Clinical Investigations for Devices: Sponsor/Investigator/IRB Responsibilities and Compliance Issues

FDLI Introduction to Medical Device Law and Regulation

November 17, 2021

FDLI

Introduction

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Polling Question

- Question: What's your favorite FDA-relevant quotable saying?

A. *Trust, but Verify*
B. *In God We Trust, All Others Bring Data*
C. *You Can Outsource Everything, Except Responsibility*
D. I can't possibly choose; I have tattoos of all these phrases.

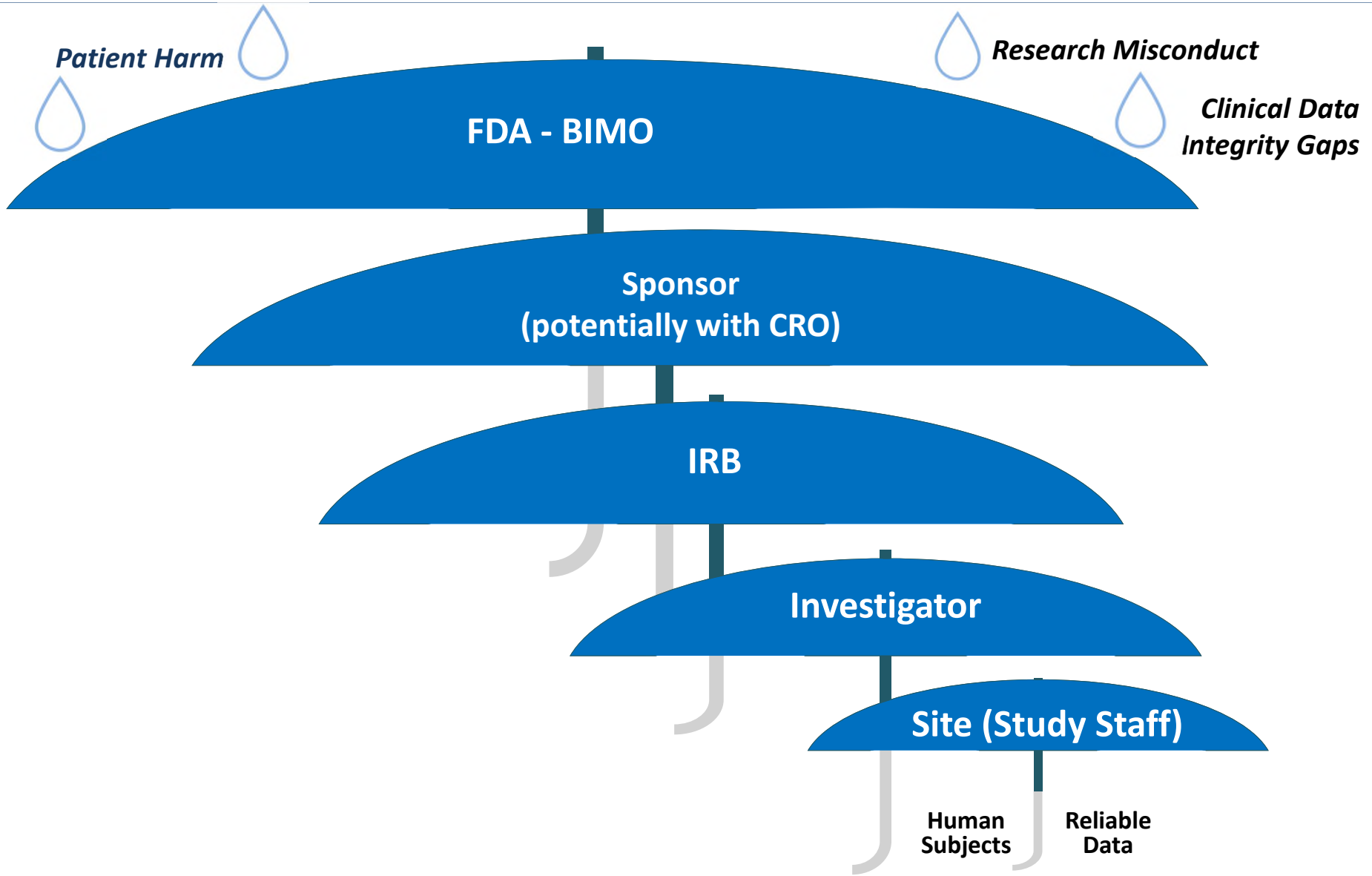
Learning Objectives

- Yesterday you learned about the IDE framework and how to get a device study up and running consistent with the regulations
- Today we'll shift to what happens next: **ongoing compliance, monitoring, and enforcement** topics; and
- Discuss the different (and sometimes overlapping) regulated roles and responsibilities

Why does compliance matter?

- Protecting human subjects
- Generating data that are reliable
- Finding solutions to medical and health challenges
- Supporting company/organizational goals
- Avoiding enforcement action

How do we collectively protect the safety and wellbeing of people and the reliability and integrity of data?


Patient Harm
Research Misconduct
Clinical Data Integrity Gaps
FDA - BIMO
Sponsor (potentially with CRO)
IRB
Investigator
Site (Study Staff)
Human Subjects
Reliable Data

Bioresearch Monitoring (BIMO)

BIMO Program

- A domestic and international program that:
  - monitors the conduct and reporting of FDA regulated research through on-site inspections and data audits
  - provides assurance for the quality and integrity of data submitted to FDA in support of marketing applications
  - additional safeguard to ensure protection of human subjects and animals involved in FDA regulated research
- The "compliance programs" for which BIMO has oversight cover topics including GCP and compliance for sponsors, CROs, and clinical trial monitors; clinical investigators, and IRBs

BIMO Program

- In Fiscal Year 2020, there were 165 CDRH BIMO Inspections
  - 106 were Clinical Investigators
  - 25 were IRBs
  - 23 were in the Sponsor/CRO/Monitor category
  - 2 were Sponsor-Investigators
  - 9 were on GLP

BIMO Program

- Common inspectional observations for Clinical Investigators:
  - Failure to follow the investigational plan; protocol deviations
  - Inadequate and/or inaccurate case history records
  - Inadequate study records
  - Inadequate accountability and/or control of the investigational product
  - Failure to comply with “investigator statement” requirements
  - Inadequate subject protection; informed consent issues
  - Safety reporting; failure to report and/or record adverse events
  - Failure to comply with 21 C.F.R. Part 56 (IRB) requirements

BIMO Program

- Common inspectional observations for IRBs included:
  - failure to have key documentation (e.g., IRB minutes, documentation of IRB activities),
  - inadequate written procedures,
  - membership criteria did not meet 21 C.F.R. § 56.107 requirements, and
  - failure to follow expedited review procedures under FDA regulations

