# FDLI Introduction to Medical Device Law and Regulation:
## Clinical Investigations

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Samantha Hong, Associate
Kleinfeld, Kaplan & Becker, LLP
1850 M Street, NW, Suite 800
Washington, DC 20036
202-223-5120
shong@kkblaw.com
www.kkblaw.com

# Learning Objectives

1. *Determine when an investigational device exemption (IDE) is needed*
2. *Learn the responsibilities of Institutional Review Boards (IRBs)*
3. *Recognize the required elements of informed consent*
4. *Understand the responsibilities of a clinical trial sponsor*
5. *Learn what FDA's bioresearch monitoring (BIMO) program looks for in a clinical trial inspection*

# Investigational Device Exemptions

# What is an IDE?

- An investigational device exemption (IDE) allows an investigational device to be used in a clinical study to collect safety and effectiveness data to support, among other things:
  - Premarket Notification (510K) submission
  - Premarket Approval (PMA) Application
  - Humanitarian Device Exemption (HDE)
  - Certain modifications or new intended uses of already cleared/approved device
- An IDE permits a device to be shipped in interstate commerce lawfully for the purpose of conducting investigations.
- Regulations located at 21 CFR Part 812.

# What is an IDE (cont.)?

- An IDE exempts devices from the following requirements of the Federal Food, Drug, and Cosmetic Act (FDCA) and associated regulations (see 21 CFR 812.1(a)):
  - Misbranding (21 U.S.C. 352)
  - Registration, listing, and premarket notification (21 U.S.C. 360)
  - Performance standards (21 U.S.C. 360d)
  - Premarket approval (21 U.S.C. 360e)
  - Banned device regulation (21 U.S.C. 360f)
  - Records and reports on devices (21 U.S.C. 360i)
  - Restricted device requirements (21 U.S.C. 360j(e))
  - Good manufacturing practices (21 U.S.C. 360j(f))
  - Color additive requirements (21 U.S.C. 379e)
  - Unique device identifier requirements (see 21 CFR 801.30)

# Types of IDE Devices

- IDE regulations broadly categorize into one of three categories:
  - Significant Risk (SR)
  - Non-Significant Risk (NSR)
  - Exempt

# Significant Risk v. Non-Significant Risk Device Studies

- Significant Risk Device means an investigational device that:
  - Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
  - 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;
  - 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
  - Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

  21 CFR 812.3(m).
- Non-Significant Risk refers to a device subject to the IDE regulation that is not a significant risk device.

# Significant Risk v. Non-Significant Risk Device Studies – Examples

- Significant Risk Device
  - Catheters for general hospital use
  - Surgical lasers
  - Tracheal tubes
  - Dental lasers
  - Breast implants
- Non-Significant Risk Device
  - Contact lens solution using active ingredients with a history of prior contact lens use
  - Dental filling materials made from traditional materials and designs
  - Jaundice monitors for infants
  - Menstrual pads or tampons (with known materials)
  - Low power lasers for treatment of pain

# When is IDE Approval Required from FDA?

- IDE approval is required if the study presents a significant risk.
  - Sponsors make the initial determination as to whether a device study is SR or NSR and present it to the IRB. The IRB makes its own determination (and modifies the sponsor determination if it disagrees).
  - FDA is the final arbiter of the SR v. NSR determination.
- SR device studies must follow *all* IDE regulations at 21 CFR Part 812 and must have an IDE application approved by FDA before the study proceeds.
- NSR device studies must follow abbreviated requirements at 21 CFR 812.2(b) regarding IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion. IRB stands in as a surrogate for FDA and no IDE application is required.
  - FDA may disagree with the IRB's conclusion and determine that a device study is significant risk and ultimately require an IDE application.

