obtain an IDE when required is in violation of 21 USC 331 prohibition on distribution of unapproved/uncleared devices

IDE Overview

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- Investigational Device Exemption (IDE) regulations (21 C.F.R. Part 812)
  - Apply to all clinical investigations of devices to determine safety and effectiveness
  - FDA oversight of conduct of study, use of device, protection of human subjects (21 C.F.R. Part 50)
  - FDA review depends upon determination of Significant Risk (SR) or Nonsignificant Risk (NSR) Device
    - Determination made by sponsor, then IRB
    - FDA oversight - submit for Study Determination (via pre-submission)

Purpose of IDE Regulations

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- To encourage,
  - to the extent consistent with the protection of public health and safety and with ethical standards,
  - the discovery and development of useful devices intended for human use
- To maintain optimum freedom for scientific investigators in their pursuit of this purpose
- To permit shipment of investigational device for clinical study

Approved IDEs are Exempt From:

- Misbranding
- Registration/Listing
- Premarket Notification
- Performance Standards
- Banned Device Regulation
- Records and Reports
- Restricted Device Requirements
- Good Manufacturing Practices
- Color Additive Requirements
- Unique Device Identifier requirements

Approved IDEs are NOT Exempt From:

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

Significant and Non-significant Risk Device Investigations. When is an IDE required?

Significant Risk vs. Non-Significant Risk Device Studies

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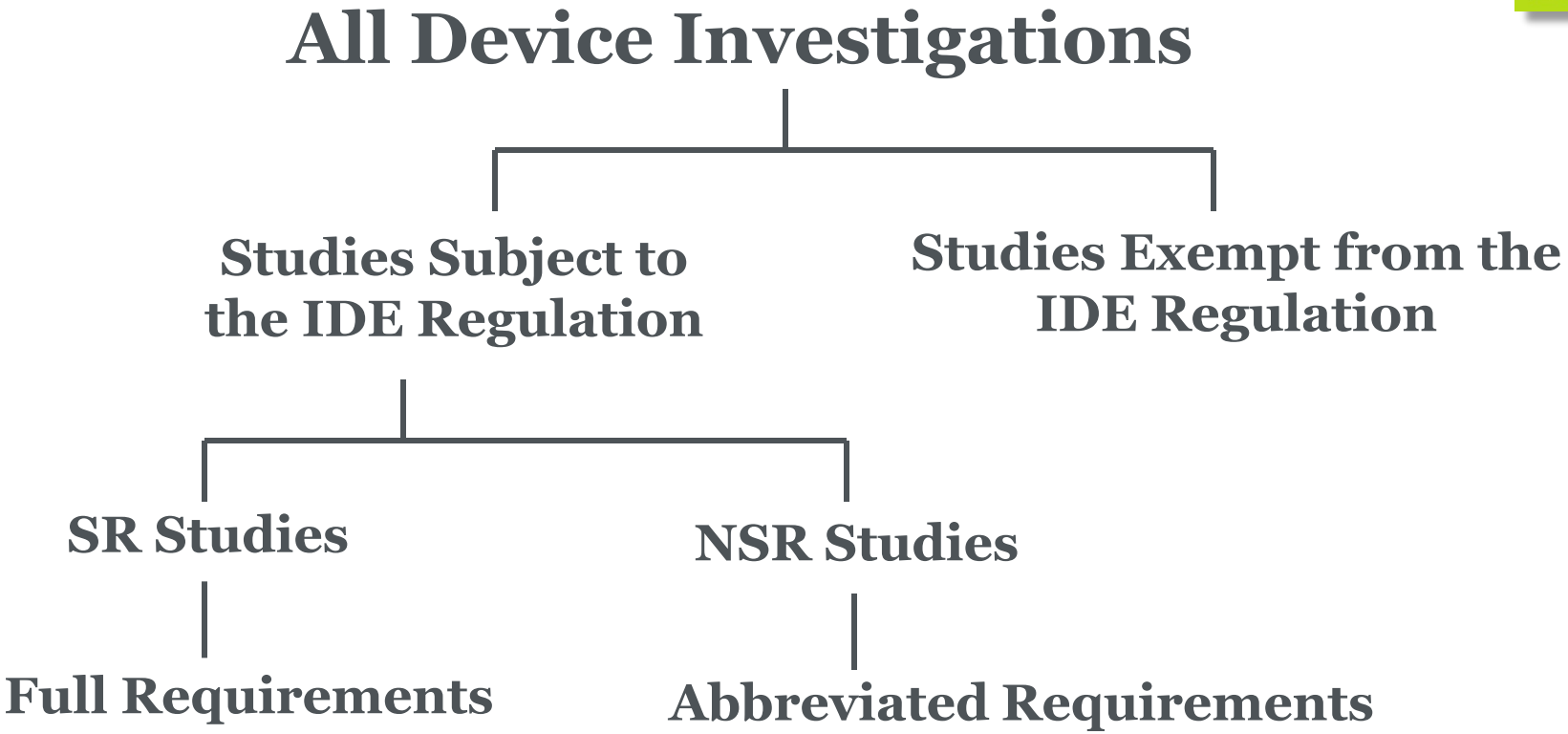

