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FDA-Regulated Research:

An Overview

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Thursday, October 13, 2022
https://research.med.cornell.edu/irb

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Today's Topics

- Federal Drug Administration (FDA): Introduction
- When Do FDA Regulations Apply?
- Investigational Drugs
- Investigational Medical Devices
- Expanded Access (Compassionate Use)
- Humanitarian Use Devices (HUD)
- Emergency Use of a Test Article (Drug, Biologic, or Device)
- FAQs

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Federal Drug Administration (FDA): Introduction

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When Do FDA Regulations Apply?

- Clinical investigation instead of research
- Test article, what's that?
- Not your typical human subject…

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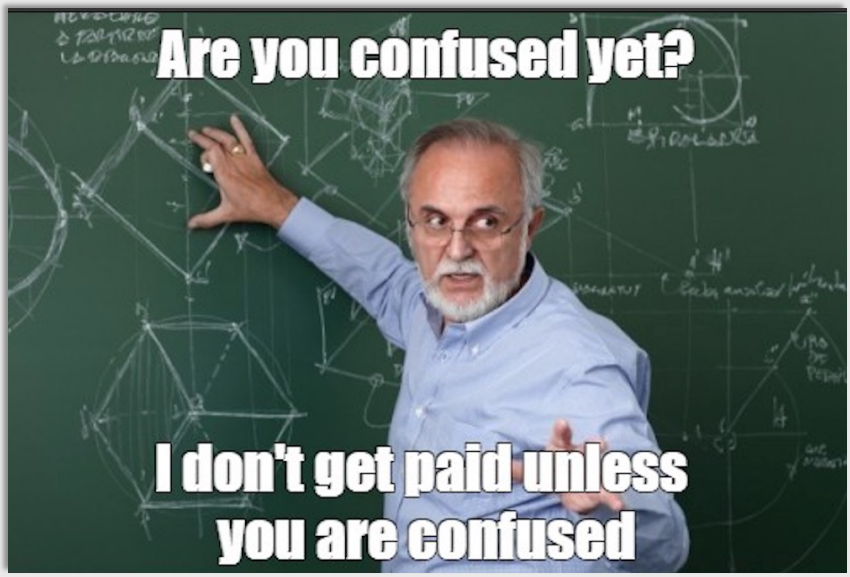

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Investigational Drugs

- Testing of unapproved drugs
- Testing of approved drugs that involves new indications or significant labeling changes

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So Why Does the FDA Need to Review INDs? Could My Study Be Exempt?

EXEMPT? Well, maybe…

Exemption from IND could be considered for:

- Clinical investigations using marketed drugs
- Bioequivalence/bioavailability studies
- Studies using radiolabeled or cold isotopes
- Studies using dietary supplements or foods
- Studies using endogenous compounds
- Pathogenesis studies using modified organisms
- Studies using wild-type organisms in challenge models
- Studies that do not have a commercial purpose

The FDA has two primary objectives in reviewing an IND:

1. to assure the safety and rights of subjects in all phases of an investigation; and
2. in phases 2 and 3, to help assure that the quality of the scientific evaluation of the drug is adequate to permit an evaluation of the drug's effectiveness and safety (21 CFR 312.22).

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Off-label Use in the Practice of Medicine

Approved products may be used by physicians outside of labeled indications for the practice of medicine

- **No IND is needed**

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Best Practice?