# Exempted Investigations

- The IDE requirements do not apply to investigations on the following device categories:
  - Pre-amendment devices – Devices on the market before 1976 when used in accordance with the indications in the labeling in effect at that time.
  - Diagnostic devices that 1) are noninvasive; 2) do not require invasive sampling procedure that presents significant risk; 3) do not introduce energy into subject; and 4) are not used as diagnostic procedures without confirmation of diagnosis by a medically established product or procedure.
  - Devices undergoing testing of consumer preference, a modification, or a combination of 2+ devices on the market if testing is not to determine safety or effectiveness and does not put subjects at risk.
  - Veterinary use devices.
  - Custom devices (devices created to comply with an individual physician order as defined at 21 CFR 812.3(b)).

# Pre-Submissions

- Pre-Submissions ("Pre-Subs") are voluntary formal written requests for FDA feedback *prior* to an IDE or other premarket submission.
  - Request should include specific questions about the IDE submission, e.g., clinical trial design.
  - Appropriate when FDA's feedback is necessary to guide development or submission preparation.
- FDA provides a formal written response, which can be followed by an in-person/teleconference meeting upon request (documented in meeting minutes).
  - Timeframe:  Sooner of 70 days 5 days prior to schedule meeting (meeting usually 60-75 days after submission, based on mutual agreement)
- Early interaction with FDA can improve quality of submission and facilitate development process (but does not guarantee approval or clearance of future submissions).

# Agreement Meetings

- Early collaboration meetings with FDA for persons planning to investigate the safety or effectiveness of a class III device or implantable device. *See* 21 U.S.C. 360j(g)(7).
- Purpose is to reach agreement on key parameters of the investigational plan, including clinical protocol, as described in IDE regulations at 21 CFR 812.25.
- Meeting is held within 30 days of the request and any agreement reached is in writing and becomes a part of the administrative record. The agreement ***is binding on the FDA***.
- Agreement Meeting request should include:
  - Description of proposed conditions of use
  - Proposed plan for determining reasonable assurance of effectiveness
  - Information regarding expected performance
  - Detailed clinical protocol

# IDE Application (Applicable to SR Devices) (21 CFR 812.20)

- Report of prior investigations and summary of investigational plan (812.25)
- Description of methods/facilities/controls used for manufacturing, processing, packing, and storage
- Example investigator agreement
- Certification that all investigators have signed the agreement
- List of IRBs and members reviewing the investigation
- Name of institution at which investigation is being conducted
- Justification for amount charged for device (i.e. why sale does not constitution commercialization)
- Copies of all labeling
- Informed consent documents

# IDE Submission – Supplements, Reports, Amendments

- After IDE submission, FDA tracks subsequent submissions to the IDE as supplements, reports, or amendments.
- Supplements – requests for new protocol, changes to the approved protocol, changes to the device (e.g. device design or manufacturing change).
- Reports – includes adverse effect reports, progress reports, semiannual investigator lists, etc.
- Amendments – response to deficiencies communicated in an FDA disapproval, approval with conditions, or deficient report letter.

# Acceptance of Data from Outside of the U.S.

- FDA amended its regulations on acceptance of data from investigations conducted outside the U.S. to support an IDE and other premarket requests in 2018.
- Requirements include:
  - Investigation must be conducted in accordance with good clinical practice (GCP), including review and approval by an independent ethics committee and informed consent. *See* 21 CFR 812.28(a)(1).
  - FDA is able to validate data through onsite inspection or other means as it deems necessary. *See* 21 CFR 812.28(a)(3); 814.15(b)(3).
  - Foreign data are applicable to U.S. population and medical practice. *See* 21 CFR 814.15(b)(1).
- Applicant can seek waiver of above requirements explaining why compliance is unnecessary or cannot be achieved. *See* 21 CFR 812.28(c).

# Clinical Investigator Selection (21 CFR 812.43)

- Sponsor is responsible for selecting investigators qualified by training and experience.
- Sponsor must obtain signed agreement with each investigator including:
  - Investigator CV and statement of relevant experience
  - Circumstances of termination from prior investigations or research, if any.
  - Investigator commitment to investigational plan, FDA regulations, ensuring informed consent, etc.
  - Financial disclosure information. Disclosure to FDA is required under circumstances such as (21 CFR 54.4):
    - Compensation to investigator could be influenced by study outcome
    - Significant payments of other types to investigator (e.g. grant for ongoing research, equipment)
    - Proprietary interest in product held by investigator
- IRBs also play a role in ensuring the adequacy of investigator qualifications during their review process.

