

Clinical and Translational
Science Institute / **CTSI**
at the University of California, San Francisco



Welcome to Online Training for
Clinical Research Coordinators

ROLE OF THE RESEARCH COORDINATOR
Investigational New Drug Application-Sponsor Responsibilities
21CFR Part 312.60-70, subpart D



Clinical and Translational Science Institute / CTSI
Accelerating Research to Improve Health

UCSF

Objectives

21 Code of Federal Regulations Part 312 is all the regulations governing drug development, and the general title for this CFR is '**Investigational New Drug**' **Application**. There are **nine subparts** all explaining different topics around managing drug products before the required FDA approval of that product.

The focus of this training is **Subpart D**. It has regulations for both the sponsor (including sponsor-investigator) and the investigator.

[Subpart D Sec. 312.50-59](#) states the **responsibilities of sponsors**. This can be UCSF investigators who write and fund their own clinical drug trials.

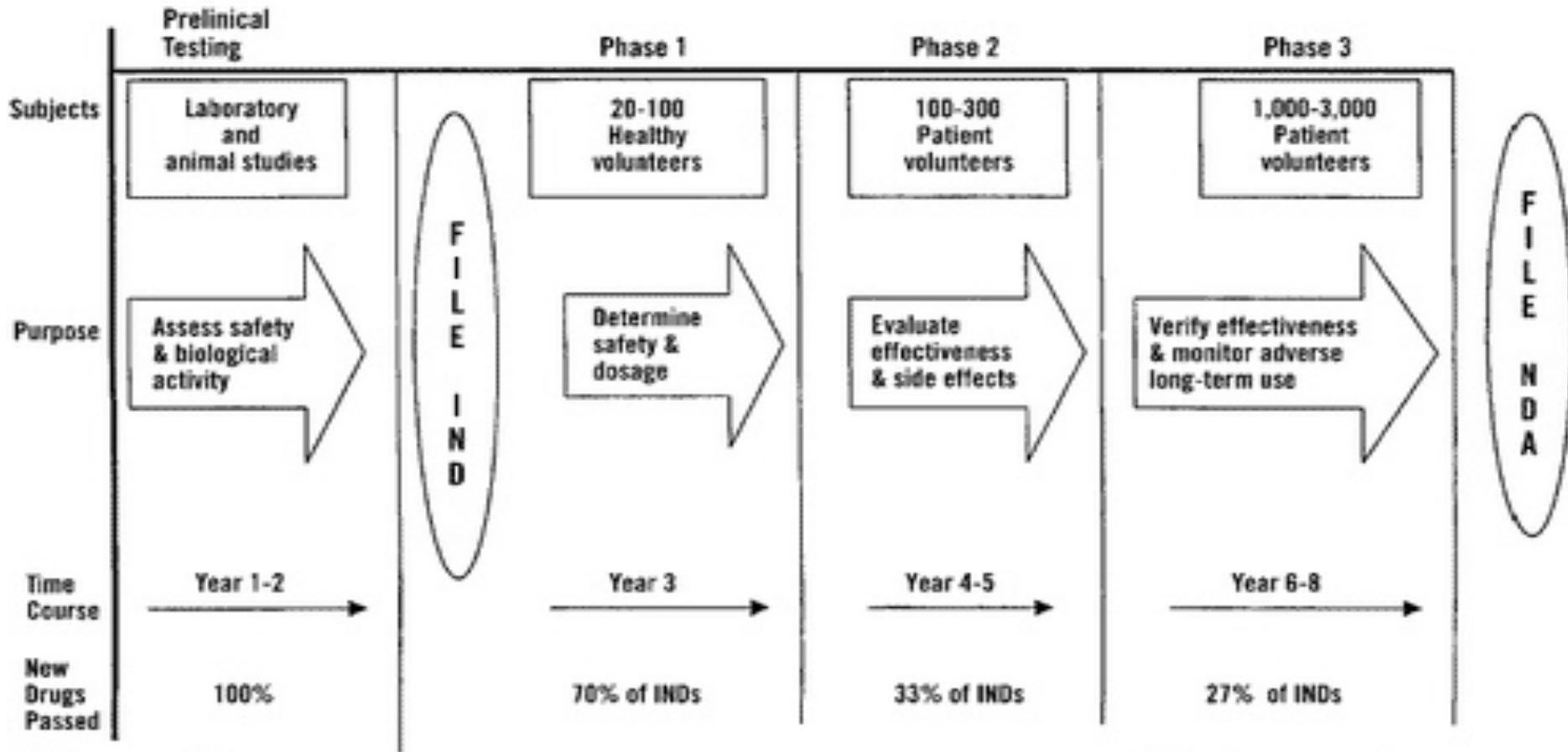
- In the majority of drug studies, the sponsor is an industry or pharmaceutical manufacturer. This section outlines their regulations.