It's a much safer path to file an IND application and have it deemed exempt than not to file and later be subject to a determination that an IND should have been requested

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Never Forget the IRB

Whether an IND is or is not required, **all clinical research must have IRB review and approval**

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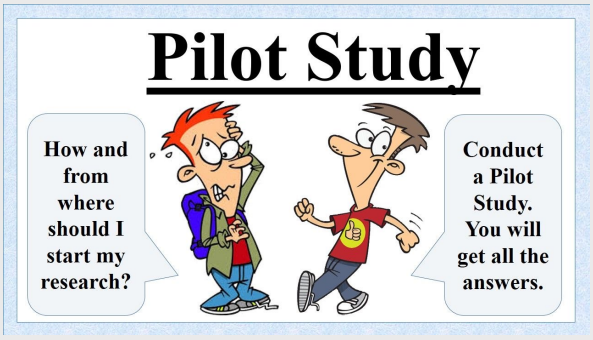
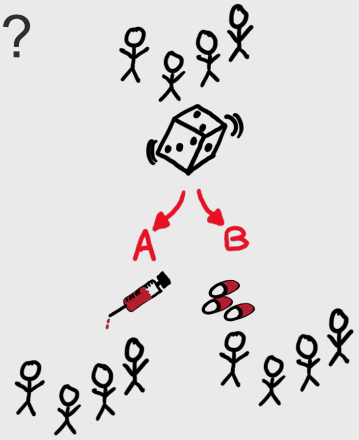
Let's Practice!

Is an IND needed?



VS.



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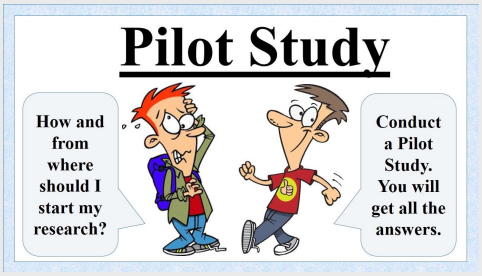
What do you think?

Is an IND needed for this ***small pilot study****?*



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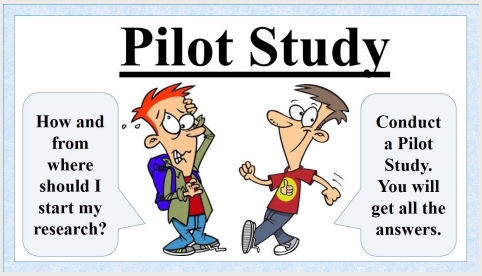
What do you think?

Is an IND needed for this ***small pilot study****?*



No!

Exempt	A small pilot study is an appropriate first step in determining whether a change in labeling should be sought	✗

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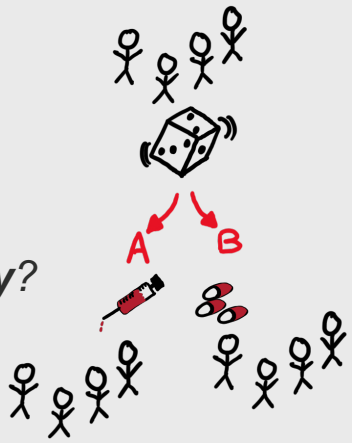
What do you think?

Is an IND needed for this ***multi-center randomized study****?*



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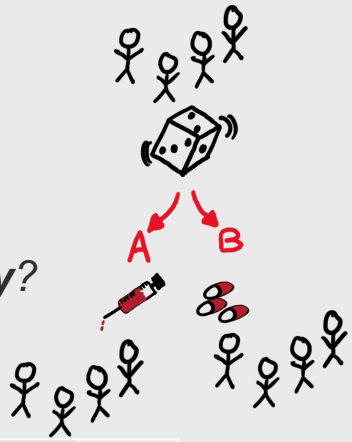
What do you think?

Is an IND needed for this ***multi-center randomized study****?*



Yes!