# Clinical Investigator Disqualification (21 CFR 812.119)

- Grounds for disqualification:  Investigator repeatedly or deliberately failed to comply with requirements or repeatedly or deliberately submitted to FDA or sponsor false information.
- If FDA determines an investigator should be disqualified:
  - Investigator is ineligible to receive test articles
  - Investigator is ineligible to conduct any clinical investigations that support an FDA application
  - Any submission to FDA containing data reported by investigator will be reviewed by FDA
- Investigator may be reinstated with adequate assurances that he/she will comply with all requirements.

# FDA Actions on IDE Applications

# IDE Decisions (21 CFR 812.30)

- IDE application and FDA approval only necessary for significant risk device studies.
- Upon receipt of IDE application, FDA sends acknowledgment email and assigns IDE number.
- IDE is considered approved 30 days after FDA receives the application *unless* FDA otherwise notifies the sponsor prior to that date that the IDE is approved, approved with conditions, or disapproved.
  - If approved, investigation can begin once IRB approval is obtained.
  - If approved with conditions, investigation can begin provided that the sponsor submits information addressing the issues identified in FDA's letter (IDE amendment) within 45 days and IRB approval is obtained. The sponsor need not wait for FDA's response to begin study enrollment.
  - If disapproved, investigation may not begin until sponsor submits an IDE amendment and receives an approval letter from FDA.
- Enrollment is considered the start of an investigation.

# IDE Decisions – Disapproval (21 CFR 812.30(b))

- FDA may disapprove an IDE application for the following reasons:
  - Failure to comply with regulatory requirements
  - Application contains untrue statements or facts (or omissions of material information)
  - Sponsor fails to respond to request for additional information with specified timeframe
  - Risks to subjects are not outweighed by anticipated benefits
  - Inadequate informed consent
  - Investigation is scientifically unsound
  - Reason to believe that device under investigation is ineffective
  - It is otherwise unreasonable to begin investigation
- FDA cannot disapprove an application on the basis that the investigation may not support the approval or clearance of a marketing application. 21 USC 360j(g)(4)(c).

# IDE Decisions – Clinical Hold (21 USC 360j(g)(8))

- FDA may prohibit sponsor from conducting an investigation ("clinical hold") if it determines that the device represents an unreasonable risk to subject safety, taking into account:
  - Investigator qualifications
  - Information about the device
  - Clinical investigation design
  - Condition for which device is being investigated
  - Health status of subjects
- Sponsor may request removal of clinical hold in writing and FDA must respond within 30 days.

# ClinicalTrials.gov

# ClinicalTrials.gov

- ClinicalTrials.gov is a publicly accessible database of ongoing and completed clinical studies managed by the NIH/National Library of Medicine.
- The FDA Amendments Act of 2007 (FDAAA) amended the Public Health Service Act to substantially expand clinical trial disclosure requirement, including expanding such requirements to medical device trials.
- FDAAA also amended the FDCA to make failure to comply with 42 USC 282(j) a prohibited act and to authorize FDA to assess civil money penalties for such prohibited acts. 21 USC 333(f)(3), (jj).

# ClinicalTrials.gov (cont.)

- HHS Final Rule on ClinicalTrials.gov (Sept. 2016)
  - Effective Jan. 2017, with April 2017 compliance date
  - Clarifies and expands regulatory requirements and procedures for submitting registration and results information for certain trials to ClinicalTrials.gov, including legal consequences for non-compliance.