IDE Exempted Investigations (§ 812.2(c))

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- Pre-1976 devices – in accordance with indications in labeling in effect at that time (pre-amendment devices)
- Substantially equivalent devices – in accordance with indications in cleared labeling
- Diagnostic devices
  - Noninvasive
  - Does not require invasive sampling that presents significant risk
  - Does not introduce energy into subject
  - Is not used for diagnosis without confirmation
- Testing of consumer preference, of a modification, or of a combination of devices in commercial distribution, when not determining safety or effectiveness and not putting subjects at risk
- Veterinary devices or research on/with laboratory animals
- Custom devices (as defined in 812.3(b)) - 3D printed devices may not be custom

Significant and Non-Significant Risk Devices

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- Dictate whether an IDE application and FDA approval is required prior to initiating the study and requirements during study
- Investigational review board and company can make an initial determination
- FDA is the final arbiter

Significant Risk Device

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- Significant risk (SR) device means an investigational device that:
  - (1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - (2) 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;
  - (3) 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
  - (4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject
- Full IDE required with FDA and IRB approval
  - Before enrolling any patients
  - For studies conducted in the United States

Nonsignificant Risk (NSR) Device

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- No significant risk to subject
- Abbreviated IDE requirements
  - No FDA approval or review of study
  - Institutional Review Board (IRB) approval required
  - Monitoring, records and reports required

Significant Risk vs. Non-Significant Risk Device Studies

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	Significant Risk	Non-Significant Risk
FDA Approval	Yes	**No**
IRB Approval	Yes	Yes
Informed Consent	Yes	Yes
Reporting	Yes	**Limited**
Record Keeping	Yes	**Limited**
Used for 510(k) or PMA	Yes	Yes

When is an IDE Required for a Cleared/Approved Device?

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- Change from a general to a specific indication for use
  - Definition: any proposed increase in the level of specificity of the indication for use of a device
  - Examples: narrow the indication for use with respect to function, target population, organ or organ system, tissue type, disease entity, or analyte
- Risk – Does a specific use introduce new risks not normally associated with the device's general use?
- Public health impact – Does a specific use impact public health to a significantly greater degree than the general use of the device (e.g., due to changes in target population)?

IDE Application

Pre-Submissions Filings/Meetings

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- A formal submission for informal advice
- Nonbinding on agency but creates a record with meeting minutes
- Company must prepare submission with required information and include concrete proposals for discussion
- 90 day review schedule (goal is 75 days)
- Appropriate topic areas:
  - Investigational plan – OUS and US
  - Complex testing
  - Novel device

The IDE Pre-Submission Program

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- Pre-IDE submission 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

IDE Application (§ 812.20)

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- Report of previous investigations (§ 812.27)
- Device description
- Description of methods/controls/facilities for manufacturing, processing, packing and storage of device
- Labeling
- Investigational plan (§ 812.25)
- Sample investigator agreement
- Certification that investigators sign agreement
- List of IRBs, institutions, and investigators
- Justification for amount charged for device
- Informed consent forms and materials

Report of Prior Investigations

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- Preclinical test reports - biocompatibility, laboratory/ bench, animal
  - Describe level of compliance with GLPs
- Bibliography of all publications
- Copies of all published/unpublished adverse information
- Summary of all other unpublished information (*e.g.*, clinical studies), including adverse events

Labeling

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- Adequate directions for use
- Caution Statement:

  "Caution - Investigational Device, Limited by Federal (or United States) Law to Investigational Use."

