FDA-Regulated Studies: What Investigators Need to Know

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Objectives:

- To understand what studies are regulated by the FDA
- To understand how studies are regulated by the FDA
- To understand the responsibilities of study sponsors and investigators
- Special considerations/circumstances

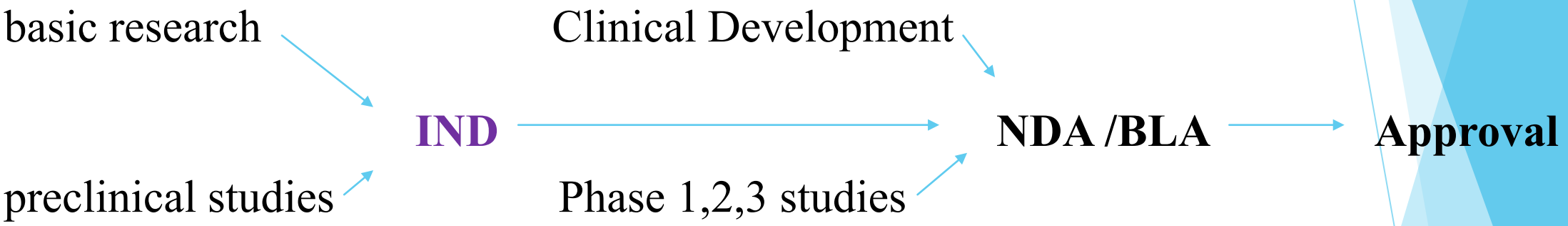
The FDA oversees clinical trials to ensure they are designed, conducted, analyzed and reported according to federal law and good clinical practice (GCP) regulations. FDA regulations and guidances for clinical trials help support efficient medical product development, while assuring trials generate the robust evidence needed to assess product safety and efficacy. The FDA regulates clinical trials for:

- **Drugs/Biological Products**
- **Medical Devices/Assays (using a risk-based, tiered classification approach)**
- **Human Cells/Tissues and Cellular/Tissue-based Products (using a risk-based approach)**

- ***Drug*** *- article (and components of such article) intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease; and articles (other than food) intended to affect the structure or any function of the body.*
- ***Biological Product -*** *a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, applicable to the prevention, treatment, or cure of a disease or condition of human beings.*
- ***Device -*** *an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, (or other similar or related article including any component, part, or accessory), intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or any function of the body, and which does not achieve its primary intended purposes through chemical action within or on the body and which is not dependent upon being metabolized for the achievement of its primary intended purposes.*

Two Phases of FDA Drug Regulation:

Pre-Approval



Post-Approval

Safety, Effectiveness, Product Integrity, Labeling, Off-label Use

Initiatives to Compress the Approval Timeline:

- **Prescription Drug User Fee Act (PDUFA)**
- **Accelerated Approval** – *for drugs/biologics that provide "meaningful therapeutic benefit…over existing treatments". Allows for use of "surrogate endpoints…reasonably likely…to predict clinical benefit". FDA usually requires postmarketing studies.*
- **Fast Track Applications** – *Product must concern life-threatening condition and address unmet medical need. FDA facilitates meetings with sponsor, prior to NDA/BLA submission.*
- **Priority Review -** *Begins when NDA/BLA is submitted for products that address unmet medical needs. Established by PDUFA.*

Part 1: INDs

When is an Investigational New Drug Application (IND) Required?

*Federal law (21CFR 312) requires drugs/biologic products to be the subject of an approved marketing application before they are **transported** across state lines. Sponsors of clinical studies to evaluate drug/biologic products must seek exemption from that legal requirement.*

An IND, filed with the FDA, is the means by which a sponsor obtains exemption and "ensures that subjects will not face undue risk of harm." An IND is required for:

- **Novel drugs/biological products used in a clinical investigation**
- **Marketed drugs/biologic products used in a clinical investigation for a new:**
  - **disease/indication**
  - **route of administration**
  - **dosage level**
  - **therapeutic combination**

A clinical study is **IND Exempt** if **all** of the following criteria are met:

- *The investigational product is lawfully marketed in the US.*
- *The investigation is not intended to be reported as a well-controlled study in support of a new indication, a significant change in labeling of the product, or to promote or commercialize the product.*
- *The investigation is not intended to support a significant change in advertising.*
- ***The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk associated with use of the product**.*
- *The investigation is conducted in compliance with the requirements for review by an Institutional Review Board (IRB) (21 CFR 56), and informed consent (21 CFR 50).*
- The investigation is not intended to promote or commercialize the product (21 CFR 312.7)