# ClinicalTrials.gov (cont.) – Reporting Requirements

- Certain clinical trial information regarding any "applicable clinical trial" (ACT) must be submitted by the "responsible party" within 21 days after the first patient is enrolled in the trial. *See* 42 USC 282(j).
  - Responsible Party (42 CFR 11.4) – typically the sponsor (i.e. the IDE holder or if no IDE, whoever initiates and has authority and control over the trial), but in some cases the principal investigator if designated by the sponsor.
  - Applicable Clinical Trial (42 CFR 11.10(a)):
    - Initiated after Sept. 27, 2007 (FDAAA enactment) or ongoing as of Dec. 26, 2007
    - Prospective clinical study of health outcomes
    - Compares an intervention with a device against a control in human subjects
    - Device needs 510k clearance, PMA approval, or HDE before it can be commercially marketed
    - Not a small feasibility study
    - (Also includes pediatric postmarket surveillance studies required under 21 USC 360l)

# ClinicalTrials.gov (cont.) – Reporting Requirements

- What clinical trial information must be submitted (42 CFR 11.28)?
  - Descriptive information – trial summary, study design, primary disease/condition being studied, intervention, primary and secondary outcome measures, target number of subjects, estimated completion date
  - Recruit information – eligibility criteria, age limits, overall recruitment status
  - Location and contact information – sponsor name, responsible party, facility name
  - Administrative data – unique protocol identification number and IDE number, if any
- When must results information be submitted (42 CFR 11.44(c))?
  - Within one year of estimated or actual trial completion date, whichever is earlier
  - Results submission may be delayed under certain circumstances (e.g. when trial is completed before device is initially cleared or approved by FDA)
- Updates to ClinicalTrial.gov must be submitted at least every year; certain other information must be updated within 30 days of event.

# ClinicalTrials.gov (cont.) – Compliance and Enforcement

- Failure to submit required information to ClinicalTrials.gov is a prohibited act under FDCA allowing FDA to apply its standard enforcement tools (e.g. injunction, criminal prosecution) for violations.
- FDA may also impose civil money penalties of up to $13,237 (in 2022) per day (with no maximum) for ongoing violations.
  - Prior to pursuing a CMP action, FDA issues a "Preliminary Notice of Noncompliance" or "Pre-Notice" to provide the responsible party 30 days to address any potential violations. Failure to comply could result in a Notice of Noncompliance, CMPs, injunction and/or criminal prosecution.
  - FDA issued 3 Notices of Noncompliance in 2021 alleging in each instance that the responsible party failed to submit required summary results information. It does not appear that FDA has pursued a CMP or other enforcement action following any of these notices.

# Clinical Trial Equity Issues – Subgroup Analysis Plans

- Section 907 of the FDA Safety and Innovation Act (FDASIA) of 2012 directed FDA to issue an action plan outlining recommendations to improve data analyses on demographic subgroups including sex, age, race, and ethnicity in summaries of product safety and effectiveness and in labeling.
- In 2018, FDA issued a guidance to outline its expectations and provide recommendation for evaluating and reporting age, race, and ethnicity-specific data in medical device clinical studies. The guidance provides recommendations regarding:
  - Diverse study participation (e.g. through enrollment)
  - Analyses of study subgroup data, including framework for considering demographic data when interpreting study outcomes
  - Expectations for reporting subgroup-specific information in data summaries and labeling

# Informed Consent

# Informed Consent
## 21 CFR Part 50

Written informed consent for studies subject to FDA regulations must meet the requirements of 21 CFR 50.20:

> Except as provided in §§ 50.23 and 50.24, no 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. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that **minimize the possibility of coercion or undue influence**. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is **made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence**.

# Informed Consent
## 21 CFR Part 50

- IRBs have the final authority for ensuring the adequacy of the information in the informed consent document.

- For studies under an IDE, FDA will also review the informed consent documents.