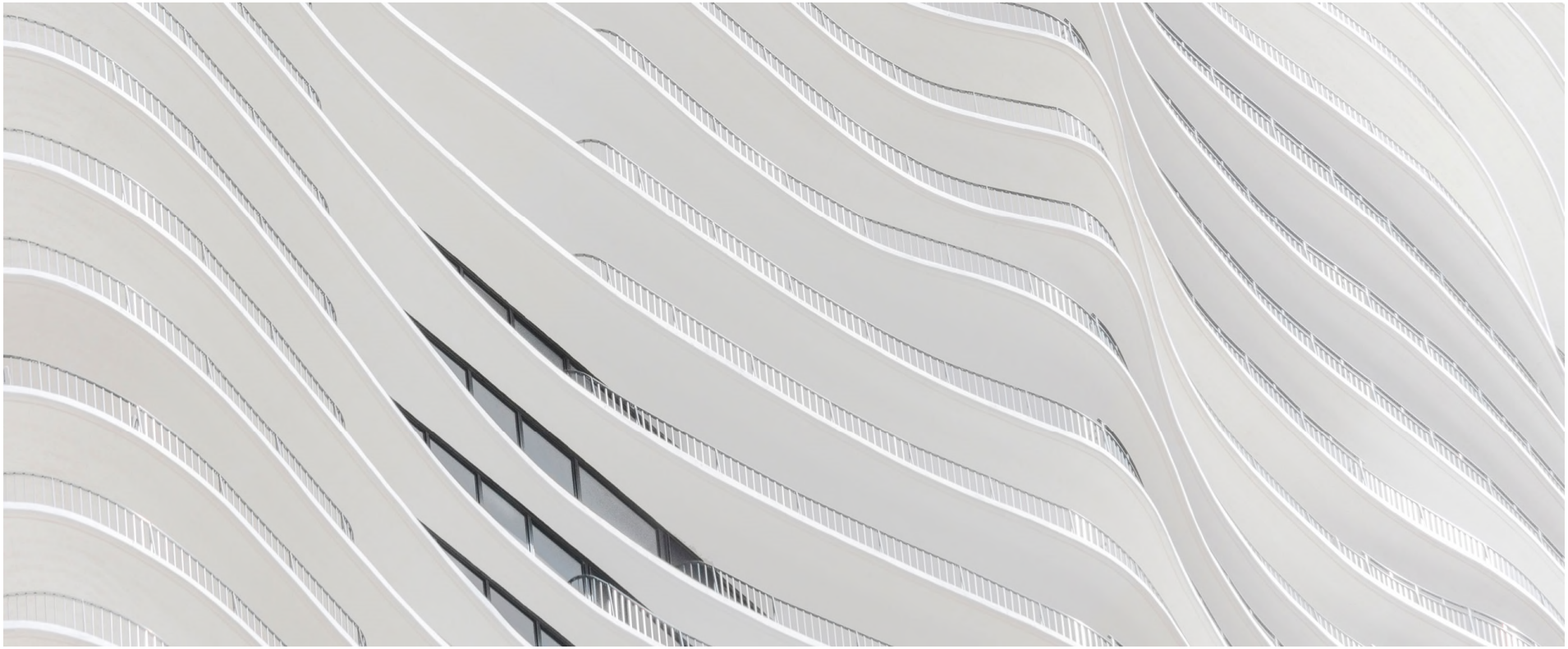
BIMO Program

- Common inspectional observations for sponsors:
  - failure to select qualified investigators or monitors; and
  - failure to maintain appropriate records (e.g., financial disclosures, investigator statement)

Key Resources

- Bioresearch Monitoring Program Information | FDA
- Bioresearch Monitoring Program (BIMO) Compliance Programs | FDA

Clinical Trial Sponsor’s Responsibilities



Sponsor Responsibilities

Subpart B—Application and Administrative Action

812.20 Application.
812.25 Investigational plan.
812.27 Report of prior investigations.
812.28 xxx
812.30 FDA action on applications.
812.35 Supplemental applications.
812.36 Treatment use of an investigational device.
812.38 Confidentiality of data and information.

Subpart C—Responsibilities of Sponsors

812.40 General responsibilities of sponsors.
812.42 FDA and IRB approval.
812.43 Selecting investigators and monitors.
812.45 Informing investigators.
812.46 Monitoring investigations.
812.47 Emergency research under §50.24 of this chapter.

Subpart G—Records and Reports

812.140 Records.
812.145 Inspections.
812.150 Reports.

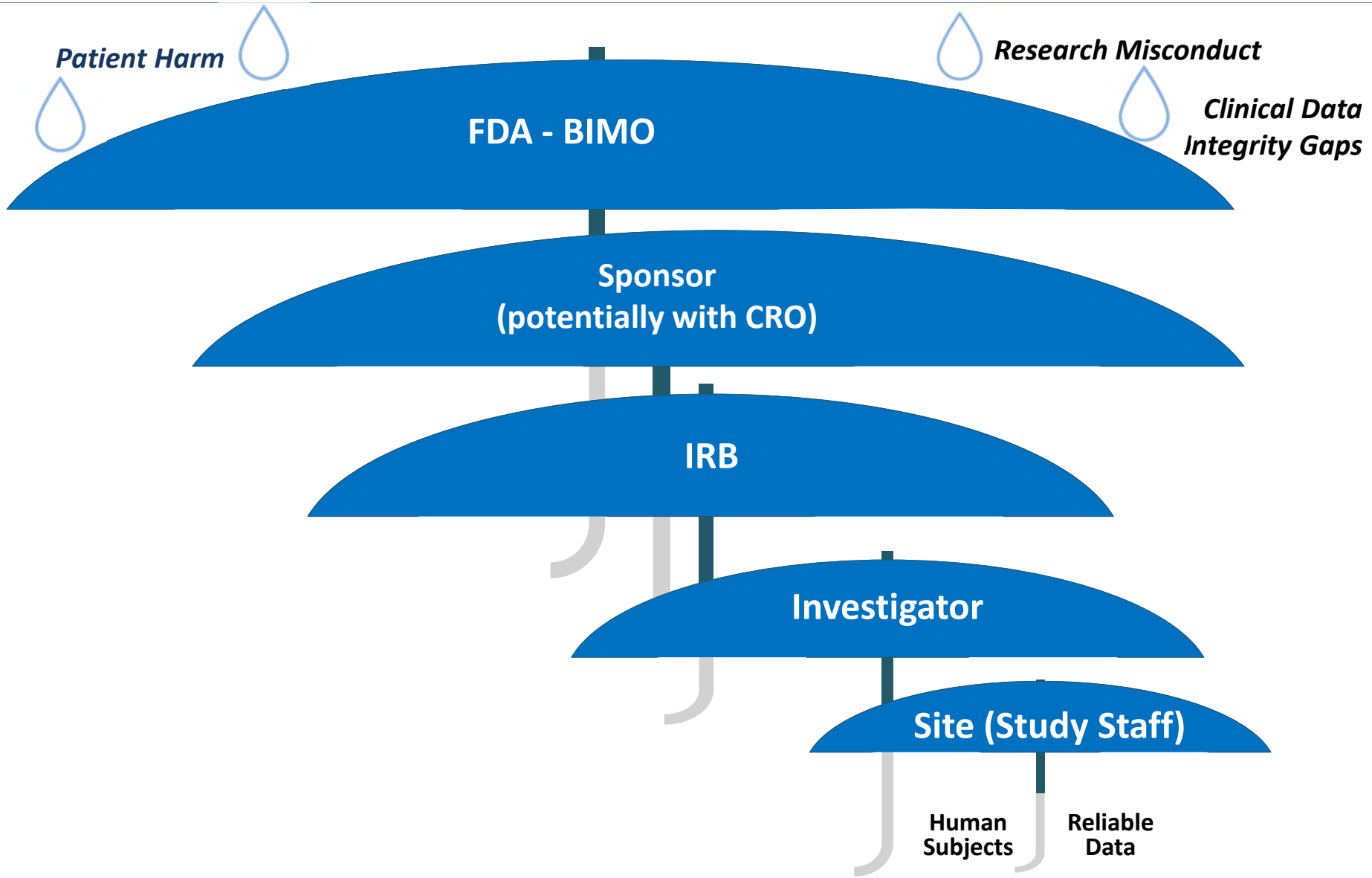
AUTHORITY: 21 U.S.C. 331, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 360bbb–8b, 371, 372, 374, 379e, 379k–1, 381, 382, 383; 42 U.S.C. 216, 241, 262, 263b–263n.

SOURCE: 45 FR 3751, Jan. 18, 1980, unless otherwise noted.

Sponsor Responsibilities

§ 812.40 General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. Additional responsibilities of sponsors are described in subparts B and G.


Patient Harm
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Sponsor (potentially with CRO)
IRB
Investigator
Site (Study Staff)
Human Subjects
Reliable Data

Sponsor Responsibilities

- To avoid a “new” device / device in development being deemed adulterated or misbranded a sponsor should keep in mind:
  - What is the status of the device?
  - What is the objective of the research?
  - What are the risks presented?
  - What are the resulting requirements that apply?
  - **Are those requirements being carried out (whether directly or indirectly) effectively and in a compliant manner?**

Drug vs Device Research: Contract Research Organizations (CROs)

- Drug regulations
  - Define transfer of responsibilities to CROs
  - CROs may be held directly responsible under the regulations
  - Broad sponsor oversight requirements still apply, but there is an additional level of responsibility and an additional regulated category

- Device regulations
  - Do not define or delineate responsibilities for CROs
  - Device sponsor is held responsible for CRO

Clinical Investigators Under Part 812

- ***"Investigator*** means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team."

Clinical Investigators Under Part 812

- ***"Sponsor-investigator*** means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include any person other than an individual. The obligations of a sponsor-investigator under this part include those of an investigator and those of a sponsor."

