
iTHRI
CARILION CLINIC
VIRGINIA TECH
UNIVERSITY of VIRGINIA
INOVA
integrated Translational Health Research Institute of Virginia

Clinical Research Exam Prep – Workshop #1

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INOVA Health System

Part 1:

IND vs. IDE

Clinical trial design (IND vs. IDE)

Part 2:

Dose Calculation

IND - Investigational New Drug Application

- Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines.
- The IND is the means through which the sponsor technically obtains this exemption from the FDA.

Two IND categories:

- Commercial
- *Research*

Three Types of IND

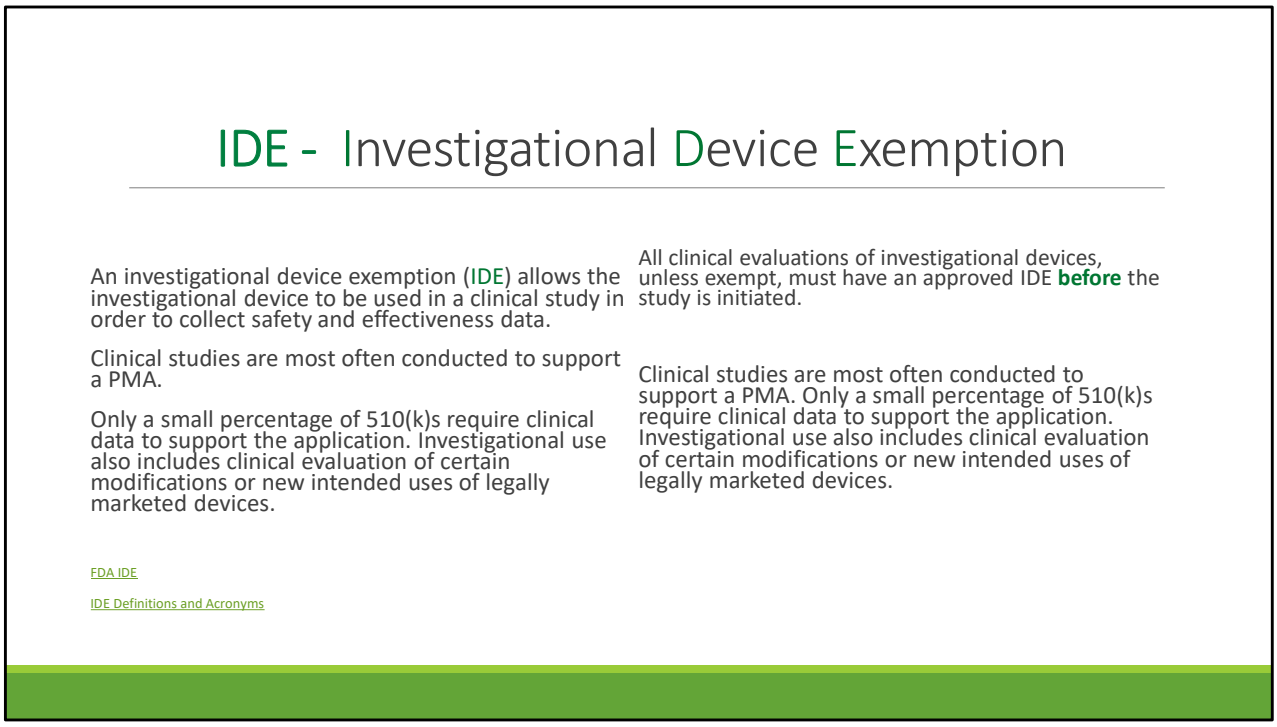
- Investigator IND
- Emergency Use IND
- Treatment IND

FDA IND

An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.



IDE –
21 CFR 812, *Investigational Device Exemptions*, 21 CFR 50, *Protection of Human Subjects*, 21 CFR 56, *Institutional Review Boards*, 21 CFR 54, *Financial Disclosure by Clinical Investigators*, 21 CFR 820 Subpart C, *Design Controls of the Quality System Regulation*,
Additional info:
21 CFR 812.1
21 CFR 812.3

Essential Documents

IND	IDE
Investigational Brochure (IB)	Instruction for Use (IFU)
Lab Manual/IP Pharmacy Manual	Didactic Training Records
Drug accountability records (including return/destruction)	Device accountability records (including return/destruction)
FDA 1572	Statement of Investigator/Financial Interest
Safety Letter/Report/DSMC/DSMB (BOTH IND + IDE)	

For IND:

NumberRegulation21CFR Part 201Drug Labeling21CFR Part 312Investigational New Drug Application21CFR Part 314INDA and NDA Applications for FDA Approval to Market a New Drug (New Drug Approval)21CFR Part 316Orphan Drugs21CFR Part 50Protection of Human Subjects21CFR Part 54Financial Disclosure by Clinical Investigators21CFR Part 56Institutional Review Boards21CFR Part 58Good Lab Practice for Nonclinical Laboratory [Animal] Studies