# Basic Elements of Informed Consent

- Description of clinical investigation
- Risks and discomforts
- Benefits
- Alternative procedures or treatments
- Confidentiality of records
- Compensation/medical treatment in event of injury
- Contact information for questions or injuries
- Voluntary participation

21 CFR 50.25(a).

# Additional Elements of Informed Consent (When Appropriate)

- Risks may be unforeseeable
- Potential for involuntary termination of subject's participation
- Additional costs to subjects
- Consequences of subject’s decision to withdraw
- Providing significant new findings to subjects
- Number of subjects

21 CFR 50.25(b)

# IRB Waiver or Alteration of Informed Consent

IRB may waive informed consent requirements under certain circumstances:

- Clinical investigation involves no more than minimal risk (defined at 21 CFR 50.3(k) or 56.102(i)) to subjects
- Waiver or alteration will not adversely affect the rights and welfare of subjects
- Whenever appropriate, subjects will be provided with additional pertinent information about the research

21 CFR 56.109(c), (d).

# Exceptions to Informed Consent

- Investigator and independent physician must certify in writing, before use of test article that:
  - Life-threatening situation necessitating use of test article
  - Subject unable to communicate informed consent
  - Insufficient time to obtain consent from representative
  - No available alternative method of approved or generally recognized therapy that provides equal or greater likelihood of saving subject's life
- If use of test article is required to preserve subject's life, and there is insufficient time to obtain independent certification before use of test article, investigator must obtain independent certification within 5 working days after use
- Submit documentation to IRB within 5 working days

21 CFR §50.23.

# Exceptions to Informed Consent – Emergency Research

21 CFR 50.24 permits research on emergency treatments without informed consent for specific life-threatening emergency conditions (e.g., head trauma, cardiac arrest, stroke), but IRB must document, among other things, that:

- Human subject is in life-threatening condition, available treatments are unproven or unsatisfactory, and collection of evidence is necessary to prove safety and effectiveness of particular intervention
- Obtaining informed consent is not feasible
- Participation in research holds out prospect of direct benefit to subject
- Clinical investigation could not practicably be carried out without the waiver

# Incentives for Enrollment

- Payment to research subjects is not considered a benefit, but a recruitment incentive
- Often used when health benefits are remote or non-existent
- Amount and schedule of payments must be neither coercive nor present an undue influence
- Credit for payment should accrue as the study progresses and not be contingent upon entire study completion
- Amounts paid as a bonus for completion should be reasonable
- Additional considerations for pediatric population due to risk that parents' consent for child's participation may be swayed by incentives as there is no personal risk to themselves
- All incentive information should be specified in the informed consent document

# Institutional Review Boards (IRBs)

# Institutional Review Boards (IRBs)
## 21 CFR Part 56

- IRB (defined in 21 CFR 56.102(g)): Board, committee, or other group formally designated by an institution to review, approve, and monitor biomedical research involving human subjects
  - IRBs must register with FDA and are subject to FDA oversight and inspection
  - May be associated with institution or may be "commercial"
- Purpose is to safeguard the rights, health, and welfare of research subjects
- Authority to approve, disapprove, or require modification of investigations
- Required to prepare and maintain adequate documentation of activities under 21 CFR 56.115

# IRB Membership Composition
## 21 CFR 56.107

- Minimum 5 members of varying professions, backgrounds, experience, expertise and diversity (including gender) who are knowledgeable of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.
- At least one member whose primary concerns are in the scientific area.
- At least one member whose primary concerns are in a nonscientific area (“consumer member”).
- At least one member who is not otherwise affiliated with the institution or part of the immediate family of a person who is affiliated.
- No conflicting interest.
- Discretionary invitation of individual(s) with specific expertise, if indicated. May not vote.

# Conflicts of Interest

No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

21 CFR § 56.107(e).

# IRB Functions and Operations
## 21 CFR 56.108

- Follow written procedures for:
  - Reviews, reports, monitoring, and ensuring compliance of investigators with the approved research activity
  - Ensuring prompt reporting to the IRB, appropriate institutional officials, and FDA of unanticipated problems, serious or continuing noncompliance, suspension or termination of IRB approval
- Review proposed research at convened meetings with majority of members present (except for expedited review procedure)

# IRB Review of Research
## 21 CFR 56.109

- Authority to:
  - Review, approve, require modifications to, or disapprove research activities
  - Review informed consent compliance with 50.25 and request modifications
  - Approve waiver of / exception to informed consent under certain circumstances including emergency use
  - Suspend or terminate approval based on non-compliance or safety (§ 56.113)
- Approval/disapproval and all other actions must be communicated in writing
- Conduct continuing review of research at least annually
- Assure compliance with part 50, subpart D for pediatric populations
- Expedited review when research involves no more than minimal risk or for minor changes in previously approved research may be conducted by IRB chairperson or subset of reviewers. 21 CFR § 56.110.