Responsibilities of Sponsors:

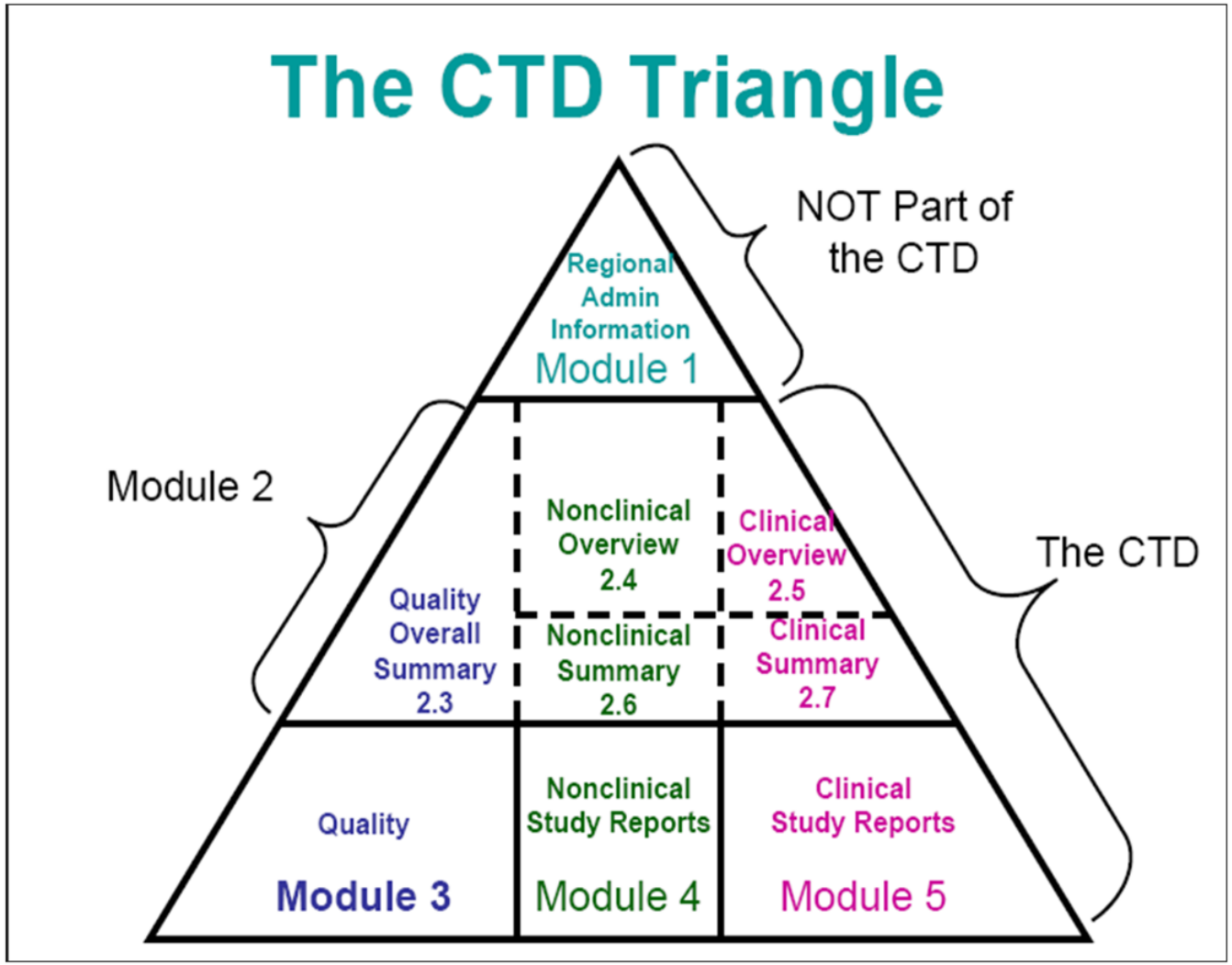
- Selecting qualified investigators, providing them with the information they need to conduct the investigation, and ensuring that FDA and all investigators are promptly informed of significant new adverse effects or risks of the drug/biologic product.
- Drug labeling-the immediate package label must bear the statement "Caution: New Drug—Limited by Federal (or United States) law to investigational use."
- Maintain control of the drug.
- Proper monitoring of the investigation and ensuring that it is conducted in accordance with the general investigational plan and protocols contained in the IND.
- Review/evaluation of evidence relating to the safety and effectiveness of the drug and reporting such information to the FDA.
- Maintaining an effective IND.