- Cannot be promoted as safe/effective for investigational use

Investigational Plan

- Purpose
- Protocol
- Risk analysis
- Device description
- Monitoring procedure
- Labeling
- Case report forms (CRFs)
- IRB information
- Other institutions
- Additional records/reports

Informed Consent

- Include all material information
- No exculpatory language
- Emphasis that participation is voluntary
- Reading level to be considered
- Required elements

Outside of the United States (OUS) IDE Data

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- FDA amended regulation on acceptance of OUS data on February 21, 2018
- OUS data must be from investigations conducted in accordance with good clinical practice (GCP) guidelines including:
  - Approval by an independent ethics committee
  - Informed consent from subjects
- Data must be applicable to the U.S. population and medical practice
- Studies conducted in accordance with local laws and regulations
- Applicants must explain GCP variances and may request a waiver from one or more applicable GCP requirements (21 C.F.R. 812.28(c))

Clinical Investigators Qualifications

- CI must be qualified by experience and training
  - Copy of current medical license
  - Copy of curriculum vitae and relevant experience
  - Board certification
  - Key opinion leaders not required but recommended
- CIs with history of the following are not recommended:
  - Significant 483s
  - Untitled letters, Warning Letters
  - Previously terminated for a clinical study
- Ability to recruit required number of subjects and appropriate subjects that meet protocol criteria
- Also note:
  - Adequate staff and facilities
  - Investigator's workload

Financial Disclosure for Clinical Investigators

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- Disclosure required for:
  - Compensation where value of compensation could be affected by outcome of investigation
  - Proprietary interest in tested product
  - Equity interest in sponsor of covered study
  - Equity interest in a publicly held company that exceeds $50,000
  - Significant payments of other types
    - Cumulative monetary value > $25,000; or
    - Made by sponsor to investigator or investigator's institution exclusive of the costs of the clinical study or other clinical studies
- Complete a certification form that these do not apply or provide the details

Disqualifying Clinical Investigators (§ 812.119)

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- Grounds for disqualification
- Repeatedly or deliberately failed to comply with regulations
  - Repeatedly or deliberately submitted false information to sponsor or in required reports
- Effect of disqualification
  - Investigator ineligible to receive test articles
  - Each application or submission to FDA containing data reported by disqualified investigator will be reviewed to determine if contains any unreliable data that was essential to approval or clearance
    - May result in withdrawal of approval
- Reinstatement
  - If investigator presents adequate assurances that they will comply with regulatory requirements for investigational devices

FDA Actions

FDA Review of IDE

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- FDA sends acknowledgement with IDE number: GYYXXXX (e.g., G160001)
- IDE sent to appropriate review division based on intended use
- Lead reviewer assembles team of experts to review the application and make decision with management concurrence within 30 days
  - Interactive questions typical prior to 30-day review deadline
- FDA issues a decision letter to the sponsor

FDA Decisions and Letters

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- **Approval**
  - Approves the trial for specified number of sites and subjects
  - Enrollment can begin once IRB approval is obtained
- **Approval with conditions**
  - Approves the trial for specified number of sites and subjects provided conditions (deficiencies) are addressed within 45 days
  - Enrollment can begin once IRB approval is obtained
- **Disapproval**
  - Study may not begin; sponsor must address deficiencies and obtain FDA approval to start study
- Other elements in letters include: study design considerations and future considerations

Disapproval of IDE Application (§ 812.30)

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- Grounds for disapproval:
  - Failure to comply with regulatory requirements
  - Failure to respond to FDA request for additional information
  - Risk to subjects outweighs benefits; investigation scientifically unsound; there is reason to believe device is ineffective
  - Untrue statement of material fact
    - Inadequate information:
    - ROPI
    - Informed consent
    - Methods, facilities or controls for manufacture, processing, packing or storage of device
    - Monitoring
- FDA can also withdraw approval

Disapproval of IDE Application (§ 812.30)

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- Food and Drug Administration Safety and Innovation Action (FDASIA)
- Secretary shall not disapprove an application under this subsection because the Secretary determines that

i. the investigation may not support a substantial equivalence or de novo classification determination or approval of the device;

ii. the investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or

iii. an additional or different investigation may be necessary to support clearance or approval of the device.