[Subpart D Sec. 312.60-70](#) states the **responsibilities of the investigator**.

- This is the **main objective** of your training, to learn and understand the legal written document for investigator responsibilities in the FDA drug development process.



Overview of Drug Development Timeline



Medscape®

<http://www.medscape.com>



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Definitions for Drug Development Timeline

[21CFR 312.21](#)

Before approval, an **IND** (Investigational New Drug) must go through the following study phases, and this will include new drugs, biological drugs, or biological products used in the body for diagnostic purposes.

- **Phase I** (few humans exposed to product)



Drug's safety & dosage determined *and if ok* →

- **Phase II** (more humans in study population)



Drug effectiveness for treating target illness determined *and if ok* →

- **Phase III**



vs.



Drug effectiveness compared against existing treatments → *and if ok*
→ Move to possible **NDA** (new drug application) with FDA review
and possible inspection (audit of study).

It's the **LAW** overseen by the **FDA!** (Food and Drug Administration for drug studies seeking approval to be used in the general public)



IND Application

- A sponsor shall not begin a clinical investigation until the IND is in effect:
 - after notification by FDA to begin investigation,
- **OR**
- 30 days after FDA receives the IND ([21 CFR 312.40](#)).
- A sponsor shall not begin a clinical investigation if FDA places the study on clinical hold, which is an order to delay or suspend an investigation ([21 CFR 312.42](#)).
- Ship study drug on 'day 31' if allowed to proceed.
- All clinical trials must be reviewed and approved by the IRB prior to subject's being consented and enrolled.



Investigator Responsibilities when managing Sponsored IND Trials

- It is all about overseeing **subject safety, data integrity** and upholding regulatory compliance!



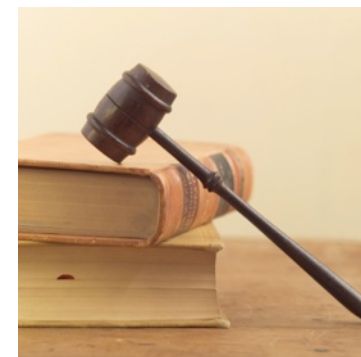
- It's that simple and it's the LAW!



What does Regulatory Compliance Look Like?

Remember the Code! [21 CFR 312.60-70 Subpart D](#)

- § 312.60 — General responsibilities of investigators
- § 312.61 — Control of the investigational drug
- § 312.62 — Investigator record keeping and record retention
- § 312.64 — Investigator reports
- § 312.66 — Assurance of IRB review
- § 312.68 — Inspection of investigator's records and reports
- § 312.69 — Handling of controlled substances
- § 312.70 — Disqualification of a clinical investigator



General Responsibilities of the Investigator

21 CFR 312.60

- Investigation conducted according to the signed investigator statement (form 1572), investigational plan, and applicable regulations
- Protect the rights, safety and welfare of subjects under their care
- Know and Follow FDA Codes and Guidance



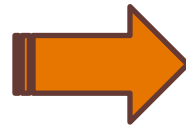
- Submit required study documents to the Institutional Review Board
- Know and Follow State Guidance including HIPAA and Subject Bill of Rights
- Know the Manufacturer Investigator Brochure (IB) safety results
- Sponsor instructions:
 - Clinical Laboratory
 - Imaging Laboratory
 - IVRS –interactive voice response system
 - Electronic Data Capture



General Responsibilities of Investigators

21 CFR 312.60

Obtain informed consent of each human subject who receives the investigational new drug



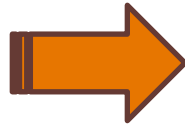
- Prior to any study procedures
- Re-consent as soon as knowledge of **new information** since the subject was last consented:
 - An Updated Investigator Brochure
 - A Safety alert
 - Added Procedures
 - New Unanticipated problems



General Responsibilities of Investigators

21 CFR 312.61

Control of investigational drugs from receipt, to storage, to dispensing, to monitoring expiration dates, to destruction at the end of the trial.