IND Needed	Data could be important and should be considered by the FDA.	✓

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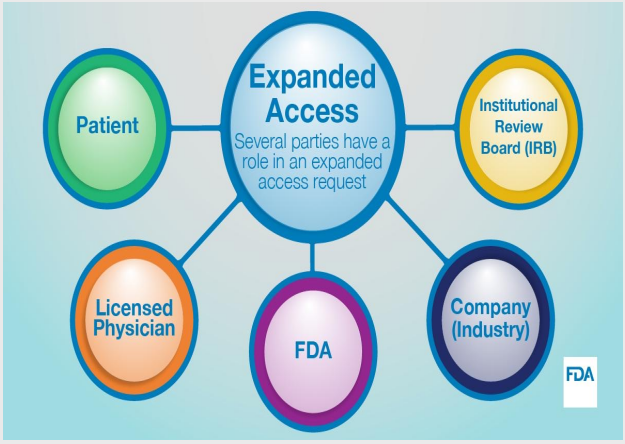
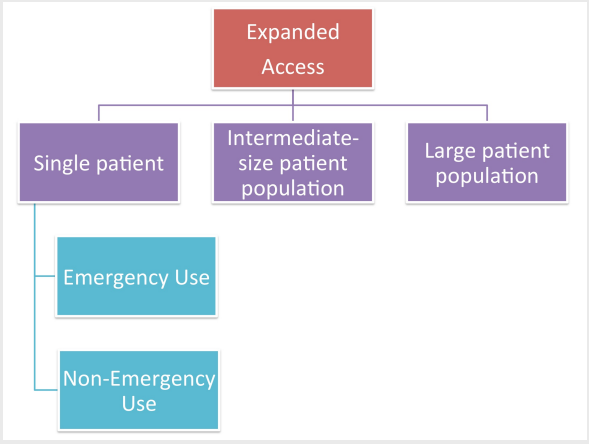
Expanded Access (Compassionate Use)





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Individual Expanded Access Involving Investigational New Drugs (SPINDs)

FDA must determine that:

- Serious/immediately life-threatening disease or condition; no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
- Potential benefit justifies the potential risks of the drug; risks are not unreasonable;
- Does not interfere with the initiation/conduct/completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use; and
- The patient cannot obtain the investigational drug under another IND or protocol.

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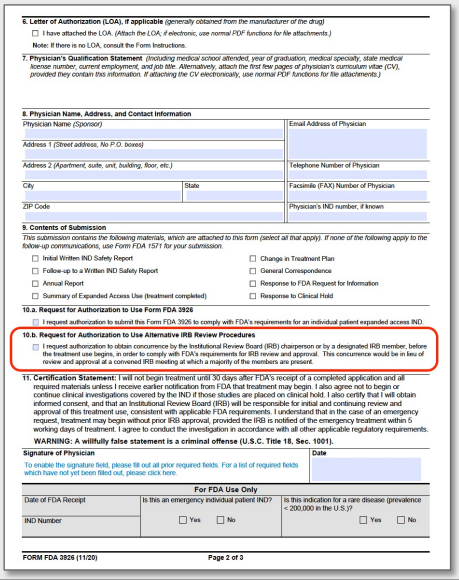
FDA Form 3296

(Emergency / Non-Emergency SPINDs): Expedited IRB Review Request



6. Letter of Authorization (LOA), if applicable *(generally obtained from the manufacturer of the drug)*
☐ I have attached the LOA. *(Attach the LOA, if electronic, use normal PDF functions for file attachments.)*
Note: If there is no LOA, consult the Form Instructions.

7. Physician's Qualification Statement *(Including medical school attended, year of graduation, medical specialty, state medical license number, current employment, and job title. Alternatively, attach the first few pages of physician's curriculum vitae (CV), provided they contain this information. If attaching the CV electronically, use normal PDF functions for file attachments.)*

8. Physician Name, Address, and Contact Information
Physician Name *(Sponsor)* | Email Address of Physician
Address 1 *(Street address, No P.O. boxes)*
Address 2 *(Apartment, suite, unit, building, floor, etc.)* | Telephone Number of Physician
City | State | Facsimile (FAX) Number of Physician
ZIP Code | Physician's IND number, if known

9. Contents of Submission
This submission contains the following materials, which are attached to this form (select all that apply). If none of the following apply to the follow-up communications, use Form FDA 1571 for your submission.
☐ Initial Written IND Safety Report ☐ Change in Treatment Plan
☐ Follow-up to a Written IND Safety Report ☐ General Correspondence
☐ Annual Report ☐ Response to FDA Request for Information
☐ Summary of Expanded Access Use (treatment completed) ☐ Response to Clinical Hold

10.a. Request for Authorization to Use Form FDA 3926
☐ I request authorization to submit this Form FDA 3926 to comply with FDA's requirements for an individual patient expanded access IND.