IDE Amendments

- After submission of an original IDE, FDA tracks subsequent submissions to the IDE as Supplements, Reports, or Amendments
- Any response to a deficiency letter is an Amendment to the submission for which the deficiency letter was sent
  - FDA does not consider responses from submitters to FDA deficiency letters to be Supplements.
- IDE deficiencies are commonly related to:
  - Inadequate report of prior investigations
  - Inadequate investigational plan
  - Inadequate/incomplete design and manufacture
- Amendments may be submitted to each of three parent document types: Original IDEs, IDE Supplements, and IDE Reports for which FDA issued the deficiency letter
- Multiple Amendments will be accepted until all deficiencies have been resolved

IDE Supplements

IDE Supplements

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- Changes in Investigational Plan
  - Change may affect scientific soundness
  - Change may affect patient's rights, safety, or welfare
  - Change may affect validity of data from investigation
  - Does not apply to changes to protect life or physical well-being of a subject in an emergency (but this must be reported to FDA within 5 working days after Sponsor learns of it)
- Significant change in device design or basic principles of operation not based on study information

Changes Requiring an IDE Supplement

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Examples:

- Change in indication
- Change in type or nature of study control
- Change in primary endpoint
- Change in method of statistical evaluation
- Early termination of the study (except for reasons related to patient safety)
- Increasing the number of investigational sites
- Increasing the number of study subjects
- Significant change in device design or basic principles of operation not based on study information

5 Day Notice (§ 812.35(a)(3))

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- Certain changes which don't meet the requirements of an IDE supplement
- Prior FDA approval not required
- Notice of the change to the IDE within 5-working days
- Changes to devices are deemed to occur on the date the device manufactured incorporating the design or manufacturing change is distributed to the investigator(s)
- A description of the change to the device or manufacturing process

Changes Requiring a 5-Day Notice

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- Examples
  - Developmental changes in the device that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of the investigation
  - Certain changes to clinical protocol
  - Modification of inclusion/exclusion criteria to better define the target patient population
  - Increasing the frequency at which data or information is gathered
  - Inclusion of additional patient observations or measurements
  - Modifying the secondary endpoints

Changes Appropriate For Annual Report

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- Changes may be reported in the annual progress report for the IDE if the changes do not affect:
  - the validity of the data or information resulting from the completion of the approved protocol or the relationship of likely patient risk to benefit relied upon to approve the protocol
  - the scientific soundness of the investigational plan
  - the rights, safety, or welfare of the human subjects involved in the investigation (812.150(b)(5))
- Examples:
  - the purpose of the study
  - risk analysis
  - monitoring procedures
  - labeling
  - Limited changes to informed consent materials
  - IRB contact information

Abbreviated Requirements (NSR Study)

Non-significant Risk IDEs

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- 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
- **No** IDE submission to FDA needed
- Abbreviated IDE requirements (labeling, IRB, consent, monitoring, reporting, prohibition on promotion)

Non-significant Risk Study Examples

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- Most functional MRI studies
- Study of non-invasive blood pressure measuring device
- Electroencephalography studies
- Studies of wound dressings
- Contact lens studies (daily wear only)
- Studies of conventional laparoscopes

Treatment Use and Humanitarian Use IDEs

Treatment IDE

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- Facilitate the availability of promising new devices to desperately ill patients
- Conditions:
  - The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition
  - No comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population;
  - Device is under investigation in a controlled clinical trial for the same use under an approved IDE, or all clinical trials have been completed; and
  - Sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence
- Must submit Treatment IDE