Sponsor Selection of Investigators

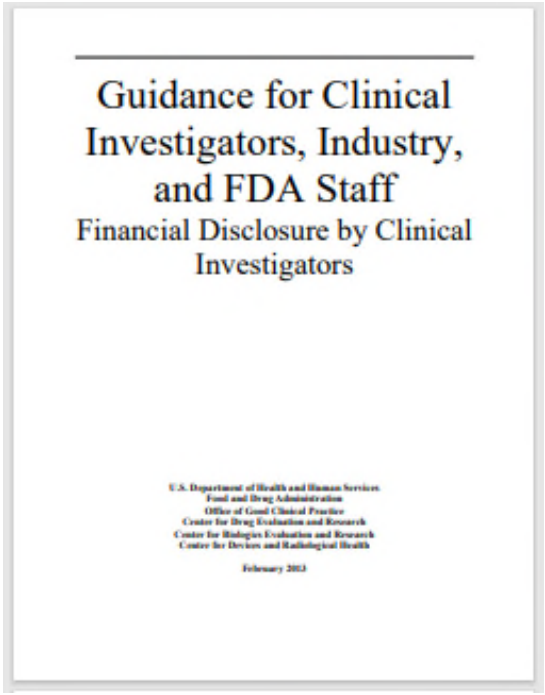
- Addressed in 21 C.F.R. § 812.43
  - Shall be qualified by training and experience
  - Investigational product shall only be shipped to qualified investigators
  - Requirement to obtain “investigator agreement”
    - Key commitments and information for compliance purposes
    - To include key financial disclosure to enable sponsor to comply with its later requirements under Part 54

Financial Disclosure by Clinical Investigators

Regulation: 21 C.F.R. Part 54

Part 54 Financial Disclosure by Clinical Investigators 54.1 – 54.6

- **§ 54.1** Purpose.
- **§ 54.2** Definitions.
- **§ 54.3** Scope.
- **§ 54.4** Certification and disclosure requirements.
- **§ 54.5** Agency evaluation of financial interests.
- **§ 54.6** Recordkeeping and record retention.



Guidance for Clinical Investigators, Industry, and FDA Staff

Financial Disclosure by Clinical Investigators

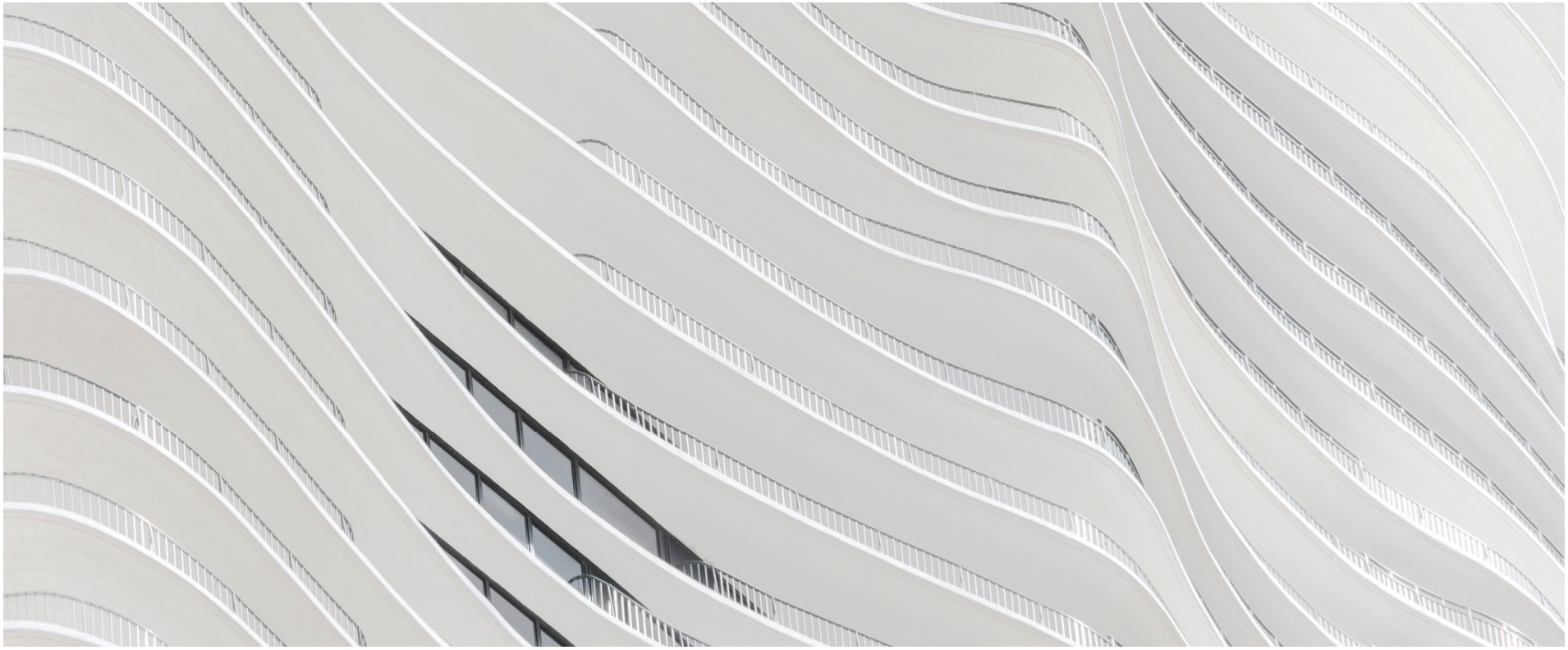
U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

February 2013

Other Legal and Regulatory Touchpoints

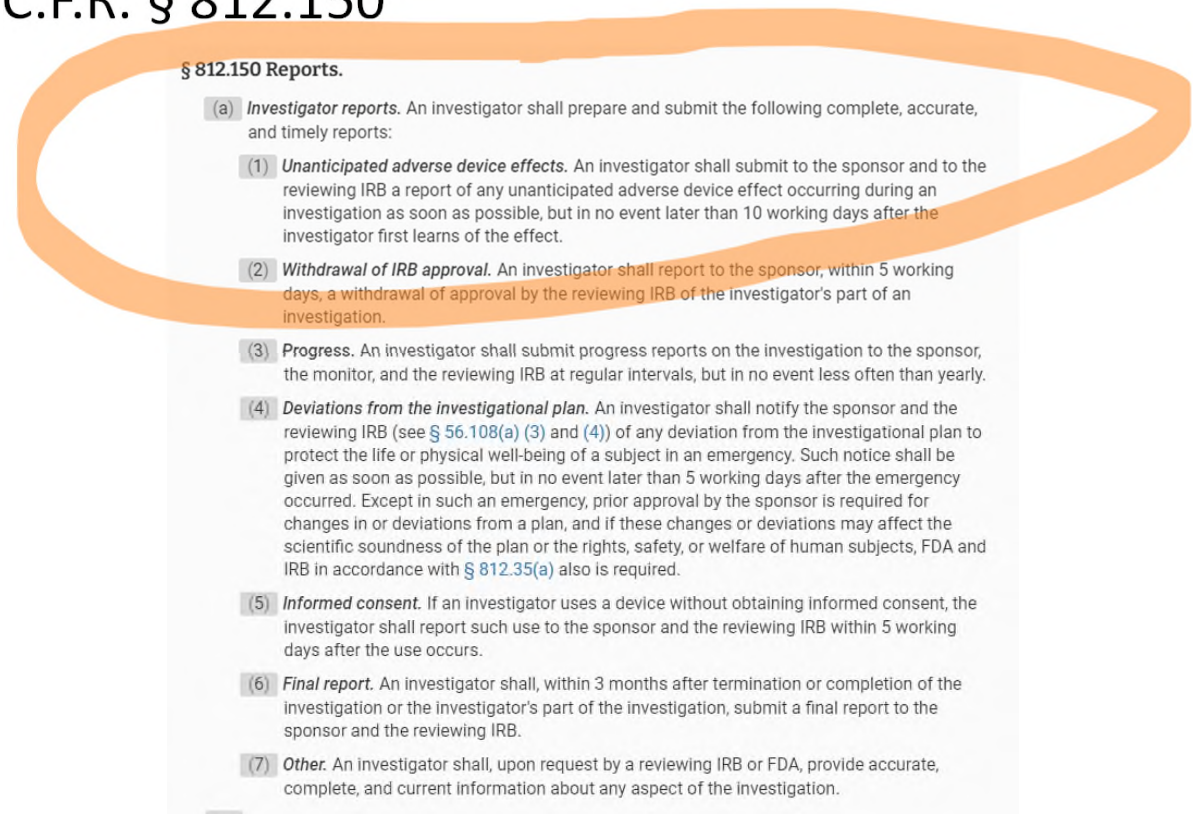
- Financial Relationships May Implicate
  - Anti-Kickback Statute
  - Sunshine Act & Rule

Adverse Event Reporting (AER)



Investigators

Regulation: 21 C.F.R. § 812.150



§ 812.150 Reports.

(a) ***Investigator reports.*** An investigator shall prepare and submit the following complete, accurate, and timely reports:

(1) ***Unanticipated adverse device effects.*** An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

(2) ***Withdrawal of IRB approval.*** An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

(3) **Progress.** An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

(4) ***Deviations from the investigational plan.*** An investigator shall notify the sponsor and the reviewing IRB (see § 56.108(a) (3) and (4)) of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with § 812.35(a) also is required.