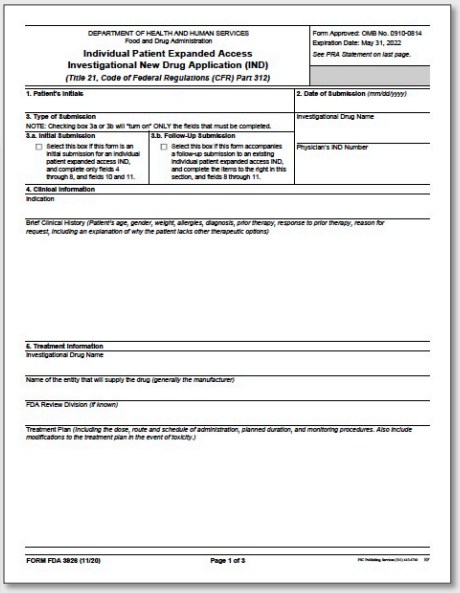
10.b. Request for Authorization to Use Alternative IRB Review Procedures
☐ I request authorization to obtain concurrence by the Institutional Review Board (IRB) chairperson or by a designated IRB member, before the treatment use begins, in order to comply with FDA's requirements for IRB review and approval. This concurrence would be in lieu of review and approval at a convened IRB meeting at which a majority of the members are present.

11. Certification Statement: I will not begin treatment until 30 days after FDA's receipt of a completed application and all required materials unless I receive earlier notification from FDA that treatment may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I also certify that I will obtain informed consent, and that an Institutional Review Board (IRB) will be responsible for initial and continuing review and approval of this treatment use, consistent with applicable FDA requirements. I understand that in the case of an emergency request, treatment may begin without prior IRB approval, provided the IRB is notified of the emergency treatment within 5 working days of treatment. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.
WARNING: A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

Signature of Physician | Date
To enable the signature field, please fill out all prior required fields. For a list of required fields which have not yet been filled out, please click here.

For FDA Use Only
Date of FDA Receipt | Is this an emergency individual patient IND? ☐ Yes ☐ No | Is this indication for a rare disease (prevalence < 200,000 in the U.S.)? ☐ Yes ☐ No
IND Number

FORM FDA 3926 (11/20) Page 2 of 3



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Form Approved: OMB No. 0910-0814
Expiration Date: May 31, 2022
See PRA Statement on last page.

Individual Patient Expanded Access
Investigational New Drug Application (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

1. Patient's Initials | 2. Date of Submission *(mm/dd/yyyy)*
3. Type of Submission
NOTE: Checking box 3a or 3b will "turn on" ONLY the fields that must be completed.
3.a. Initial Submission ☐ Select this box if this form is an initial submission for an individual patient expanded access IND, and complete only fields 4 through 8, and fields 10 and 11.
3.b. Follow-Up Submission ☐ Select this box if this form accompanies a follow-up submission to an existing individual patient expanded access IND, and complete the items to the right in this section, and fields 9 through 11.
Investigational Drug Name
Physician's IND Number
4. Clinical Information
Indication
Brief Clinical History (Patient's age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy, reason for request, including an explanation of why the patient lacks other therapeutic options)
5. Treatment Information
Investigational Drug Name
Name of the entity that will supply the drug *(generally the manufacturer)*
FDA Review Division *(if known)*
Treatment Plan (including the dose, route and schedule of administration, planned duration, and monitoring procedures. Also include modifications to the treatment plan in the event of toxicity.)