Compassionate Use

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- Protocol deviation to treat specific patient or limited group of patients
- Prior FDA approval required
- IDE supplement
  - Patient's condition and the circumstances necessitating treatment;
  - Why alternatives therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition
  - Identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient
  - Patient protection measures that will be followed

ClinicalTrials.gov

ClinicalTrials.gov

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- A web-based resource that provides patients, their family members, health care professionals, researchers, and the public with access to information on publicly and privately supported clinical studies
- Created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA)
- Information on ClinicalTrials.gov is provided and updated by the sponsor or principal investigator (responsible party) of the clinical study

What Trials Must be Registered

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- All prospective clinical studies of health outcomes comparing an intervention with a device to a control in human subjects that meet one of the following criteria:
  - Under U.S. IDE;
  - Not under IDE, but of a device that was previously cleared/approved in the United States;
  - Not under IDE, but used to support a U.S. marketing application (i.e., 510(k), PMA, or HDE); or
  - Not under IDE and conducted outside the United States, but having a nexus to the U.S. (e.g., the device is manufactured in the U.S. and exported for study abroad, or a study site is in the U.S.)
- All such above trials that:
  - Were initiated after September 27, 2007;
  - Were initiated before September 27, 2007, but still on-going on as of December 26, 2007

Additional Registration Information

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- Registration requirements also include:
  - Pediatric postmarket surveillance of a device ordered by FDA under Section 522 of the FDCA (although not a clinical trial)
  - Combination products having a device primary mode of action
- Which trials do not have to be registered?
  - Retrospective studies, ad hoc analyses, and meta-analyses
  - Feasibility studies: phase 1 studies, pilot studies, prototype studies, or introductory trials

When and What to Provide

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- By when do trials have to be registered?
  - Within 21 days after enrolling the first participant
- What information must be provided?
  - Descriptive information (e.g., study title, design, primary purpose, intervention);
  - Recruitment information (e.g., eligibility, overall recruitment status);
  - Location and contact information (e.g., name of sponsor, responsible party, facility information); and
  - Administrative information (e.g., unique protocol identification number, IDE/IND number, human subjects protection review board status)

Study Update Requirements

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- All submitted information must be updated at least once per year
- Certain information must be updated in a timely manner (typically within 30 days)
  - e.g., the responsible party information and overall recruitment status must be updated within 30 days of an applicable change

2016 Final Rule re: ClinicalTrials.gov

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- Final rule published September 16, 2016
- Added certain provisions, including:
  - Requirement to submit study results for completed trials of products not yet approved, licensed or cleared by FDA.
    - Registration information for these products will not be made public until clearance or approval is received from FDA
  - Requirement to submit protocol and statistical analysis plan (SAP)
  - Sponsor may designate the study principal investigator as the "responsible party" for submitting study information.
    - Responsible party must submit study results irrespective of ultimate FDA clearance or approval

Results Submission Timing Requirements

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- Trial results must be submitted:
  - Within 1 year after the primary completion date
  - Primary completion date:
    - Date the final subject examined or received an intervention to collect study data
- Extensions available for up to 2 years if responsible party:
  - Certifies the product is not yet approved, licensed, or cleared for marketing and is still under development by the manufacturer
  - Certifies the manufacturer will seek approval, licensing, or clearance for marketing from FDA for the investigational product within one year
  - Requests an extension for “good cause” or a permanent waiver of the results reporting requirements for “extraordinary circumstances”
- Pediatric postmarket surveillance; no later than 30 days after date final report submitted to FDA

Results Submission Data Requirements

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- The Final Rule requires that the following trial data be submitted in tabular form:
  - Participant flow;
  - Demographic and baseline characteristics;
  - Primary and secondary outcomes, including results of any scientifically appropriate statistical tests;
  - Administrative information, including points of contact for clinical results information and employment status of principal investigator; and
  - Adverse event information
- For adverse event information, tables must be submitted that include:
  - Summaries of all serious adverse events;
  - Adverse events that exceeded a frequency of 5% in any treatment arm; and
  - All-cause mortality

Institutional Review Board (IRB)