# IRB Review of Documents

- Review study documents that provide information regarding the risks, benefits, commitments, and compensation of involved subjects, which at a minimum include:
  - Investigator's curriculum vitae and medical license
  - Study protocol, amendments and administrative changes
  - Investigator's brochure and any safety reports or updates
  - Draft informed consent form and any proposed changes to the document
  - Language describing any payments or compensation to involved subjects
  - Advertisements and/or recruitment forms
  - Written documents provided to the subjects that are related to the study

# IRB Criteria for Approval of Research
## 21 CFR 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 appropriately documented from each prospective subject or legally authorized representative in accordance with Part 50
- Research plan makes adequate provision for monitoring data collected to ensure safety of subjects
- Adequate provisions to protect subject privacy and maintain data confidentiality
- Safeguards to protect vulnerable populations are in place

# IRB Records and Reports
## 21 CFR § 56.115

- Research proposals reviewed, accompanying scientific evaluations, approved sample consent documents, investigator progress reports and reports of injuries
- Minutes of IRB meetings
- Continuing review activities
- Correspondence between IRB and investigators
- List of IRB members with detailed information
- Written procedures as required by §§ 56.108(a) and (b)
- Statements of significant new findings provided to subjects, per § 50.25(b)(5)
- Records retained for at least 3 years after completion of the research, and accessible for FDA inspection

# IRB Records and Reports – Continuing Review

- The IRB must review its research studies at least once a year with the following being reported to the IRB:
  - Deviations from the protocol to eliminate hazards to the trial subjects
  - Changes increasing the risk to subjects and/or significantly affecting the conduct of the trial
  - Adverse drug reactions that are both serious and unexpected
  - New information that may adversely affect the safety of the subjects or the conduct of the trial

21 CFR 56.108(a), 56.109(f).

# Vulnerable Populations

- FDA regulations describe vulnerable categories of subjects as including “children, prisoners, pregnant women, or handicapped or mentally disabled persons” and require IRB membership to consider the inclusion of individuals who are knowledgeable about and experienced working with those subjects. 21 CFR 56.107(a).
- FDA regulations do not otherwise contain specific parameters regarding vulnerable populations.

# Vulnerable Populations: 45 CFR Part 46
# IRB Considerations, Membership: 45 CFR § 46.107(a)

*[populations "vulnerable to coercion or undue influence"]*

Issues IRBs must consider when reviewing research with vulnerable populations:

- Ability to provide informed consent
- Coercion
- Choice of subjects

Types of Potential Vulnerability

- Cognitive or communicative: ability to consent
- Institutional: e.g. students or prisoners
- Deferential: informal subordination
- Medical: e.g. terminally ill
- Economic: e.g. poverty
- Social: "lower" perceived social status

# Prohibition on Promotion / Commercialization

# Prohibition on Promotion and Commercialization (21 CFR 812.7)

- Sponsor, investigator, or anyone acting on their behalf, shall not:
  - Promote or test market an investigational device until *after* FDA approval for commercial distribution
  - Commercialize an investigational device by charging subjects or investigators for a higher price than necessary to recover costs of manufacture, research, development, and handling
  - Unduly prolong an investigation – if data reveals that premarket approval cannot be justified (for class III device) or applicable performance standard cannot be met (for class II device), sponsor must terminate the investigation immediately
  - Represent that an investigational device is safe or effective for purposes being investigated
- Investigational device must bear label with the following statement (21 CFR 812.5):
  - "CAUTION – Investigational device. Limited by Federal (or United States) law to investigational use."