Question 1:

Which of the following is an FDA mandated responsibility that represents the investigator's responsibility to the sponsor?

a) Submission of an updated 1572
b) Completion of a delegation log
c) Retention of records for 3 years
d) Update the investigator's CV annually

Answer: a

Question 2:

An IND is needed for which of the following: (Choose *all* that apply.)

a) A new chemical entity
b) A new or unapproved indication
c) A & B only
d) A new dosage form or dosage level or new drug combination)
e) Off label use at the discretion of the physician
f) A, B, & D

Answer: f (A, B, & D)

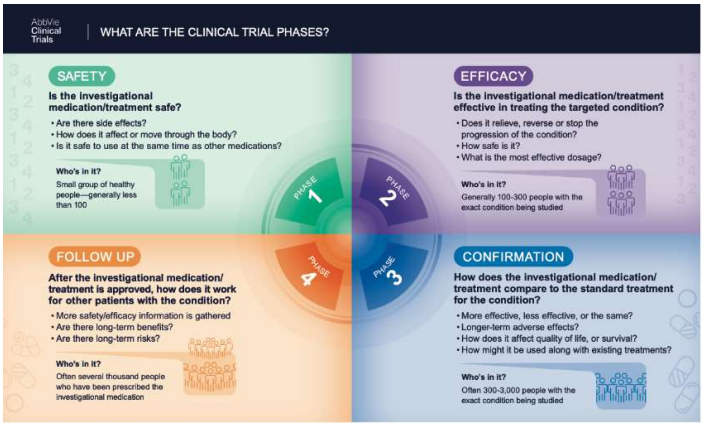
Question 3:

All of the following items are required on a Form 1572 except

a) The principal investigator's CV
b) Information of sub investigators
c) Laboratory facilities utilized
d) Financial disclosures of the principal investigator
e) IRB information