IRB Basics

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- Appropriately constituted group that has been formally designated to review and monitor biomedical research involving human
  - an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research
- Purpose of IRB review is to assure, both in advance and by periodic review, appropriate steps are taken to protect the rights, safety and welfare of humans participating as subjects in the research
  - IRBs use a group process to review research protocols and related materials (e.g., informed consent documents)
- IRB initially determines if an investigation involves a significant risk or non-significant risk study device
- IRBs must comply with all applicable requirements of the IRB regulation (Part 56) and the IDE regulations (Part 812) in reviewing and approving device investigations involving human testing
  - Registered with FDA and FDA does periodic inspections of IRB's records and procedures to determine compliance with regulations

IRB Composition of Members

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- At least five members with varying backgrounds/professions
  - Diversity of members including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes
  - At least one member whose primary concerns are in scientific areas
  - At least one member whose primary concerns are in nonscientific areas
  - At least one member not affiliated with the institution
- Members must be sufficiently qualified through experience and expertise
- Members with conflicting interest cannot participate in review

IRB Registration

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- Registration required (§ 56.106)
  - Prior to review of clinical investigation
  - Renew every 3 years
- Not an accreditation or certification
- BiMo audits
- FDA can take action
  - Suspend enrollment of ongoing studies
  - Terminate studies
  - Disqualify IRB (regulatory hearing) (§ 56.121)

IRB Operations (§ 56.108)

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- Follow written procedures:
  - Initial and continuing review of research
  - Determining which projects require review more often than annually
  - Ensuring reporting to IRB of changes in research activity
  - Ensuring IRB review and approval obtained for changes to research, except where an immediate hazard
  - Reporting its findings
- Follow written procedures for reporting:
  - Unanticipated problems involving risks to human subjects or others
  - Any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB
  - Any suspension or termination of IRB approval

IRB Records and Reports (§ 56.115)

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- Copies of all research proposals reviewed, including scientific evaluations, consent documents, progress reports, and reports of injuries
- Minutes of IRB meetings including attendance
- Continuing reviews
- Correspondence between IRB and investigators
- List of IRB members
- Written procedures
- Statements of new findings presented to subjects

IRB Approval

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- Requirements for approval (§ 56.111):
  - Risks to subjects are minimized
  - Risks to subjects are reasonable in relation to anticipated benefits
  - Selection of subjects is equitable
  - Informed consent will be sought and documented
  - Research plan makes adequate provisions for monitoring
  - Additional safeguards are in place for vulnerable populations to be free from coercion or undue influence
- Review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas
- Research must be approved by a majority of those members present at the meeting

NSR Determination Inquiries

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- If an IRB is uncertain whether a study is exempt, significant risk or nonsignficant 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

Informed Consent

FDA's Informed Consent Regulations

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- "[N]o investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative."
  (§ 50.20)
- These regulations cover "all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration. . ." (§ 50.1)

Informed Consent Requirements

- Information about the investigation to enable the subject to decide whether to participate
- Considers reading level of subject
- Must be obtained before any and all procedures
- Include all potential risks
- No exculpatory language
- Emphasis that participation is voluntary
- Adequate time to consider information and ask questions
- Written consent
- Copy given to person signing
- Reviewed by FDA and IRB
- Required elements

Required Elements for Informed Consent (§ 50.25)

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- Study involves research
- Purpose
- Duration
- Procedures
- Experimental procedures
- Risks/discomforts
- Benefits
- Alternative procedures
- Confidentiality of records and participation
- Compensation/treatment for injury
- Contact for subject's rights/inquiries
- Participation voluntary

Additional Elements of Informed Consent

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- Unforeseeable risks, including risks to an embryo, fetus, or if the subject is or becomes pregnant
- Termination by investigator without subject consent
- Additional costs related to participation
- Consequences of withdrawal from the study
- Significant new findings which may related to willingness to participate will be provided to subjects
- Number of subjects
- Additional information will be available at clinicaltrials.gov
- Information required by state or local laws

Waivers

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- IRB may waive informed consent requirements if research presents
  - no more than minimal risk of harm to subjects and
  - involves no procedures for which written consent is normally required
- Emergency use or research