# Permissible Activities

- FDA considers direct advertising for study subjects to be the start of informed consent and subject selection process
- Sponsor may advertise for research subjects to solicit participation (e.g. newspaper, radio, TV, bulletin boards, posters, flyers)
- Advertisements should be reviewed and approved by IRB to ensure that recruitment is not unduly coercive and does not promise a certainty of cure; no claims should be made that device is safe or effective
- Advertisements may state that subjects will be paid, but should not emphasize this fact (e.g. using larger or bold type)

# Bioresearch Monitoring and Enforcement Actions

# Bioresearch Monitoring (BIMO) Program

- Comprehensive program of on-site inspections and data audits to monitor FDA regulated research
- Established to assure quality and integrity of data submitted to FDA in support of new product approvals and marketing applications and to protect rights and welfare of human subjects
- BIMO Program monitors sponsors, IRBs, and clinical investigators
- Inspection classifications
  - No action indicated (NAI)
  - Voluntary action indicated (VAI)
  - Official action indicated (OAI)

# Inspection of IDE Studies

IDE Regulations require permitting authorized FDA employees to:

- Enter and inspect (at reasonable times in a reasonable manner) any establishment where devices are held
- Inspect and copy all records relating to an investigation (at reasonable times and in a reasonable manner)
- Inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading

21 CFR 812.145.

# CDRH BIMO Inspections FY 21

- In FY 2021, there were a total of 49 CDRH BIMO inspections broken down as follows:
  - 27 Clinical Investigator inspections
  - 15 IRB inspections
  - 6 Sponsor / Contract Research Organization inspections
  - 0 Sponsor-Investigator inspections
  - 1 Good Laboratory Practice inspection
- Down from 165 CDRH BIMO inspections in FY 2020 due to COVID-19 pandemic
- For reference, in FY 2019, there were a total of 215 CDRH BIMO inspections

# CDRH BIMO Inspections FY 21 (cont.)

- Common Clinical Investigator Inspectional Observations
  - Failure to follow investigational plan
  - Inadequate study records
  - Inadequate subject protection; informed consent issues
  - Failure to comply with 21 CFR Part 56 IRB requirements
- Common IRB Inspectional Observations
  - Failure to conduct initial and/or continuing review of research
  - Failure to have IRB meeting minutes in sufficient detail
  - Failure to conform membership to required criteria
  - Failure to prepare and maintain documentation of IRB activities
- Common Sponsor/CRO Inspectional Observations
  - Failure to select qualified investigators and/or monitors
  - Failure to ensure that study is conducted in accordance with investigational plan

# FDA Warning Letters and Enforcement

- Warning Letter to Philip R. Kennedy (Feb. 27, 2020) – clinical investigator
  - Failure to ensure proper monitoring and IRB review and approval (21 CFR 812.40) – no documentation of monitoring or continuing review by IRB for over 10 years
  - Failure to submit complete and accurate progress reports (21 CFR 812.150(b)(5)) – no correspondence with IRB for 10 years
  - Failure to maintain records of shipment, receipt, use, or disposition of device (21 CFR 812.140) – no documented device accountability information
- Warning Letter to Victor Scheeren, UVLrx Therapeutics, Inc. (Sept. 25, 2017) – sponsor
  - Failure to obtain IRB approval (21 CFR 812.2(b)(1)(ii)) – no IRB approval of protocols, increasing enrollment and # of clinical investigators
  - Failure to monitor investigation (21 CFR 812.2(b)(1)(iv)) – failure to monitor resulted in investigational devices being shipped to unapproved/unqualified investigators, exceeding IRB approved enrollment numbers, and more
  - Failure to maintain required records (21 CFR 812.2(b)(4), (5))

# FDA Warning Letters and Enforcement

- Warning Letter to Abington Memorial Hospital, IRC (June 24, 2019) – IRB
  - Failure to review proposed research at convened meetings at which a majority of members of the IRB are present, including at least one member whose primary concerns are in non-scientific areas (21 CFR 56.108(c))
  - Failure to prepare and maintain adequate documentation of IRB activities (21 CFR 56.115(a)(2) and (5))

# Questions?