FORM FDA 3926 (11/20) Page 1 of 3

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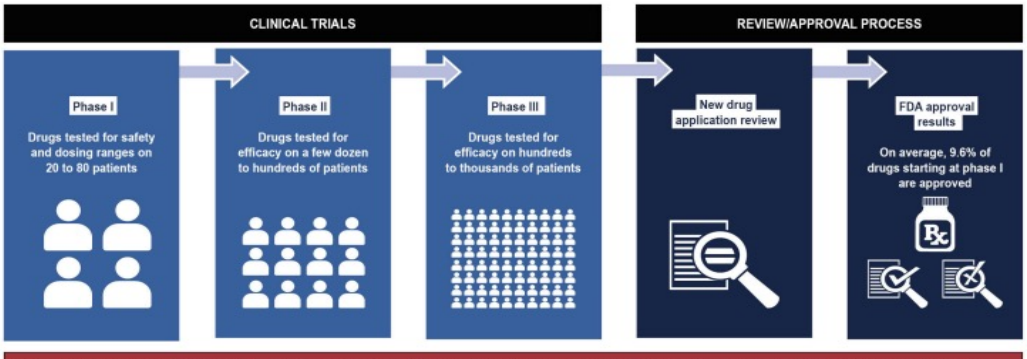
Expanded Access for Intermediate-size Patient Populations and Widespread Use of a Treatment IND

Figure 2: Types of Expanded Access Requests that Occur throughout the Food and Drug Administration's (FDA) Typical Drug Development and Approval Process



Single-patient expanded access requests (emergency and non-emergency) can generally occur during or after phases I, II, or III clinical trials.

Intermediate expanded access requests are generally initiated during or after phase II clinical trials.

Treatment expanded access requests are generally initiated during phase III clinical trials or once clinical trials are complete when a manufacturer is pursuing FDA's approval for marketing in the U.S.

Source: GAO analysis of FDA data. | GAO-17-564

Note: According to FDA officials, there can be wide variation in the number of patients involved in the different clinical trial phases, and, when a new drug is being tested for a life-threatening ailment, the drug development process may be expedited by going through only one or two phases of clinical trials before an application is submitted to FDA for marketing approval.

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Expanded Access- Information- Physicians

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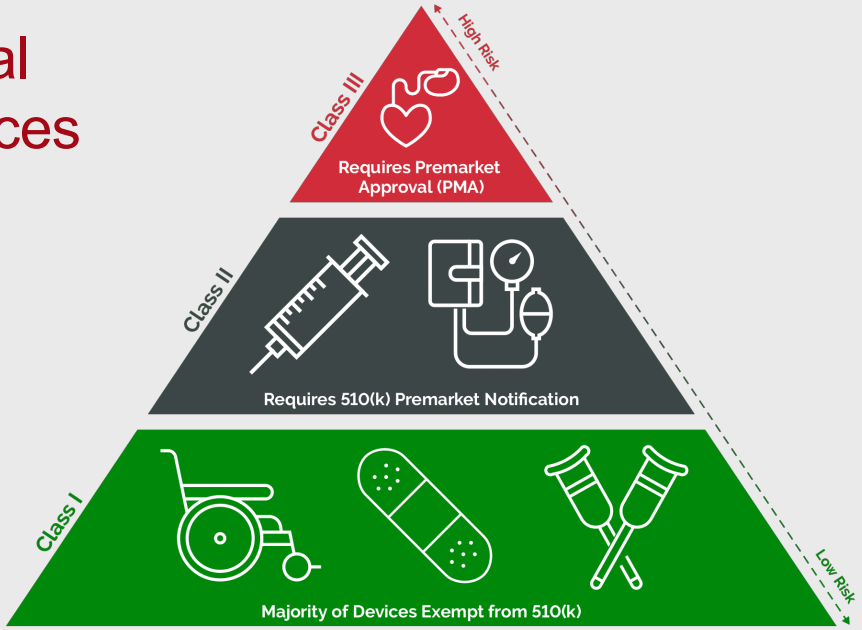
Investigational Medical Devices



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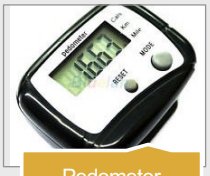
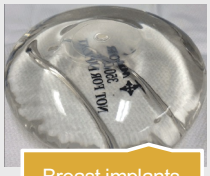
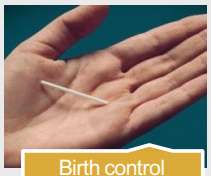
Let's Practice!