Emergency Use of Unapproved Device

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- May occur when:
  - IDE for the device does not exist;
  - When a physician wants to use the device in a way not approved under the IDE; or
  - When a physician is not an investigator under the IDE
- Conditions:
  - The patient has a life-threatening condition that needs immediate treatment;
  - No generally acceptable alternative treatment for the condition exists; and
  - Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use
- Follow-up report must be submitted to FDA

Emergency Use Patient Protection Measures

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- Informed consent from the patient or a legal representative
- Clearance from the institution as specified by their policies
- Concurrence of the IRB chairperson
- An independent assessment from an uninvolved physician
- Authorization from the IDE sponsor, if an approved IDE exists for the device

Clinical Trial Agreements

Investigator Agreements

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- Regulatory agreement
- Sponsor must obtain signed document that includes investigator's agreement:
  - To follow investigational protocol
  - To supervise testing
  - To maintain adequate and complete patient records
  - To ensure informed consent and IRB review and approval requirements are met
  - To provide financial disclosure information
  - To use investigational device only in IDE study
  - Regarding publication rights

Clinical Trial Agreements

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- CTAs are business contracts, not regulatory investigator agreements
- Should be separate from Investigator Agreements required under IDE regulations
- Parties to CTAs
  - Sponsor – Device Manufacturer
  - Institution – University, hospital, or private hospital
  - Principal investigator – PI will appoint co- or sub-investigators
  - Co-investigators – should sign an exhibit
  - Ancillary personnel – interns, residents, etc.
  - CRO (potentially)

Provisions of CTA

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- Scope of work
- Compliance with investigational plan and applicable law and regulations (FDA, HIPAA, state laws)
- Compensation and financial arrangements
- Intellectual property ownership
- Publication and disclosure
- Representation and warranties
- Insurance and indemnity

Compliance and Consequences

Bioresearch Monitoring (BiMo) Program

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- Objectives of the BiMo program:
  - To verify quality and integrity of data
  - To protect the rights and welfare of human research subjects
- Functions:
  - Audits of clinical data contained in PMA and some 510(k) submissions, ordinarily prior to approval
  - Inspections of nonclinical laboratories that perform medical device-related safety testing
  - Inspections of IRBs that review investigational device studies

Inspection of Clinical Investigators

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- Study Administration
- Protocol
- Patient Records
- Informed Consent
- IRB Approval
- Test Article Accountability
- Record Retention
- Electronic Data Systems

Study-Oriented Inspections

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- Submitted data compared with all available supporting data
- Records may reviewed from the physician's office, hospital, nursing home, laboratories and other sources
- Pre-study diagnosis reviewed and lack of interfering medication or treatment prior to study initiation confirmed
- Follow-up records reviewed and reporting of all signs and symptoms reasonably attributable to the product's use confirmed

Inspection Classifications

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- Establishment Inspection Report (EIR) -- a detailed record of the inspection and findings
- Assigned to inspections to indicate whether or not the establishment is operating in compliance with the regulations
  - NAI - No Action Indicated
  - VAI - Voluntary Action Indicated
  - OAI - Official Action Indicated

Potential Consequences

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- Inspection expanded to include other submissions
- Integrity hold on submissions
- Warning Letters
- Data thrown out from violative center
- Re-analysis of data
- Third party audit
- SOPs development
- Ethics training
- Supplementary study could be required
- Delays in time to approval/clearance (or non-approval/clearance)

Sponsor Warning Letters

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- Failure to adequately monitor
- Failure of investigator to follow SOPS
- Failure to maintain accountability or adequate control of investigational products
- Failure to submit progress reports to FDA
- Shipment of investigational product to non-participants
- Non-compliance with IDE labeling regulations

Investigator Warning Letters

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Failure to:

- Prospectively obtain informed consent
- Conduct investigations according to the investigational plan
- Prepare adequate and accurate case histories
- Report adverse events to the Sponsor
- Keep accurate record of the disposition of the investigational device
- Obtain IRB approval prior to enrolling patients
- Make progress reports to the IRB and FDA