- *A Sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug. Before permitting an investigator to begin participation in an investigation, the Sponsor shall obtain a signed investigator statement (**Form FDA 1572**) and financial disclosure information (21 CFR 54).*

- *A Sponsor shall select a monitor, qualified by training and experience, to monitor the progress of the investigation.*

- *A Sponsor that determines the investigational drug presents an unreasonable and significant risk to subjects shall discontinue investigations that present the risk, notify the FDA, IRB, and all investigators, and assure the disposition of the drug. The Sponsor shall discontinue the investigation as soon as possible, $\leq$ 5 working days after making the determination.*

What is included in an IND:



Responsibilities of Investigators:

Form FDA 1572 *includes a commitment by the Principal Investigator that they:*

- Will conduct the study in accordance with the current protocol and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, the rights, or welfare of subjects.
- Will personally conduct or supervise the study and maintain complete records.
- Will inform potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent and IRB review and approval are met.
- Will report adverse experiences that occur during the investigation, to the Sponsor.

- Have read and understand the information provided by the Sponsor (*e.g., in the Investigator's Brochure*), including the potential risks and side effects of the drug.

- Will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations to meet the commitments above (*including research laboratory personnel*).

Special Considerations/Circumstances:

- Expanded Access
- Cancer studies
- Companion Diagnostics

Expanded Access

Allows use/treatment outside of a clinical trial for life-threatening illness when no other option or supporting safety and efficacy data exists. There are three tiers of access (individual, intermediate, treatment) based on size of the population and evidence of safety and efficacy.

Individual-Patient IND (Form FDA 3926 can be used by a licensed physician to streamline approval)

> **Emergency**- If emergency requires the patient to be treated before a written submission can be made, FDA may authorize use by telephone; the written submission must be made within 15 days of authorization.

Marketed Drug/Biological Products for Cancer

In 2004, the FDA recognized the following in their risk paradigm for review:

"Off-label" therapy: Common in the clinical practice of oncology.

Approved cancer therapies may be associated with significant risks: Significant toxicity, even potentially lethal toxicity, is described in the labeling.

The maximal tolerated dose often becomes the recommended dose: With the understanding that the dose may be reduced if it is not tolerated by a patient.

Additional Considerations for Cancer Studies

Standard of Care: When standard therapy in the study population is effective, use of an investigational regimen may expose subjects to significant risk by receiving a potentially less effective therapy.

Route and schedule of administration: Unless adequately described in the literature, additional nonclinical studies should be conducted to support safety and efficacy for new routes or schedules of administration.

Combination therapies: Usually, less information is available about the safety, efficacy, and dose-response of a product used in combination than for the product used alone.

- A nonclinical model should be used to demonstrate that the combination is likely to have greater activity, a more durable response, or a better toxicity profile in the study population.
- Because of the potential for synergistic toxicity, initial clinical studies of a new combination should be conducted under an IND.

Companion/*In Vitro* Diagnostics

A companion diagnostic is a medical device, often an in vitro diagnostic (IVD), which provides information essential for the safe and effective use of a corresponding drug/biological product to:

- *identify patients who are most likely to benefit from treatment*
- *identify patients likely to be at increased risk for serious side effects of treatment*
- *monitor response to adjust treatment to improve safety or effectiveness*

Inadequate performance of the test could have serious consequences (erroneous results could lead to withholding appropriate therapy or unnecessary exposure to a toxic product).

The FDA uses a risk-based approach to determine the regulatory pathway (i.e., an IND alone, or both an IND and IDE) to support the clinical study.

Part 2: IDEs

Device Classifications:

- **Class I -** low-risk devices (e.g., bandages, handheld surgical instruments, and nonelectric wheelchairs). Often exempt from FDA review but must comply with manufacturing and quality standards.

- **Class II-** intermediate-risk devices (e.g., CT scanners, infusion pumps, diagnostic assays). Typically undergo premarket notification [510(k)] review for clearance as "substantially equivalent" to an existing device.

- **Class III -** high-risk devices important to health or sustaining life (e.g., pacemakers, deep brain stimulators). Typically require premarket approval (PMA) review for safety and efficacy. FDA conducts post-marketing monitoring.

When is an Investigational Device Exemption (IDE) Required?

(21 CFR 812) An IDE permits a device to be shipped lawfully for clinical evaluation.