- Temperature, light, humidity controls for storage
- Secure, limited access
 - Investigational Pharmacy
 - Transport to infusion center
 - Storage in infusion center prior to subject administration
- Investigational drug *sent home* with the subject
 - Transport of investigational drug
 - Storage controls at home



General Responsibilities of Investigators

[21 CFR 312.61](#)



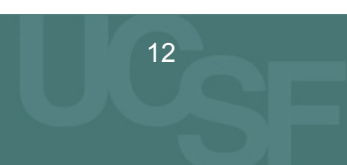
- Administer investigational drug only to consented subjects who are:
- Under the investigator's personal supervision, or,
- Under the supervision of a sub-investigator listed on the 1572 as delegated by the principal investigator.
- Shall not supply the investigational new drug to any person not authorized to receive it by being listed on a 1572 (even if it is a physician)



Record Keeping Responsibilities of Investigators

[21 CFR 312.62](#)

- **Adequate Case History documentation** for subjects that receive the investigational new drug or are *randomized as a control in the investigation*
- Documentation records for each subject who gave informed consent
- The investigator is responsible for the record documenting all observations and other data showing compliance to the protocol and an understanding of data collection integrity. Managing the copies of documents filed is delegated to the CRC.



Record Keeping Responsibilities of Investigators

21 CFR 312.62

What must be done to prepare and maintain adequate and accurate case (subject) histories?

- ✓ Document all clinical information required by protocol, including subject counseling on pregnancy or drug administration
- ✓ Maintain adequate records of Disposition of drug –use by subjects dates and quantity and lot number;
- ✓ Document assessment of abnormal findings in Radiology, Pathology and Laboratory reports
- ✓ Document any instance of subject non-compliance to protocol visits or drug intake
- ✓ Documents that collect subject information, i.e. quality of life questionnaires or diaries of when the pill was taken at home.



Record Keeping Responsibilities of Investigators

21 CFR 312.62

Record Keeping Rule #1: If it is not documented, it did not happen.

- ☑ Informed Consent Process Documentation
- ☑ Informed Consent Form
- ☑ Eligibility Checklist
- ☑ Diagnostic Study Reports
 - blood, urine, pathology
- ☑ Study Worksheets
- ☑ Procedures
 - X-ray/MRI/CT
 - Photographs
- ☑ Clinic Notes
- ☑ Hospital Notes
- ☑ ER Notes
- ☑ Urgent Care Notes
- ☑ OR Notes
- ☑ Doctors, Nurses, and Research Staff Notes
- ☑ Study Worksheets
- ☑ Pharmacy Worksheets
- ☑ Subject Compliance Diaries

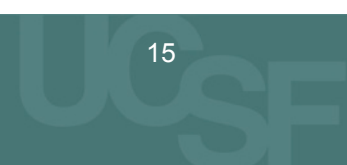


Record Keeping Responsibilities of Investigators

21 CFR 312.62

Retain all records

- required to be maintained under this CFR for a period of **2 years following the date a marketing application is approved** for the drug for the indication for which it is being investigated;
- or, if no application is to be filed or if the application is not approved for such indication, **until 2 years after the investigation is discontinued** and FDA is notified.
- An approximate storage time if 15 years...BUT Never destroy pharmaceutical study patient case files and regulatory files until receiving approval from them.



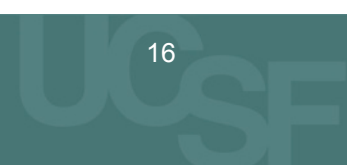
Inspection of Records and Reports

21 CFR.68

- All records will be inspected; both paper or electronic in format and must show signatures of person creating document
- Particular training should be provided to investigators and staff on ALCOA and other good documentation practice requirements. ALCOA(Attributable-Legible-Contemporaneous-Original-Accurate)
- Changes in documentation must be made by qualified research staff on study team and first documentation must be crossed out but legible.

One of the most common inspection findings in investigator site inspections is lack of reliable, accurate and adequate source documentation.

See next slide for FDA inspection report →



3. You failed to conduct the studies or ensure they were conducted according to the investigational plan [21 CFR 312.60].

A. The protocol specified that to be included in the study, the subject was to have documentation of **(b) (4)** as follows:

1. There is electrocardiogram (ECG) documented **(b) (4)** on the day of screening or randomization;
2. The patient has had a symptomatic episode of paroxysmal or persistent **(b) (4)** documented by 12 lead ECG within six months prior to randomization; or
3. There is documentation of symptomatic or asymptomatic paroxysmal or persistent **(b) (4)** on two separate occasions, at least one day apart, one of which is within six months prior to randomization.

Source documents showed that Subjects #003 and #015 did not meet this inclusion criterion, but were randomized into the study and dispensed study drug.

B. The protocol specified that subjects with severe renal impairment (estimated creatinine clearance < 30 mL/min) were to be excluded from the study. Lab results identified that Subject #003's screening creatinine clearance was 21 mL/min and thus met this exclusionary criterion. We note, however, that your site randomized this subject into the study.