(5) ***Informed consent.*** If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

(6) ***Final report.*** An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.

(7) ***Other.*** An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Sponsors

Regulation: 21 C.F.R. § 812.150

(b) ***Sponsor reports.*** A sponsor shall prepare and submit the following complete, accurate, and timely reports:

(1) ***Unanticipated adverse device effects.*** A sponsor who conducts an evaluation of an unanticipated adverse device effect under § 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

(2) ***Withdrawal of IRB approval.*** A sponsor shall notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.

(3) ***Withdrawal of FDA approval.*** A sponsor shall notify all reviewing IRB's and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.

(4) ***Current investigator list.*** A sponsor shall submit to FDA, at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. The sponsor shall submit the first such list 6 months after FDA approval.

(5) ***Progress reports.*** At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's. In the case of a significant risk device, a sponsor shall also submit progress reports to FDA. A sponsor of a treatment IDE shall submit semi-annual progress reports to all reviewing IRB's and FDA in accordance with § 812.36(f) and annual reports in accordance with this section.

(6) ***Recall and device disposition.*** A sponsor shall notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.

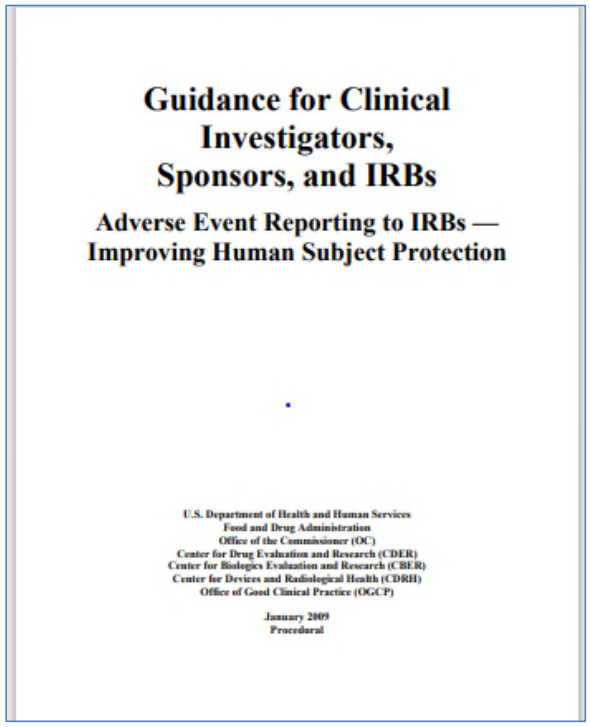
(7) ***Final report.*** In the case of a significant risk device, the sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing the IRB's and participating investigators within 6 months after completion or termination. In the case of a device that is not a significant risk device, the sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion.

(8) ***Informed consent.*** A sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.

(9) ***Significant risk device determinations.*** If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.

(10) ***Other.*** A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

Guidance



Guidance for Clinical Investigators, Sponsors, and IRBs

Adverse Event Reporting to IRBs — Improving Human Subject Protection

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner (OC)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of Good Clinical Practice (OGCP)

January 2009
Procedural

IV. REPORTING AEs TO IRBs IN CLINICAL TRIALS OF DEVICES UNDER THE IDE REGULATIONS

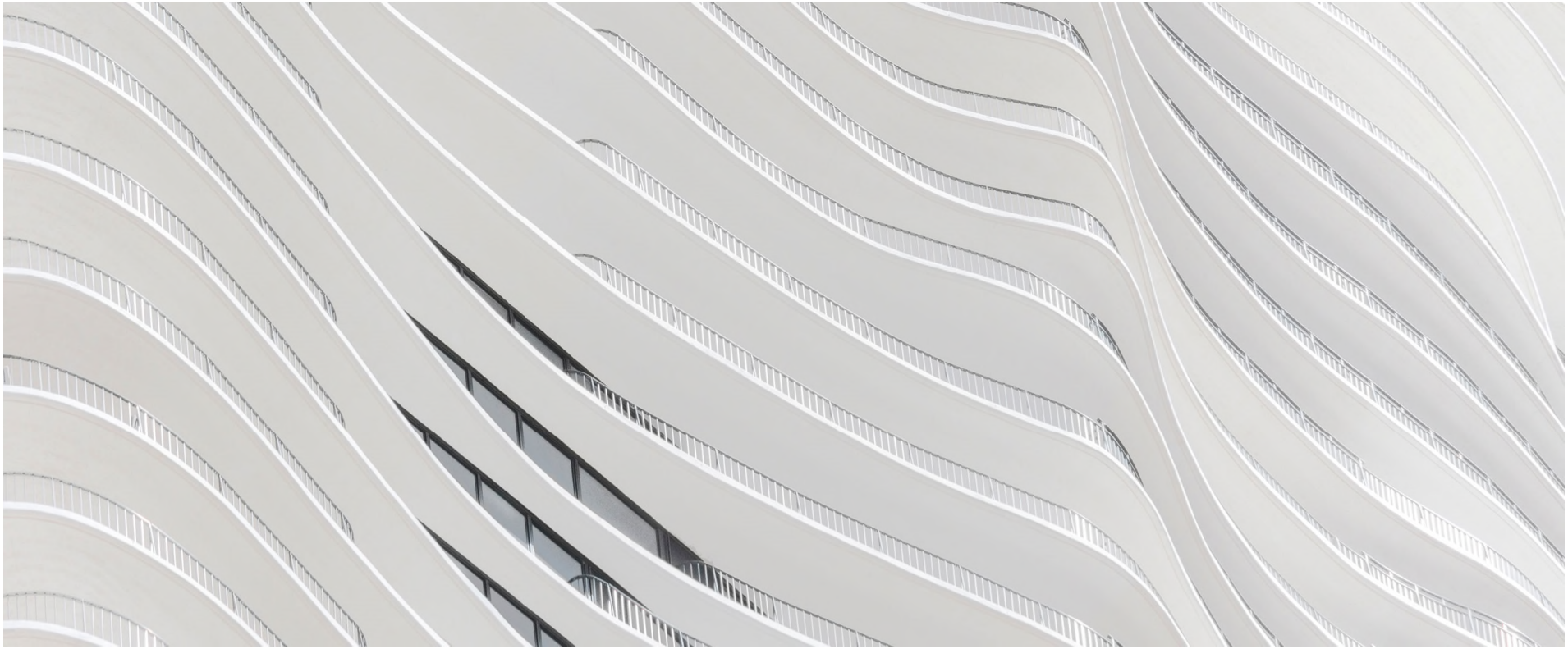
The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).

- Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the recommendations made above for the reporting of unanticipated problems under the IND regulations.

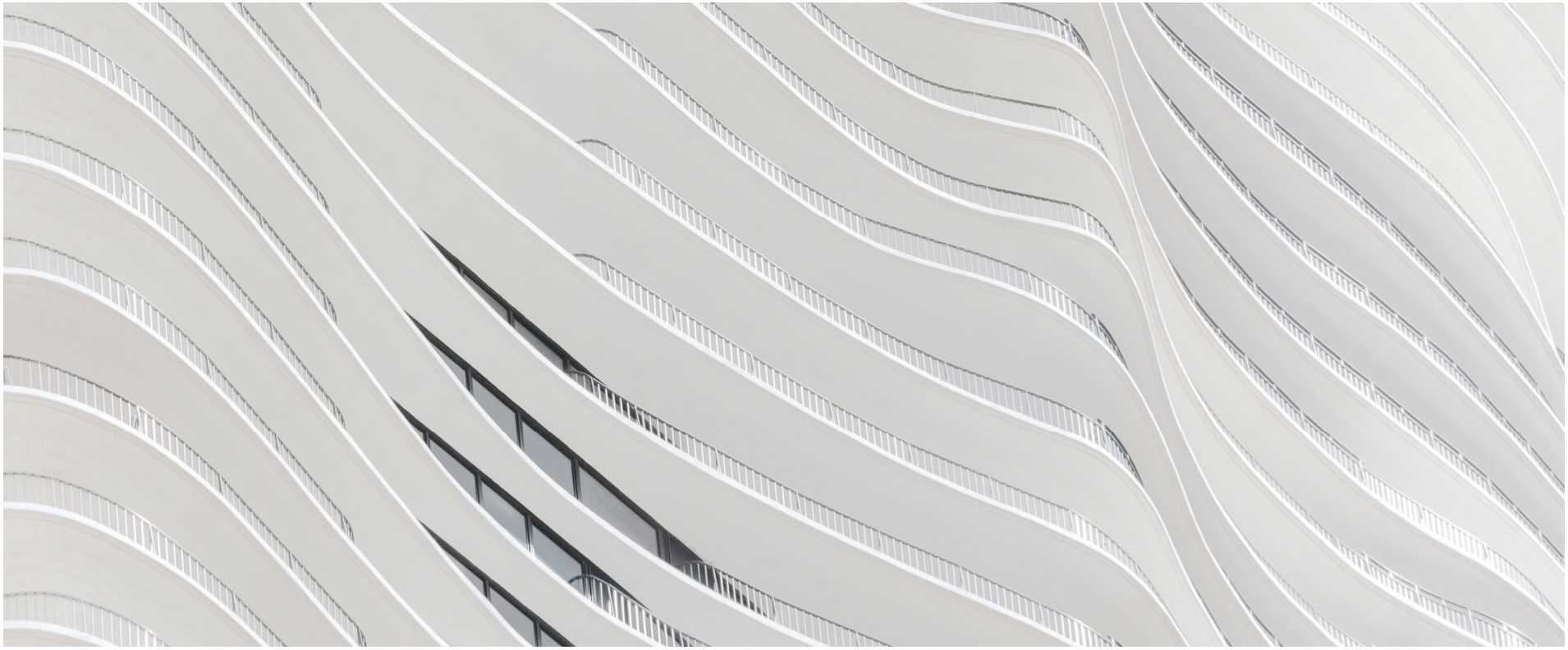
Investigator Restriction/Disqualification