Clinical evaluation of a device that is not "approved" or "cleared" by the FDA for the proposed use requires:

- An investigational plan approved by an IRB
- Informed consent from subjects
- Labeling indicating that the device is for "investigational use only"
- Study reporting, records, and monitoring
- An FDA-approved IDE (if proposed use presents a "significant risk")

A device study is **exempt** from the IDE requirement if use of the device:

- Is noninvasive
- Does not require an invasive sampling procedure that presents significant risk
- Does not by design or intention introduce energy into a subject
- Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure

What is included in an IDE:

- Report of prior investigations and investigational plan
- Manufacturing, processing, packing, and storage of device
- Investigator agreement
- List of the name, address, and chairperson of each IRB
- Participating institutions
- Charge for device
- Environmental assessment
- Labeling
- Subject materials including informed consent

In Vitro Diagnostic Devices/Assays

IVD devices are "reagents, instruments, and systems intended for use in diagnosis of disease or other conditions," designed or manufactured completely or partly outside of the laboratory where they are used.

*FDA review of IVD device studies may be carried out collaboratively between CDRH and CDER/CBER to determine whether the device has been validated to meet standards for safety and efficacy for the intended use.

What about CLIA?

The Centers for Medicare & Medicaid Services regulates laboratory testing through the Clinical Laboratory Improvement Amendments (CLIA). The objective of the CLIA program is to ensure quality laboratory testing. (Although all clinical laboratories must be properly certified to receive Medicare or Medicaid payments, CLIA has no direct Medicare or Medicaid program responsibilities.)

The CLIA program regulates the ability to use results from a particular test in a particular lab for clinical decision making. The FDA regulates use in research.

Significant Risk vs. Nonsignificant Risk Device Studies

Significant Risk:

- Use in the study poses a serious risk to the health, safety, or welfare of a subject.

Non-significant Risk:

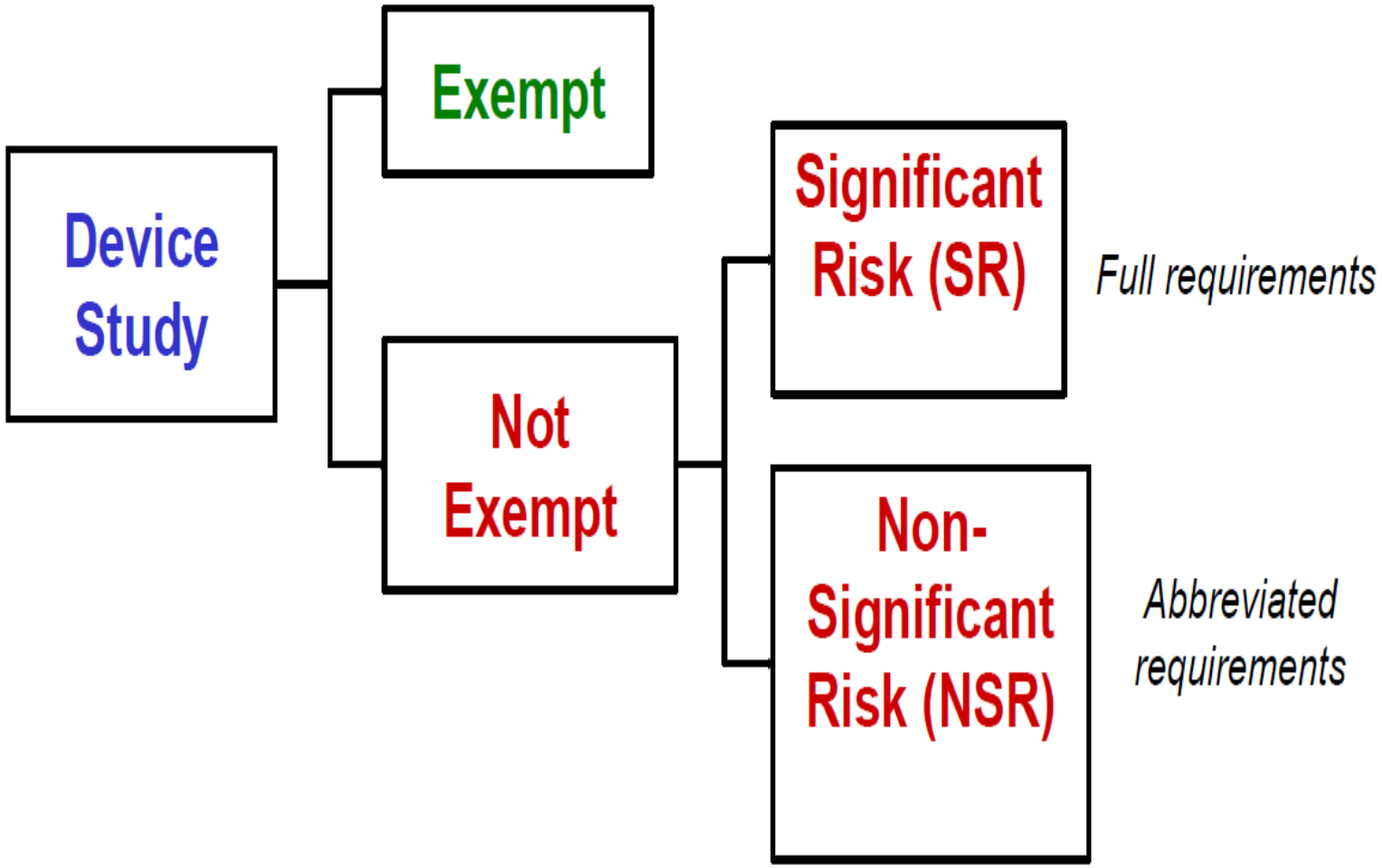
- Use in the study does not pose a serious risk to the health, safety, or welfare of a subject.