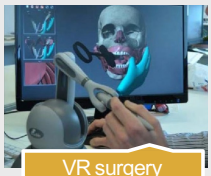
Which of the following is a medical device?


Pedometer


Home blood glucose test


Breast implants


Birth control implant


VR surgery simulator

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What do you think?

*Is a **pedometer** a medical device?*

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What do you think?

*Is a **pedometer** a medical device?*

No!

OR	Is it intended to **diagnose, cure, mitigate, treat,** or **prevent** disease?	✗
OR	Is it intended to **affect the structure** or any **function** of the body?	✗
AND	Primary intended purpose **NOT** achieved by **chemical action** or by being **metabolized**?	N/A

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What do you think?

*Is a **blood glucose test kit for home use** a medical device?*

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What do you think?

*Is a **blood glucose test kit for home use** a medical device?*

Yes!

OR	Is it intended to **diagnose, cure, mitigate, treat,** or **prevent** disease?	✓
	Is it intended to **affect the structure** or any **function** of the body?	✗
AND	Primary intended purpose **NOT** achieved by **chemical action** or by being **metabolized**?	✓

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What do you think?

*Are **silicone breast implants** medical devices?*

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What do you think?

*Are **silicone breast implants** medical devices?*

Yes!

OR	Intended to **diagnose, cure, mitigate, treat,** or **prevent** disease?	✗
OR	Intended to **affect the structure** or any **function** of the body?	✓
AND	Primary intended purpose **NOT** achieved by **chemical action** or by being **metabolized**?	✓

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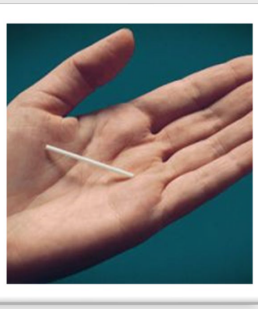
What do you think?

*Is a **subdermal birth control implant** [regulated as] a medical device?*



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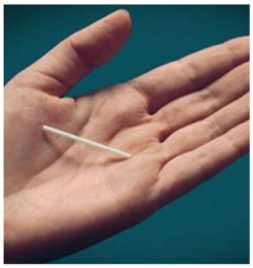
What do you think?

*Is a **subdermal birth control implant** [regulated as] a medical device?*

No!



OR	Is it intended to **diagnose, cure, mitigate, treat,** or **prevent** disease?	✗
OR	Is it intended to **affect the structure** or any **function** of the body?	✓
AND	Primary intended purpose **NOT** achieved by **chemical action** or by being **metabolized**?	✗

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What do you think?

*Is a **VR surgical simulator** a medical device?*

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What do you think?

*Is a **VR surgical simulator** a medical device?*

Yes!

OR	Is it intended to **diagnose, cure, mitigate, treat,** or **prevent** disease?	✓
	Is it intended to **affect the structure** or any **function** of the body?	✗
AND	Primary intended purpose **NOT** achieved by **chemical action** or by being **metabolized**?	✓

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Great JOB!!!