Investigator Restriction/Disqualification

- FDA may initiate a "disqualification" proceeding
  - There is a process; opportunity for investigator to present his or her case
- Check the list!
- "Restricted": Lesser sanction than "Disqualified"
  - Can receive investigational product, but subject to heightened oversight

Enforcement Action



Emerging Enforcement

ClinicalTrials.gov Enforcement

- Expanded clinical trial registry and results reporting requirements in place for some time: statute in 2007, regulations in 2017
- Potential for civil monetary penalties
- FDA Guidance Finalized in August 2020: *Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank*
- In 2021, we have begun to see FDA initiate enforcement action against companies for noncompliance under FDAAA and 42 CFR Part 11
- Process provides for notification and opportunity to correct before fines would be imposed
  - Notice of Noncompliance
  - 30 days to submit results or potentially face civil money penalties of no more than $10,000 for all violations identified by FDA in a proceeding
  - Notice of Noncompliance was not the first time FDA had raised the issue in the two examples

Warning Letter: Sponsor-Investigator

- **Steiner Laboratories** (Jun 2017: device study)
  - Sponsor-investigator in significant risk device study
  - Failure to submit IDE / obtain approval from FDA, and to obtain IRB approval
    - **Combination of two 510(k)-cleared devices deemed to present a significant change or modification**
    - **Deemed significant risk because implants, presenting potential serious risk to health, safety, or welfare of a subject**
  - Failure to maintain records – including protocols, enrollment logs and records, inclusion/exclusion criteria, and signed informed consent documents
  - Failure to obtain informed consent:
    - Consent document lacked required elements
    - Consent document was not approved by an IRB

Warning Letter: Sponsor-Investigator

"A sponsor must submit an IDE application for a [Significant Risk] device to the FDA . . . ."

1. Failure to submit IDE application to the FDA, and obtain approval of the IDE from FDA and an Institutional Review Board (IRB), before allowing subjects to participate in the investigation. [21 CFR 812.20(a)(1) and (a)(2), 21 CFR 812.40, 21 CFR 812.42, and 21 CFR 812.110(a)]

Neither **(b)(4)** nor **(b)(4)** has been approved or cleared by the FDA. Although it appears that these devices are both made up of two previously cleared devices, Socket Graft (K113049) and OsseoConduct (K101718),[1] the combination of these devices constituted a significant change or modification that requires new 510(k)s (see 21 CFR 807.81(a)(3)). The change in materials and chemical composition (i.e., different calcium phosphate minerals and particle sizes), for example, could change the resorption profile of the devices, and thus could significantly affect the devices' safety or effectiveness (see 21 CFR 807.81(a)(3)(i)). As such, you were correct in submitting a new 510(k) for each of these devices.

It is our determination that your activities constitute investigations, as defined in 21 CFR 812.3(h), because you were conducting research involving one or more subjects to determine the safety or effectiveness of the devices. Moreover, FDA has determined that the investigations are of SR devices because the devices are implants that present a potential for serious risk to the health, safety, or welfare of a subject as defined in 21 CFR 812.3(m)(1).

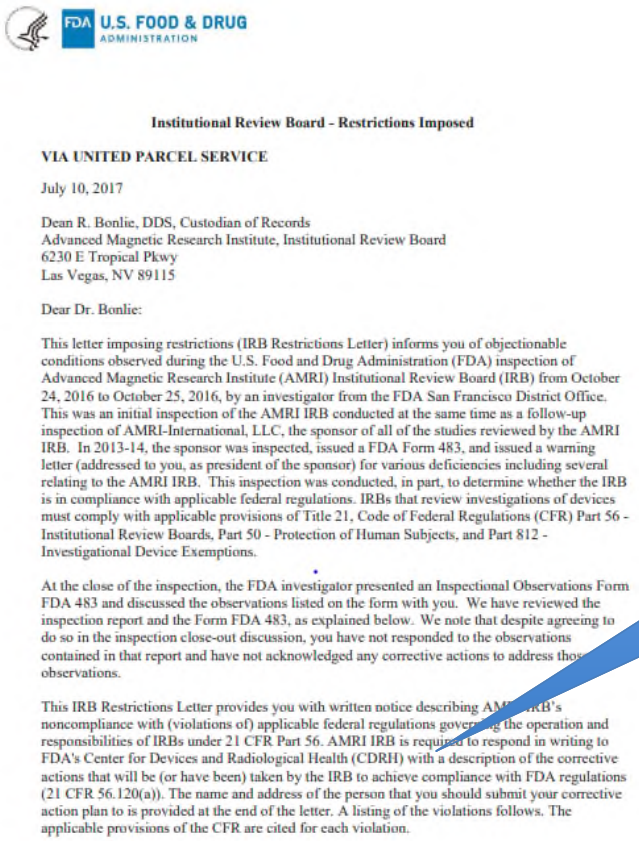
As a sponsor-investigator, defined in 21 CFR 812.3(o), you have responsibilities of being both the sponsor of the investigation who initiates the investigation and the clinical investigator who conducts and monitors the investigation. A sponsor must submit an IDE application for a SR device to the FDA (21 CFR 812.40), and shall not begin an investigation or part of an investigation until an IRB and FDA both have approved the IDE application or supplemental application relating to the investigation or part of an investigation (21 CFR 812.20(a)(1), 812.20(a)(2), and 812.42). As an investigator, you may determine whether or not potential subjects would be interested in participating in an investigation, but shall not allow any subject to participate before obtaining IRB and FDA approval (21 CFR 812.110(a)).

"As an investigator . . . you shall not allow any subject to participate before obtaining IRB and FDA approval."

Enforcement Against IRBs

- 483 Inspectional Observations
- Warning Letters
- “Restrictions Imposed” Letters
- Disqualification Proceedings

IRB Restrictions Imposed Letters



U.S. FOOD & DRUG ADMINISTRATION

Institutional Review Board - Restrictions Imposed

VIA UNITED PARCEL SERVICE

July 10, 2017

Dean R. Bonlie, DDS, Custodian of Records
Advanced Magnetic Research Institute, Institutional Review Board
6230 E Tropical Pkwy
Las Vegas, NV 89115

Dear Dr. Bonlie:

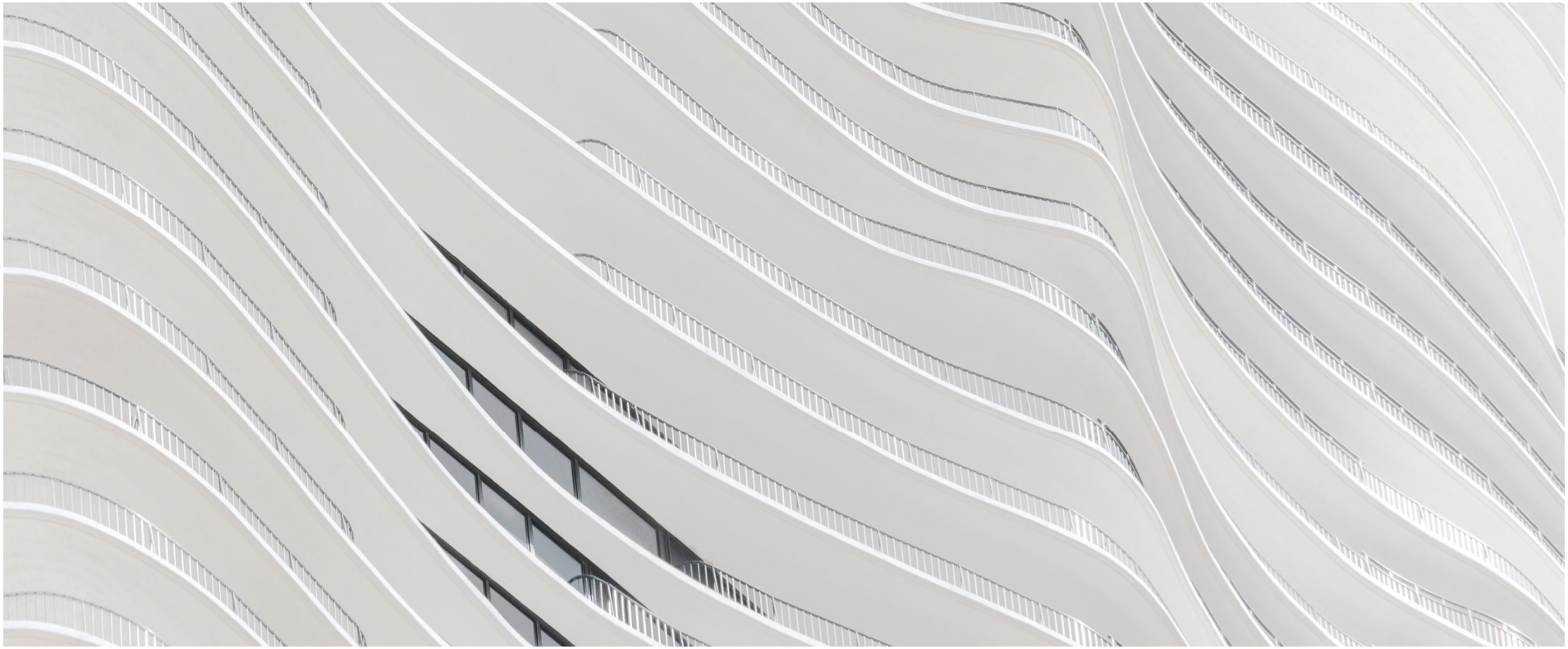
This letter imposing restrictions (IRB Restrictions Letter) informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection of Advanced Magnetic Research Institute (AMRI) Institutional Review Board (IRB) from October 24, 2016 to October 25, 2016, by an investigator from the FDA San Francisco District Office. This was an initial inspection of the AMRI IRB conducted at the same time as a follow-up inspection of AMRI-International, LLC, the sponsor of all of the studies reviewed by the AMRI IRB. In 2013-14, the sponsor was inspected, issued a FDA Form 483, and issued a warning letter (addressed to you, as president of the sponsor) for various deficiencies including several relating to the AMRI IRB. This inspection was conducted, in part, to determine whether the IRB is in compliance with applicable federal regulations. IRBs that review investigations of devices must comply with applicable provisions of Title 21, Code of Federal Regulations (CFR) Part 56 - Institutional Review Boards, Part 50 - Protection of Human Subjects, and Part 812 - Investigational Device Exemptions.

At the close of the inspection, the FDA investigator presented an Inspectional Observations Form FDA 483 and discussed the observations listed on the form with you. We have reviewed the inspection report and the Form FDA 483, as explained below. We note that despite agreeing to do so in the inspection close-out discussion, you have not responded to the observations contained in that report and have not acknowledged any corrective actions to address those observations.

This IRB Restrictions Letter provides you with written notice describing AMRI IRB's noncompliance with (violations of) applicable federal regulations governing the operation and responsibilities of IRBs under 21 CFR Part 56. AMRI IRB is required to respond in writing to FDA's Center for Devices and Radiological Health (CDRH) with a description of the corrective actions that will be (or have been) taken by the IRB to achieve compliance with FDA regulations (21 CFR 56.120(a)). The name and address of the person that you should submit your corrective action plan to is provided at the end of the letter. A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

IRB is "required to respond in writing" to CDRH "with a description of the corrective actions . . . to achieve compliance with FDA regulations."

Ethical Issues



Let's Try a Hypothetical

- Company ABC is the sponsor of a clinical trial for a device to address a serious health condition impacting children.
- The study is open to children 2 – 5 years old.
- An investigator and site (a children's hospital) are running into enrollment challenges for the study.
- "Flippy the Magic Monster Truck" is the hottest toy of the upcoming holiday season. It lights up! It talks! It flips! Ads are running constantly across all media channels. But "Flippy" is nearly impossible to find available. The original price of Flippy was $100 but some sources are now charging up to $750.
- A Company ABC board member has a connection to the company that makes "Flippy" and wants to give 100 trucks to the children's hospital that is a clinical trial site, to be offered to potential study subjects.
- The investigator wants to promote this offer on social media, targeting parents.

Question

- **What potential ethical and compliance issues do you see?**

Question

- **True or False: As long as the IRB signs off, the sponsor will be “fine” and does not need to evaluate the scenario?**

Question

- **True or False: As long as the IRB signs off, the sponsor will be "fine" and does not need to evaluate the scenario?**

FALSE

Informed Consent: Incentives for Enrollment

Payment and Reimbursement to Research Subjects - Information Sheet

Guidance for Institutional Review Boards and Clinical Investigators

The Institutional Review Board (IRB) should determine that the risks to subjects are reasonable in relation to anticipated benefits [21 CFR 56.111(a)(2)] and that the consent document contains an adequate description of the study procedures [21 CFR 50.25(a)(1)] as well as the risks [21 CFR 50.25(a)(2)] and benefits [21 CFR 50.25(a)(3)].

Paying research subjects in exchange for their participation is a common and, in general, acceptable practice. Payment to research subjects for participation in studies is not considered a benefit that would be part of the weighing of benefits or risks; it is a recruitment incentive. FDA recognizes that payment for participation may raise difficult questions that should be addressed by the IRB. For example, how much money should research subjects receive, and for what should subjects receive payment, such as their time, inconvenience, discomfort, or some other consideration. In contrast to payment for participation, FDA does not consider reimbursement for travel expenses to and from the clinical trial site and associated costs such as airfare, parking, and lodging to raise issues regarding undue influence. Other than reimbursement for reasonable travel and lodging expenses, IRBs should be sensitive to whether other aspects of proposed payment for participation could present an undue influence, thus interfering with the potential subjects' ability to give voluntary informed consent. Payment for participation in research should be just and fair. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence [21 CFR 50.20].

Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to subjects who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn. For example, in a study lasting only a few days, an IRB may find it permissible to allow a single payment date at the end of the study, even to subjects who had withdrawn before that date.

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable to FDA, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

Office of Good Clinical Practice, Updated Jan. 25, 2018

" . . . IRBs should be sensitive to whether other aspects of proposed payment for participation could present an undue influence, thus interfering with the potential subjects' ability to give voluntary informed consent."

Polling Question

- Have you ever participated as a subject in a clinical trial?
- If yes, do you remember whether you were compensated and what you received?

Vulnerable populations

Informed Consent: Vulnerable Populations

- Examples given by FDA: “children, prisoners, pregnant women, or handicapped or mentally disabled persons.”
  21 C.F.R. 56.107(a)
- Protections can also present challenges in representations of groups in research