* For IVDs, risk is primarily determined by the potential consequences of an incorrect test result (a test result to assign a subject to different stratum to balance the characteristics of subjects in different treatment arms does not pose a serious risk since the result does not determine which treatment the subject receives; similarly, a test result assessing a baseline characteristic to be used in later analyses would not pose a serious risk).

Who determines risk?

Sponsors should present to the reviewing IRB an explanation why the device does not pose a significant risk. If the IRB disagrees and determines that the device poses a significant risk, the sponsor must report this finding to the FDA within five working days.

The FDA considers an investigation of a nonsignificant risk device to have an approved IDE when the IRB concurs with the nonsignificant risk determination and approves the study.


Device Study
Exempt
Not Exempt
Significant Risk (SR)
Full requirements
Non-Significant Risk (NSR)
Abbreviated requirements

Responsibilities of Sponsors:

- *Selecting qualified investigators and providing them with the information they need to conduct the investigation properly*
- *Labeling - the device must bear the statement "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use“*
- *Ensure proper monitoring of the investigation*
- *Maintain specified records and make reports to investigators and IRBs*
- *Sponsors who determine that an unanticipated adverse device effect presents an unreasonable risk to subjects must terminate all investigations or parts of the investigations presenting that risk as soon as possible (≤ 5 working days after making the determination and ≤ 15 working days after receiving notice of the effect).**

*Sponsors of studies involving significant risk devices are required to submit an IDE application to the FDA. Sponsors of studies involving nonsignificant risk devices must meet “abbreviated IDE requirements” (i.e., are **not** required to submit an IDE application to the FDA).

*Laboratory developed tests (LDTs) are IVD products intended for clinical use and designed, manufactured, and used within a single clinical laboratory.

On September 29, 2023, the FDA proposed a rule to clarify their intention to provide greater oversight through a phaseout of their enforcement discretion approach for most LDTs.

Responsibilities of Investigators:

The Principal Investigator is responsible for ensuring that the investigation is conducted according to the signed agreement, the investigational plan and protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of devices under investigation, including:

- Obtaining Informed Consent
- Financial Disclosure to Sponsor
- Records and Reports

Expanded Access:

- **Individual Patient, Emergency use**

When an individual patient is in a life-threatening situation and needs immediate treatment, there are no alternative options, and no time to get FDA approval for the use (Informed Consent, IRB concurrence; independent assessment from an uninvolved physician; and authorization from the device manufacturer are required before use). The FDA must be notified of the emergency use within 5 days.

- **Compassionate use**

To treat or diagnose an individual patient or a small group of patients with a serious disease or condition when there are no available alternative options. FDA pre-approval is required.

- **Treatment IDE**

To treat or diagnose a group of patients with a serious or immediately life-threatening disease or condition when the device is also being studied for the same use under an approved IDE.

Additional Information:

- https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application
- https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/investigational-device-exemption-ide
- https://www.fda.gov/medical-devices/products-and-medical-procedures/in-vitro-diagnostics
- **https://www.fda.gov/regulatory-information/search-fda-guidance-documents**

Questions?

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