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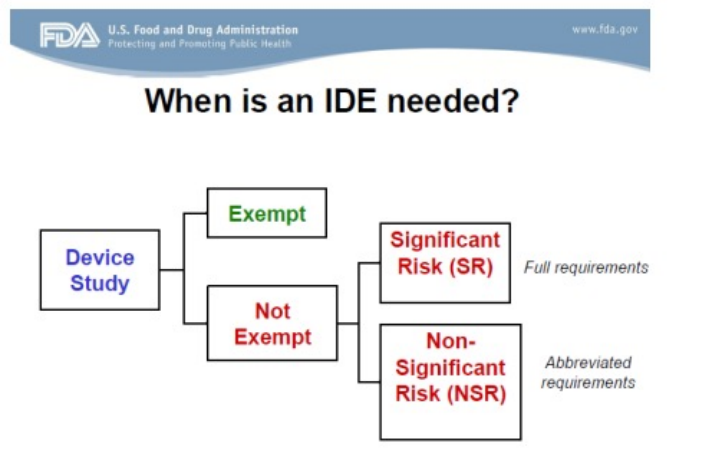
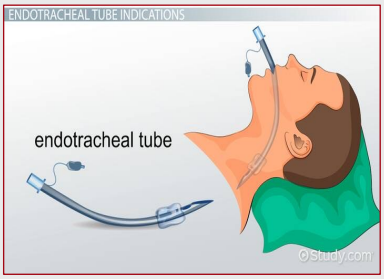
Does My Study Need an IDE?





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Who Decides Whether A Device Study is SR or NSR?

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Let's talk about HUDs!

Use is intended to benefit patients with rare conditions or diseases (affecting not more than 8,000 people in the United States per year) and

HUD is exempt from the effectiveness requirements

The use of the device does NOT constitute research; however, federal regulations require the local IRB approve the use of a HUD before it is administered to local patients

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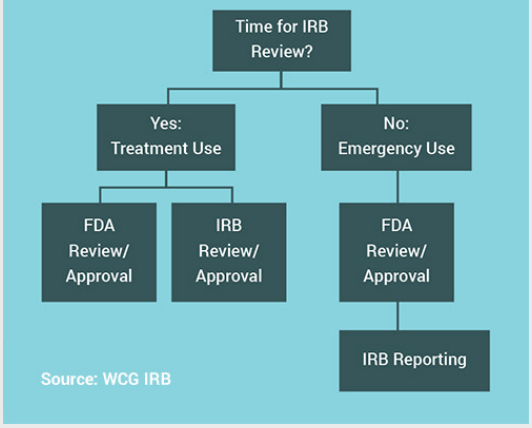
Emergency Use of a Test Article (Drug, Biologic or Device)

Figure 1: Emergency Use or Treatment Use



Life-threatening

- Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes where the end point of clinical trial analysis is survival.
- The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

Severely Debilitating

- Diseases or conditions that cause major irreversible morbidity.
- Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

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What About Informed Consent and IRB Reporting of eINDs?

Informed Consent is waived IF:

- the patient is confronted by a life-threatening situation necessitating the use of the test article;
- informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the patient;
- time is not sufficient to obtain consent from the patient's legal representative;
- no alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the patient's life.

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IRB reporting

- ✓ Reporting of the Emergency Use to the IRB is required of the investigator *within five working days* after use in a patient.
- ✓ This reporting is done via submission of an *"Emergency Use of an investigational test article"* application form in WRG and contains:
  - *Completed form 3926 or 1572/1571*
  - *Letter of approval from the FDA/sponsor*
  - *Treatment plan*
  - *Independent physician concurrence to the proposed treatment plan*
  - *Consent form (signed if there was time to seek consent from the patient)*

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FAQs

Q: Can I submit my IRB application before I know if I need an IND?

***A: Yes**, it is possible to submit an IRB application for a clinical study before an IND submission; however, if the IRB determines an IND may be needed, the study may not proceed until confirmation of IND exemption or acknowledgment of IND receipt is obtained from FDA and the 30-day review period has passed.*

Q. I'm using both a drug and a device on my study and I do not qualify for exemption. Do I need both an IND and an IDE?

***A: No**. Whether you need an IND, or an IDE depends on which product is the primary mode of action in the study. If an investigational drug product is the primary mode of action, you may need an IND. If an investigational device product is the primary mode of action, you may need an IDE. Product accountability and assessment of safety events should still occur for secondary (and other) investigational products.*