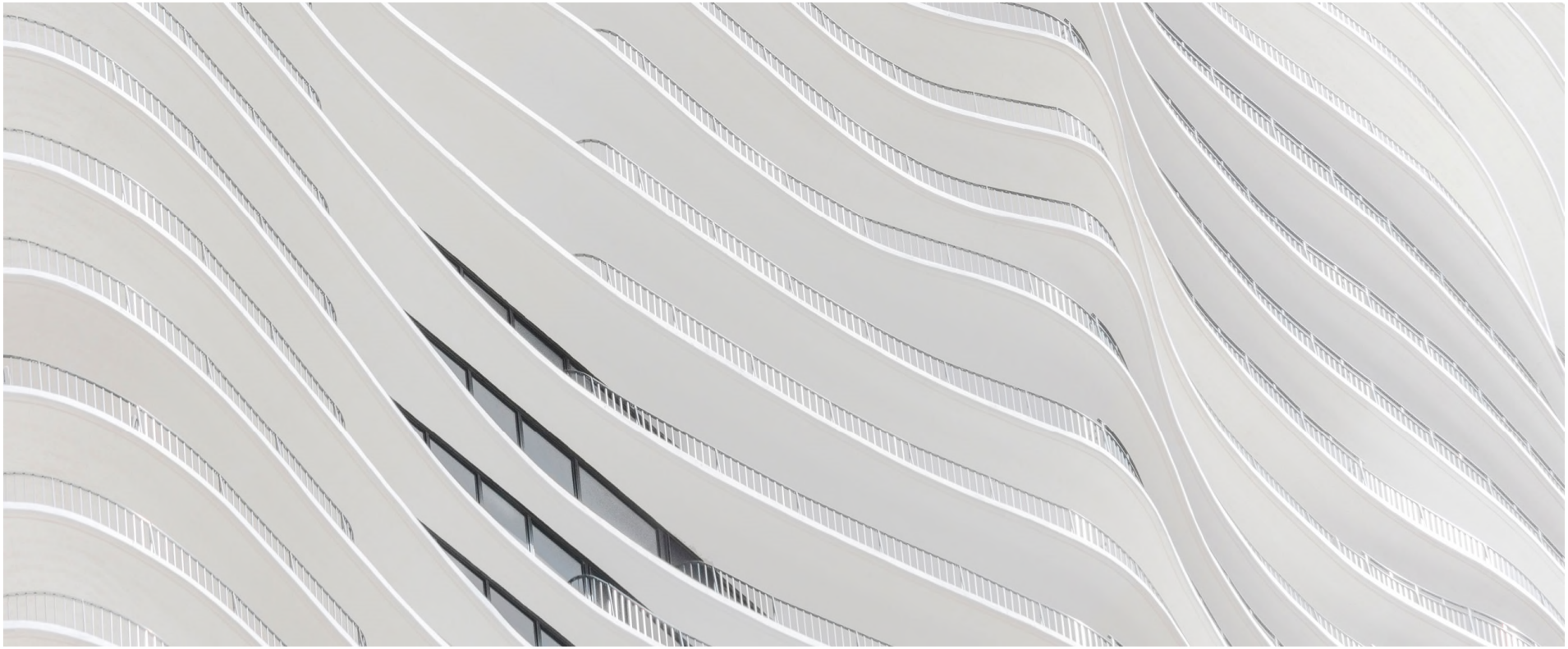
Informed Consent: Vulnerable Populations

- Specific regulations on additional safeguards for children
  - Requires seeking assent of child and permission of parent or guardian
  - In addition, if greater than minimal risk *and* potential direct benefit:
    - Risk justified by anticipated benefits
    - Risk-benefit ratio at least as favorable as alternative approaches
  - In addition, if greater than minimal risk and *no* direct benefit:
    - Must be only minor increase over minimal risk
    - Research experiences "reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations"
    - Likely to yield vitally important generalizable knowledge about child's disease/condition

Informed Consent: Vulnerable Populations

- Other potential scenarios?
  - *Where might there be a high potential pressure to participate as a study subject (even if just perceived pressure)?*

Real-World Data and Evidence



FDA Views on Data from Nontraditional Sources

Overview of Recently Enacted Authorities and Recently Adopted Guidance

- 21st Century Cures Act (2016)
  - Real World Evidence (Applies to drugs.)
  - Patient Experience Data (Applies to drugs.)
- FDA, Draft Guidance, *Submitting Documents Utilizing Real-World Data and Real-World Evidence to FDA for Drugs and Biologics* (May 2019)
- FDA, Guidance, *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020)
- FDA, Guidance, *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices* (August 2017)
- FDA, Guidance, *Use of Electronic Health Record Data in Clinical Investigations* (July 2018)
- FDA, Guidance, *The Least Burdensome Provisions: Concept and Principles* (February 2019)

Guidance for Device Companies

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

- "Under the right conditions, data derived from real world sources can be used to support regulatory decisions. RWD and associated RWE **may constitute valid scientific evidence depending on the characteristics of the data**. This guidance…describes the circumstances under which RWD may be used to support a variety of FDA decisions based on the existing evidentiary standards."

Key Concepts

Real-World *Data*

- Real-world ***data*** are data relevant to patient health status and/or health care delivery collected from various sources. RWD can come from a number of sources including, for example:
  - Electronic health records (EHRs)
  - Claims and billing activities
  - Product and disease registries
  - Patient-generated data including in home-use settings
  - Data gathered from other sources that can inform on health status, such as mobile devices

Key Concepts

Real-World *Evidence*

- Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Device Guidance on RWE

Quality Matters

- FDA will maintain its evidentiary standards through the process of regulatory decision-making, by evaluating "whether the available RWE is of **sufficient quality to address the specific regulatory decision being considered**. FDA believes that the increased use of electronic data systems in the healthcare setting has the potential to generate substantial amounts of RWD. Because these systems can vary greatly in terms of quality, not all RWD can by itself generate sufficient evidence to support an FDA regulatory decision. Nevertheless, these RWD may still provide a valuable contribution to the totality of evidence considered for the decision."
  - FDA, Guidance, *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*, at 9 (August 31, 2017)

IDEs for RWD Collection?

- Fact-specific assessment of the situation is needed
  - Device used in normal course of medical practice?
    - IDE likely not required
  - Data being gathered to determine safety and effectiveness of device?
    - IDE may be required
  - Data gathering process would influence treatment decisions?
    - IDE may be required

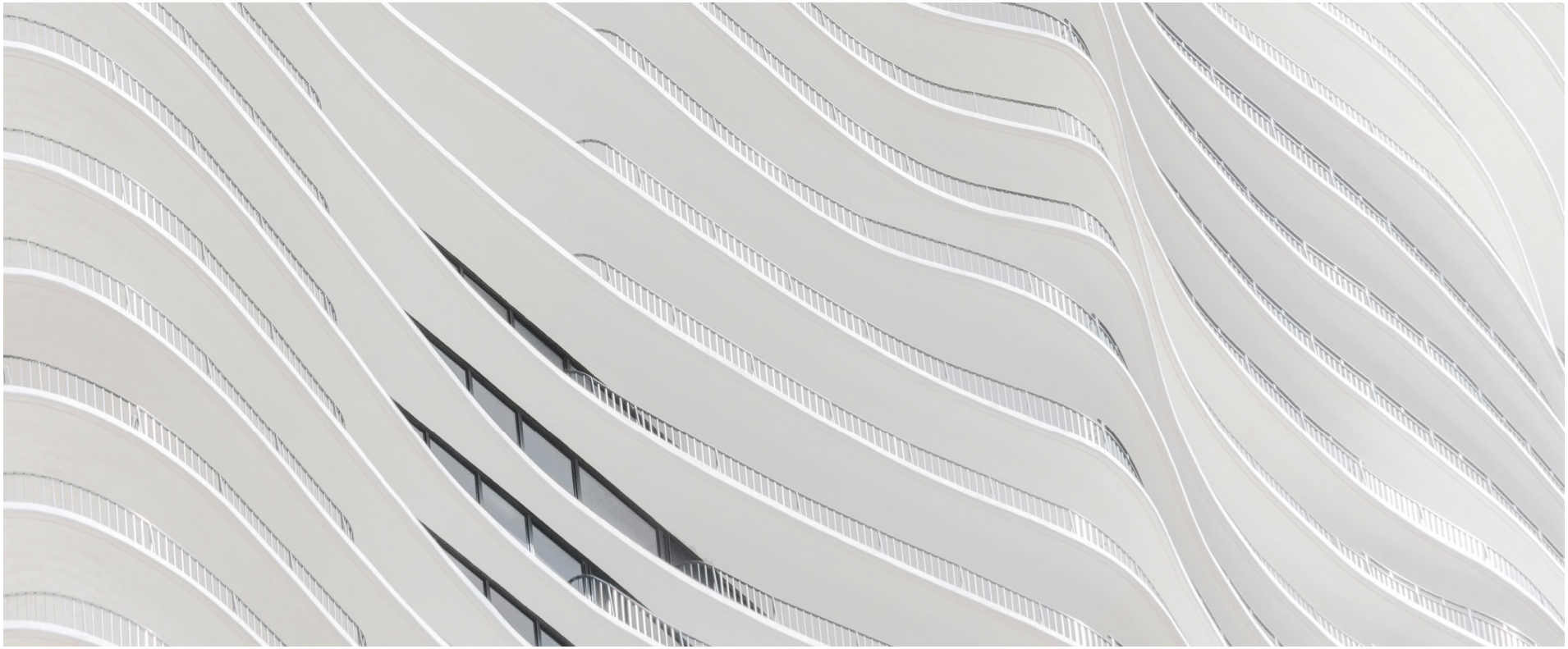
Other Protections Applicable?

- Even if the IDE regulations do not apply, the following may still apply to RWD collection and RWE generation
  - IRB Regulations (Review and Oversight)
  - Informed Consent Regulations
  - Financial Disclosure
  - Other federal state and local human subject protections
  - Don’t forget privacy laws!