C. The protocol stated that subjects with active liver disease, including but not limited to (a) Persistent ALT, AST, Alkaline Phosphatase > 2 X Upper Limit of Normal (ULN); (b) known active Hepatitis C; (c) active Hepatitis B; and (d) active Hepatitis A were to be excluded from the study. The protocol further noted that patients with a known history of Hepatitis B or C must undergo hepatitis serology for Hepatitis B and C prior to inclusion in the study.



Investigator Reports

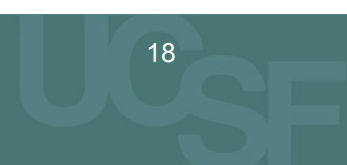
[21 CFR 312.64](#)

Progress Reports

- To sponsor who is responsible for collecting and evaluating the results obtained.
- Sponsor submits IND Annual Report to the FDA

Safety Reports

- An investigator must **immediately** report to the sponsor any serious adverse event, whether or not considered drug related
- The investigator must record non-serious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol



Investigator Reports

[21 CFR 312.64](#)

Final report

- Provide to sponsor adequate report shortly after completion of the investigator's participation in the investigation



Investigator Reports

[21 CFR 312.64](#)

Financial Disclosure Report

The investigator provides the Sponsor

1. Adequate information to allow Sponsor to submit complete and accurate certification or disclosure statements
2. Promptly update information of any relevant changes for the investigator's financials in respect to the study
 - During course of clinical trial
 - 1 year following the completion of the trial

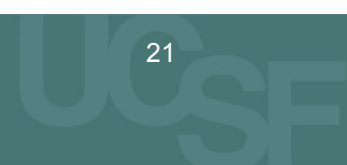


Assurance of IRB Review

21 CFR 312.66

Investigator assures that the provisions of the Institutional Review Board (IRB) complies with the proposed clinical study

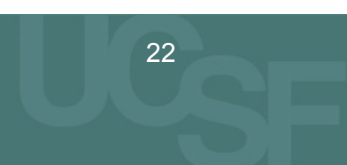
- Initial review and approval;
- Continuing review and approval;
- Changes in the research activity and does not initiate changes until IRB approval is granted;
- All serious unanticipated problems involving risk to human subjects or others, in accordance to the local IRB timelines and guidance.



Assurance of IRB Review

[21 CFR 312.66](#)

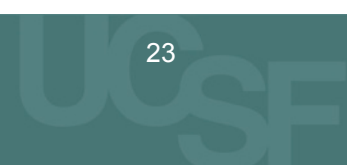
- The Investigator will not make any changes in the research without IRB approval, **except when necessary to eliminate immediate hazards** to human subjects
- The Investigator must stop all protocol activity until contacting the IRB immediately for directions on how to handle subjects if the protocol expires.
- When the investigator's study IRB approval expires, this is considered a protocol violation and the IRB will determine if the investigator can receive a re-approval.



Disqualification of a Clinical Investigator

21 CFR 312.70

- (a) If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has submitted to FDA or to the sponsor false information in any required report, the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research **will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference.** If an explanation is offered but not accepted by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research, the investigator will be given an opportunity for a regulatory hearing under part 16 on the question of whether the investigator is entitled to receive investigational new drugs.



Investigator Warning Letters

...are public information



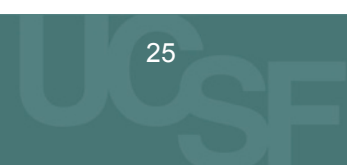
<http://www.fda.gov/iceci/enforcementactions/WarningLetters/default.htm>



Takeaways...



- Research Staff should know and understand the investigator responsibilities of FDA 21 CFR Part 312 subpart D
- Principal Investigators MUST Understand and adhere to responsibilities of the FDA 21 CFR Part 312 subpart D
- Principal Investigators MUST Understand and adhere to responsibilities of the FDA 21 CFR Part 50 and 56
- Principal Investigators MUST Administer and Control study drug according to the FDA 21 CFR Part 312 subpart D
- Principal Investigators MUST Submit all required reports to the FDA as requested by the sponsor or directly if the PI is the investigator-sponsor according to the FDA 21 CFR Part 312 subpart D
- **It's the Law! If inspected, non-compliance is penalized!**



Takeaways...



- The Principal Investigator is responsible for the delegation of responsibilities as written in the 21 CFR 312.60-70
- Each staff member must have the right education, training, and experience to :
- Obtain consent,
- Administer investigational product,
- Document their assessments



The regulations are written to...

Protect the Rights, Safety, and Welfare of Study Subjects!