Answer: d

Clinical Trial Design: IND



AbbVieClinicalTrials.com

FDA Drug Approval Infographic


U.S. Food and Drug Administration
Drug Approval Process
What is a drug as defined by the FDA?
A drug is any product that is intended for use in the diagnosis, cure mitigation, treatment , or prevention of disease; and that tis intended to affect the structure or any function of the body.
PRE-CLINICAL
Drug Sponsor's Discovery and Screening Phase
Drug Developed
Drug sponsor develops a new drug compound and seeks to have it approved by FDA for sale in the United States.
1
Animals Tested
Sponsor must test new drug on animals for toxicity. Multiple species are used to gather basic information on the safety and efficacy of the compound being investigated/researched.
2
IND Application
The sponsor submits an Investigational New Drug (IND) application to FDA based on the results from intial testing that include, the drug's composition and manufacturing, and develops a plan for testing the drug on humans.
IND REVIEW
FDA reviews the IND to assure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate informed consent and human subject protection.
FDA's Center for Drug Evaluation and Research (CDER) evaluates new drugs before they can be sold.
The center's evaluation not only prevents quackery, but also provides doctors and patients the information they need to use medicines wisely. CDER ensures that drugs, both brand-name and generic, are effective and their health benefits outweigh their known risks.
CLINICAL
Drug Sponsor's Clinical Studies/Trials
3
PHASE 1
20-80
The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal here in this phase is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted.
4
PHASE 2
100's
The typical number of patients used in Phase 2; this phase emphasizes effectiveness. This goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment--usually a placebo, or a different drug. Safety continues to be evaluated, and short-term side effects are studied.
FDA
DRUG SPONSOR
At the end of Phase 2, FDA and sponsors discuss how large-scale studies in Phase 3 will be done.
5
PHASE 3
1000's
The typical number of patients used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and uses the drug in combination with other drugs.
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Who reviews new drug submissions?
A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists review the drug sponsor's data and proposed labeling of drugs.
What other drug products are regulated by FDA?
Drugs include more than just medicines. For example, fluoride toothpastes, antiperspirants (not deodorant), dandruff shampoos, and sunscreens are all considered drugs.
NDA REVIEW
FDA's New Drug Application (NDA)Review
POST-MARKETING
FDA's Post-Approval Risk Assessment Systems
10
Drug Labeling
FDA reviews the drug's professional labeling and assures appropriate information is communicated to health care professionals and consumers.
11
Facility Inspection
FDA inspects the facilities where the drug will be manufactured.
DAY 60
8-9
Application Reviewed
After an NDA is received, FDA has 60 days to decide whether to file it so it can be reviewed. If FDA files the NDA, the FDA Review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.
7
NDA Application
The drug sponsor formally asks FDA to approve a drug for marketing in the United States by submitting an NDA. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.
6
Review Meeting
FDA meets with a drug sponsor prior to submission of a New Drug Application.
FDA
DRUG SPONSOR
FASTER APPROVALS
The Accelerated Approval program allows earlier approval of drugs that treat serious diseases and that fill an unmet medical need. The approval is faster because FDA can base the drug's effectiveness on a "surrogate endpoint," such as a blood test or X-ray result, rather than waiting for results from a clinical trial.
The Fast Track program helps reduce the time for FDA's review of products that treat serious or life-threatening diseases and those that have the potential to address an unmet medical need. Drug sponsors can submit portions of an application as the information becomes available ("rolling submission") instead of having to wait until all information is available.
12 FDA
Drug Approval
FDA reviewers will approve the application or issue a response letter.
PHASE 4
Because it's not possible to predict all of a drug's effects during clinical trials, monitoring safety issues after drugs get on the market is critical. The role of FDA's post-marketing safety system is to detect serious unexpected adverse events and take definitive action when needed.
Once FDA approves a drug, the post-marketing monitoring stage begins. The sponsor (typically the manufacturer) is required to submit periodic safety updates to FDA.
www.fda.gov/medwatch
(800) FDA-1088 (322-1088) phone
(800) FDA-0178 (322-0178) fax
MEDWATCH
FDA's MedWatch voluntary system makes it easier for physicians and consumers to report adverse events. Usually, when important new risks are uncovered, the risks are added to the drug's labeling and the public is informed of the new information through letters, public health advisories, and other education. In some cases, the use of the drug must be substantially limited. And in rare cases, the drug needs to be withdrawn from the market.
PDUFA
Prescription Drug User Fee Act
Since the PDUFA was passed in 1992, more than 1,000 drugs and biologics have come to the market, including new medicines to treat cancer, AIDS, cardiovascular disease, and life-threatening infections.
PDUFA has enabled the Food and Drug Administration to bring access to new drugs as fast or faster than anywhere in the world, all while maintaining the same thorough review process. Under PDUFA, drug companies agree to pay fees that boost FDA resources, and FDA agrees to time frames for its review of new drug applications.
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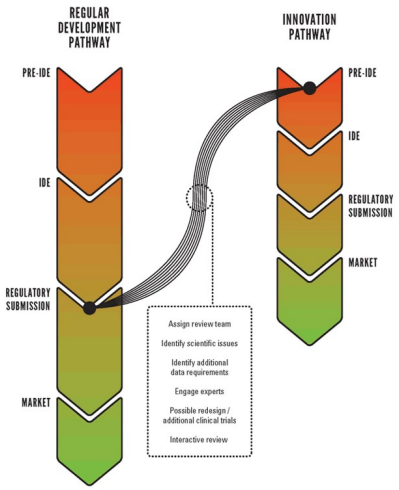
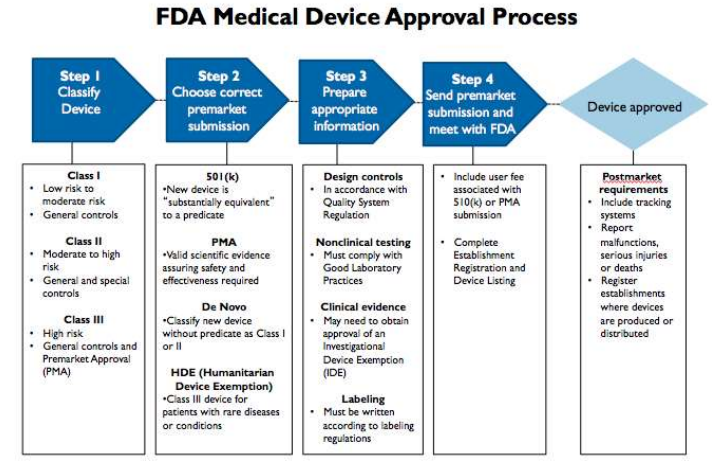
Device Development Process



FDA Device Approval Pathway



Question 4

A Phase 1 study is likely to evaluate

a) DLT (dose limiting toxicity)

b) MTD (maximum tolerated dose)

c) Half-life

d) All of the above

Answer: d

Question 5

Patients who enroll in clinical trials on the assumption that they will be cured are subject to:

a) self-deception

b) misinterpretation

c) optimism

d) therapeutic misconception

Answer: Therapeutic Misconception

"Although there has been controversy regarding a consensus definition, therapeutic misconception is then thought to include beliefs that research protocols will be individualized to the personal needs of the participant, unrealistic expectations of personal benefit through participation in the research trial, and a failure to understand that the primary goal of research is pursuit of generalizable knowledge, not personal care."