Use of Foreign Clinical Data

- Potential for acceptance of foreign data even if the study was not conducted under an IDE if criteria are met
- History
  - Declaration of Helsinki
  - International Standards (ICH / ISO)
- Change to the Regulations
  - For Drug Studies: Movement to “Good Clinical Practice” in 2008
  - For Device Studies: Update to regulations to reference GCP as the standard became effective February 21, 2019

IRB Responsibilities: Key Examples



What is FDA looking for, from the IRB?

- Chapter 48: Bioresearch Monitoring (fda.gov)

FOOD AND DRUG ADMINISTRATION

COMPLIANCE PROGRAM PROGRAM 7348.809

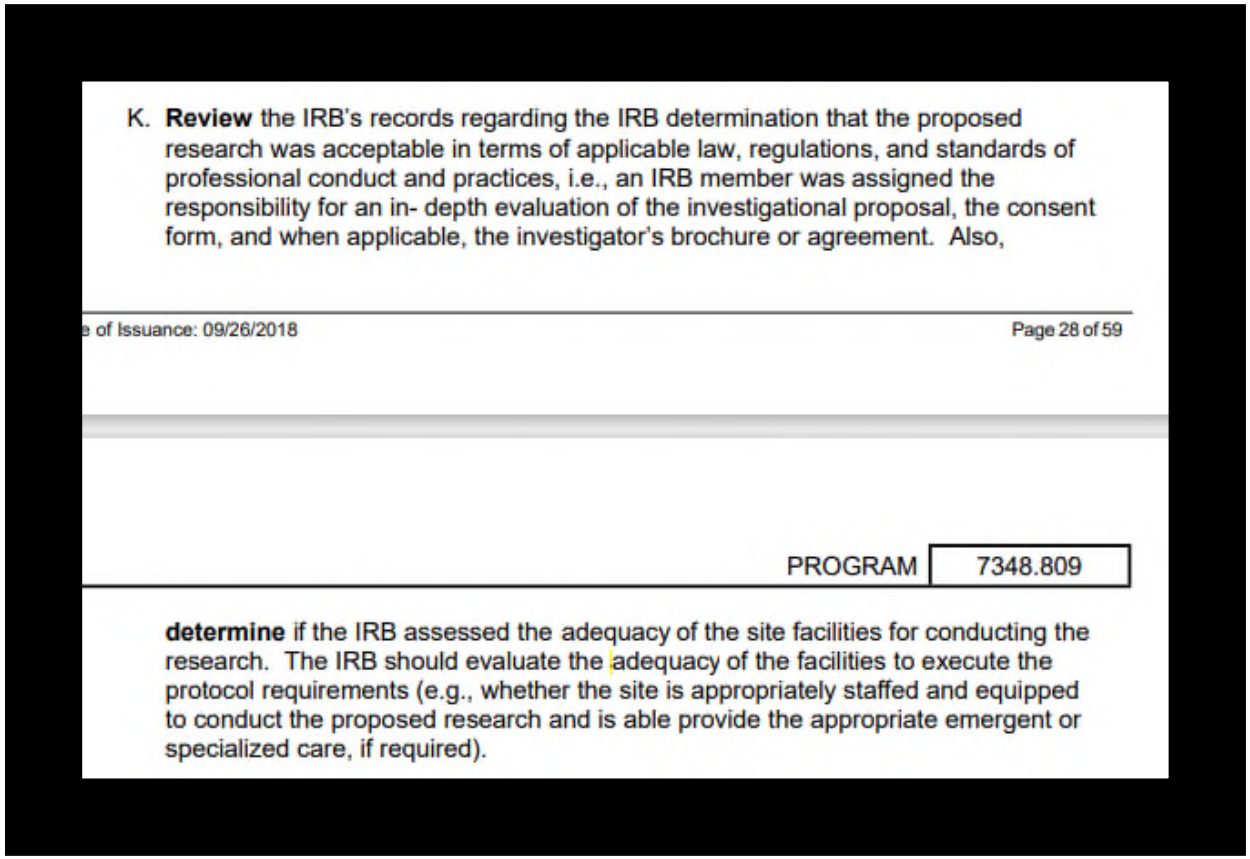
CHAPTER 48: Bioresearch Monitoring

SUBJECT: Institutional Review Boards	IMPLEMENTATION DATE: 09/26/2018
DATA REPORTING	
PRODUCT CODES	PRODUCT/ASSIGNMENT CODES
FACTS/eNSpect does not require product codes for Bioresearch Monitoring inspections.	09809: Foods
	41809: Biologics- Human Cellular, Tissue and Gene Transfer
	42809: Biologics- Blood and Blood Products
	45809: Biologics- Vaccines and Allergenic Products
	48809: Human Drugs
	83809: Medical Devices
	98809: Tobacco Products

What is FDA looking for, from the IRB?

An IRB should perform an evaluation of the clinical investigator qualifications to determine if she/he is qualified by training and experience to oversee and perform the research, i.e., curricula vitae, current medical license, if applicable, professional references, and/or research training and experience. For research involving novel technologies and/or the potential for increased risk of mortality and/or morbidity, the IRB should evaluate any additional information documenting the clinical investigator's previous specific experience in this field (e.g., as demonstrated by recent presentations or publications) and with the test article. Should questions arise regarding clinical investigator qualifications during an inspection, please contact the BIMO reviewer.

What is FDA looking for, from the IRB?



K. **Review** the IRB's records regarding the IRB determination that the proposed research was acceptable in terms of applicable law, regulations, and standards of professional conduct and practices, i.e., an IRB member was assigned the responsibility for an in- depth evaluation of the investigational proposal, the consent form, and when applicable, the investigator's brochure or agreement. Also,

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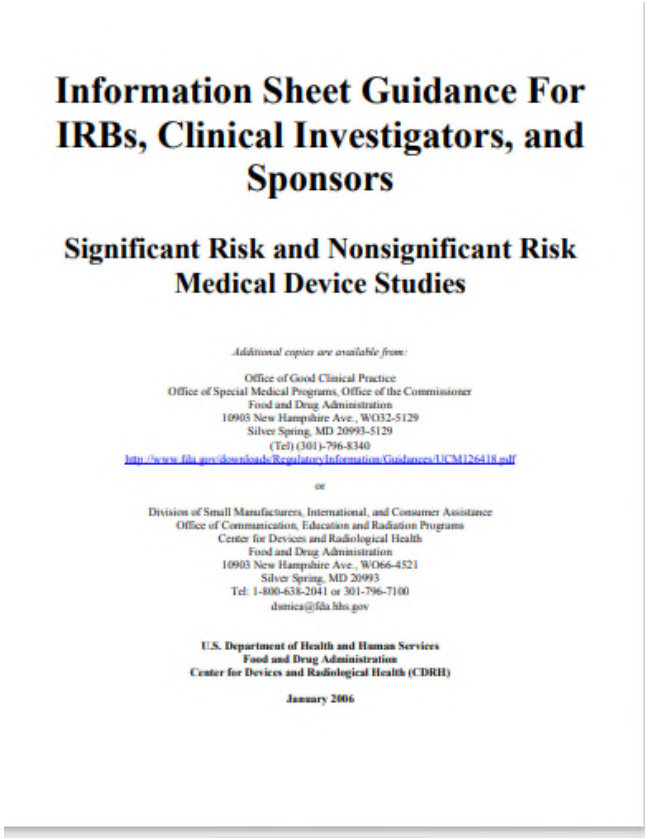
determine if the IRB assessed the adequacy of the site facilities for conducting the research. The IRB should evaluate the adequacy of the facilities to execute the protocol requirements (e.g., whether the site is appropriately staffed and equipped to conduct the proposed research and is able provide the appropriate emergent or specialized care, if required).

Who decides whether an IDE must be submitted to FDA?

- Sponsors and IRBs must determine if a study presents Significant Risk (SR), Nonsignificant Risk (NSR), or if they believe the study is IDE exempt
  - Sponsors are responsible for making the initial risk determination and presenting it to the IRB
  - The IRB is responsible for review and assessment
  - FDA is also available to help the sponsor, clinical investigator, and IRB in making the risk determination

Unless FDA agrees, you may face enforcement



Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

Significant Risk and Nonsignificant Risk Medical Device Studies

Additional copies are available from:

Office of Good Clinical Practice
Office of Special Medical Programs, Office of the Commissioner
Food and Drug Administration
10903 New Hampshire Ave., WO32-5129
Silver Spring, MD 20993-5129
(Tel) (301)-796-8340
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

or

Division of Small Manufacturers, International, and Consumer Assistance
Office of Communication, Education and Radiation Programs
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., WO66-4521
Silver Spring, MD 20993
Tel: 1-800-638-2041 or 301-796-7100
dsmica@fda.hhs.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)

January 2006

Closing Thoughts