Corrective Actions to Establish Reliability

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- Cooperate fully with FDA
- Identify all individuals who were or may have been associated with fraudulent acts
- Assure that individuals associated with fraudulent acts are removed from matters under jurisdiction of FDA
- Conduct a credible internal review
- Commit, in writing, to developing and implementing a corrective action operating plan
- Until fraud review complete, all filings reviewed more carefully

Prohibition on Promotion/Commercialization

Prohibition Against Promotion

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- Sponsor may advertise for investigators or research subjects to participate in study
- Sponsor, investigator, or any person acting for on behalf of Sponsor/investigator must not (§ 812.7)
  - Promote or test market an investigational device, until after FDA has approved the device for commercial distribution
  - Commercialize an investigational device by charging the subjects or investigators a higher price than that necessary to recover costs of manufacture, research, development, and handling
  - Unduly prolong an investigation. If data developed by the investigation indicate that premarket approval (PMA) cannot be justified, the Sponsor must promptly terminate the investigation
  - Represent that an investigational device is safe or effective
- Label of investigational devices must contain the following:

  "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use."

Prohibition Against Promotion

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- FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process
- Study advertisements must be reviewed and approved by the IRB:
  - Assure that it is not unduly coercive
  - Does not promise a certainty of cure beyond what is outlined in the consent and the protocol
  - No claims should be made, either explicitly or implicitly, that the device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other device
    - Ads should not say “new treatment” without explaining that device is investigational
    - Ads should not promise “free medical treatment” if intent is only that subjects are not charged for participating in the study

Payments

- Payment to physicians/patients is permissible, but
  - Keep reasonable
  - Ensure all study conditions are met
  - Tie to milestones/objectivity
  - OK to say subjects will be paid but do not overemphasize payment or amount

Common Rule

Common Rule

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- The Federal Policy for the Protection of Human Subjects; originally promulgated as the "Common Rule" in 1991 (45 CFR 46, Subpart A)
- The Common Rule purposes: To promote uniformity, understanding, and compliance with human subject protections and to create a uniform body of regulations across the federal departments and agencies
- FDA amended its regulations in 21 CFR parts 50 and 56 to conform to the Common Rule with a few exceptions because of differences in FDA's mission or statute.
- 21st Century Cures Act directed HHS to harmonize differences between the HHS' human subject regulations and FDA's human subject regulations

Common Rule Revisions

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- HHS 2017 Common Rule revisions ("2018 Requirements") were intended to better protect human subjects involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators; created certain differences between the FDA and HHS human subject regulations
- FDA guidance "Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations" (October 2018)
- Notes that:
  - Common Rule revisions related to informed consent (e.g., content, organization, and presentation of information) are not inconsistent with FDA requirements
  - Differences related to IRB review procedures for minimal risk research and IRB continuing remain. FDA notes it is working to harmonize its pertinent regulations accordingly

FDA COVID-19 Impact on Clinical Trials

FDA COVID-19 Impact on Clinical Trials

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- FDA guidance *Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic* issued on Mar. 18, 2020
- assist sponsors of clinical studies of medical products in assuring the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to data integrity
- Reinforced sponsor's ability to change protocol for minimize or eliminate immediate hazards or to protect the life and well-being of research participants without prior IRB approval or filing an amendment to the investigational plan

FDA COVID-19 Impact on Clinical Trials

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- "[s]ponsors, clinical investigators, and IRBs should consider establishing and implementing policy and procedures, or revise existing policy and procedures, to describe approaches to be used to protect trial participants and manage study conduct during possible disruption of the study as a result of COVID-19 control measures at study sites."
- Sponsors should ask *whether study subjects' safety, welfare, and rights are best served by continuing in the study, discontinuing use of investigational products, or withdrawing from the study altogether*

FDA COVID-19 Impact on Clinical Trials

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- Mitigation strategies:
  - Alternatives to in-person visits (telephone, video conference, alternative site (e.g., lab))
  - Changes or delays to assessment schedules
  - Change to method of assessment administration
  - Home use rather than use in clinic
  - Alternative travel and accommodations
  - Proctoring surgeries via live feed
- Guidance indicated that FDA will be flexible regarding *COVID-19 related* protocol deviations, however, documentation is critical
- Changes to SAP still need to be approved by FDA

Questions?

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