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7141972/#:~:text=Although%20there%20has%20been%20controversy,the%20research%20trial%2C%20and%20a

Question 6

In a phase 3 trial the following treatment scheme is adopted. Group A participants are started on the investigational drug and after a period of time is switched over to the control group. Group B participants are started on the control drug and the switched over to the investigational drug. This is an example of:

a) parallel design

b) factorial design

c) crossover design

d) matched pair design

Answer: crossover design

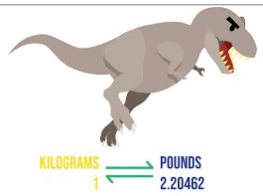
Clinical Trial Design – (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7331444/)
Factorial trial
A factorial trial study design is adopted when the researcher wishes to test two different drugs with independent effects on the same population.

Cross-over clinical trial
In cross-over clinical trial study design, there are two groups who undergoes the same intervention/experiment at different time periods of the study

Dose Calculations

UNIVERSAL FORMULA

$$\frac{\text{D (desired amount)}}{\text{H (amount on hand)}} \times \text{Q (quantity)} = \text{Dose}$$



Examples

Oral Dose

Cephalexin (Keflex) 750 mg P.O. every 12 hours is ordered. The pharmacy stocks 250 mg tablets. How many tablets should be administered per dose?

$$\frac{D}{H} = \frac{750\ mg}{250\ mg} \times 1\ tablet = 3\ tablets$$

Dosage Calculation Conversions

1 mg = 1000 mcg
1 gm (g) = 1000 mg
1 L = 1000 mL
1 mL = 1 cc
5 mL = 1 Tsp
3 Tsp = 1 Tbsp
15 mL = 1 Tbsp
30 mL = 1 oz
1 oz = 2 Tbsp
8 oz = 1 cup
1 kg = 1000 gm (g)
1 kg = 2.2 lbs

NursingSOS

Question 7:

If the patient's weight is 123 lbs, what is the weight in kg?

A. 31

B. 48

C. 56

D. 271

Question 7: Answer

Answer: C

Math Calculations_ Conversion:

(1 lb = 0.4536 kg)

Participant weighs 123 lb

123 = X

X lb x 0.4536 = Y kg

123 x 0.4536 = 55.8 kg

Rounded up = 56 kg

Math Caculations_Conversion:
(1kg = 2.2 lb)

Participant weighs 123 lb
123 = X

X lbs / 2.2046 = Y kg

123/2.2046 = 55.9 kg
Rounded up = 56 kg

Question 8:

Twenty-six subjects were enrolled in a pneumonia trial. The site received 100 bottles of IP. Each subject received two bottles. Four subjects did not return their trial bottles. How many bottles are available for the CRC to return to the sponsor at the end of the trial?

A. 44

B. 48

C. 92

D. 96

Question 8: Answer

Answer: C

Math Calculations:

IP in stock = 100 bottles

100 (in stock) - (4 patients x 2 bottles each) = # bottles of IP to return

100 – 8 = 92 (bottles of IP to return)

Question 9:

A subject is issued 120 tablets and is instructed to take 2 tablets 4 times a day. He returns 88 tablets on the morning of day 9 fasting for laboratory tests. What percent compliant is he?

A. 50%

B. 64%

C. 78%

D. 100%

Formula:

(#pills taken)/(#pills should have taken)x100

Question 9: Answer

Answer: A

Math Calculation –

120 = # dispensed,

120 (#dispensed) - 88 (# returned) =32 (# actually taken),

8 days X 8 tablets per day = 64 (# that *should* have been taken)

32 (# taken)/64 (# should have been taken) x 100= 50% compliant

Question 10:

A subject is participating in a clinical trial where only the pharmacist and the sponsor know the identity of the IP. The pharmacist has no direct contacts with the trial subject and the clinical team. Which of the following

A. Open-label

B. Single-blind

C. Double-blind

D. Triple-blind

Question 10: Answer

References: E6 1.10; E8 5.5

- A is incorrect: open label is when both the researchers and subjects know which treatment is being administered.

- B is incorrect: single blind is when subjects are not aware of which treatment is administered.

- C is correct: Double blind is when the subjects and the researchers are unaware (or blinded) to the treatment being administered

- D is incorrect: Triple blind is not a term used in clinical studies.

Questions?

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https://www.ithriv.org/
https://portal.ithriv.org

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References:

IND

IDE

ICH GCP E6

- E6 1.10

ICH GCP E8 General Considerations for clinical studies

- E8 5.5

Lad, P.M.(2022).*CCRC Exam Question Bank ACRP Certification 500 Practice Questions*.

Where to find sample questions: Quizlet, ACRP website, SOCRA Website