Q. I submitted an IDE application and 30 days have passed. Can I start my study?

***A: No**. Unlike an IND, IDEs require approval by the FDA before the study can commence.*

Q. If I'm using an approved drug (or device); do I need an IND (or IDE)?

***A:** If the use of the drug or device product on the protocol is per the approved product labeling, the study **may be exempt** from IND (or IDE) requirements.*

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FAQs (continued)

Q. How do I obtain a device study risk determination?

A: *The Sponsor or Sponsor-Investigator of the study should make and document an initial risk determination. The risk determination should take into account the use of the device on the protocol. This risk determination should be presented to the IRB. The IRB also needs to make a risk determination. If the IRB deems the device to be of non-significant risk, the Sponsor or Sponsor-Investigator will hold an abbreviated IDE. If the IRB determines the device to be of significant risk, the investigator must submit an IDE application to the FDA.*

Q. Do I need an investigator's brochure and what should it include?

A: *An investigator's brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) relevant to the IND/IDE. If an IND/IDE includes more than one investigational product, clinical and nonclinical data on each investigational product should be included. A medically qualified person should generally contribute to the authoring of an IB.*

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What We Covered

- Federal Drug Administration (FDA): Introduction
- When Do FDA Regulations Apply?
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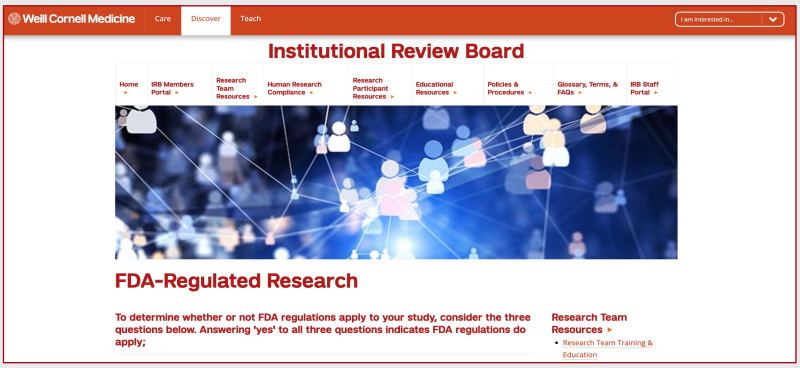
For More Information on FDA-Regulated Research:

Please visit the WCM IRB website:

https://research.weill.cornell.edu/compliance/human-subjects-research/institutional-review-board/research-team-resources/fda-regulated



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FDA Resources

- **Investigator-Initiated Investigational New Drug (IND) Applications: https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application**
- **Individual Patient Expanded Access Applications: https://www.fda.gov/drugs/investigational-new-drug-ind-application/physicians-how-request-single-patient-expanded-access-compassionate-use**
- **Information for Sponsor-Investigators Submitting INDs: https://www.fda.gov/drugs/investigational-new-drug-ind-application/information-sponsor-investigators-submitting-investigational-new-drug-applications-inds**
- **Investigational Device Exemption (IDE): https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/investigational-device-exemption-ide**
- ***FDA Guidance Document: Humanitarian Device Exemption (HDE) Program Guidance for Industry and Food and Drug Administration Staff*, issued September 6, 2019, **supersedes "*Guidance for HDE holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff, Humanitarian Device Exemptions (HDE) Regulation: Questions and Answers*," issued July 8, 2010 – https://www.fda.gov/media/74307/download**
- **Expanded Access Contacts:**
  - FDA's Office of Health & Constituent Affairs at 301-796-8460 or PatientNetwork@fda.hhs.gov
  - CDER's Division of Drug Information at 855-543-3784 or druginfo@fda.hhs.gov
  - CBER at 800-835-4709 or industry.biologics@fda.gov

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Other Resources

or

Email:
WCM IRB Office: irb@med.cornell.edu
HRPO team: hrpo@med.cornell.edu

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