

# Investigator Responsibility

## Legal and Ethical Aspects



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# Learning Objectives

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**At the completion of this training it is expected that you will be more knowledgeable about:**

- ▶ The extent of the legal and ethical Responsibility of the PI in studies involving human subjects
- ▶ The responsibility of the other players in the drug and device development industry
- ▶ The continued reference to the PI throughout the regulations and the ICH guidelines
- ▶ ...

# Learning Objectives

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- ▶ The legal requirements / responsibilities of investigators per the Form FDA 1572 and in Title 21 CFR 312.60 - 321.69
- ▶ For Device studies, the legal the requirements / responsibilities laid out in the “Statement of the Investigator” and in Title 21 CFR 812.100 - 812.150
- ▶ That, if not followed, the Investigator faces disqualification+ per 21 CFR 312.70 & 812.119
- ▶ What the FDA Monitoring and Audit systems look for and do to detect errors or worse

# The Physician Investigator

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**Has a dual responsibility and a potential conflict of commitment**

- ▶ Goal of **clinical care** is to diagnose, treat, and cure disease or to reduce pain and suffering in individual patients - **Patient care oriented**.
- ▶ The goal of **clinical research** is to systematically collect information from groups of persons to produce generalizable findings to ..... in a whole population - **Drug effect oriented**

# The Dilemma

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**Physicians in practice engaged in clinical research may paradoxically see such research as affecting patient care by:**

- ▶ interfering with the individualization of care or
- ▶ providing superior care

The performance of clinical research has always been acknowledged to entail an essential conflict between individualization of patient care and the standardization of the scientific method.

**Grundberg & Cefalu, NEJM 2003;348 914:1386-1388**

# Phases of Clinical Research

|          | <b>I</b>                                      | <b>IIa</b>                               | <b>IIb</b>              | <b>III</b>              | <b>FDA</b>    | <b>IV</b>                                       |
|----------|---|--|-------------------------|-------------------------|---------------|---|
| Subjects | Healthy Normal                                | First time in Patients                   | Patients                | Patients                | <b>Safety</b> | Patients  |
| Number   | 20-100  | 25-27                                    | 50-200                  | >300                    |               | >1000   |
| Measure  | Dosage, Kinetics, <b>Safety</b> , Equivalence | Dose range, MOA, Efficacy, <b>Safety</b> | Efficacy, <b>Safety</b> | Efficacy, <b>Safety</b> |               | R:B ratio, New uses <b>Safety</b>               |
| Value    | Kinetics, Dynamics                            | Proof of Concept                         | Confirm how drug works  | Confirm use             |               | <b>PMS</b> , Patent extension, Market expansion |
| Time (y) | 1-1.5   | 1  | 1-1.5                   | 3-6                     | 2-3           | 1-5   |

# Is this perception accurate?



# Statement of the Investigator

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## Is a legally binding agreement between the Principal Investigator and FDA

- ▶ The Form 1572 is required by the FDA when an investigational **drug** is administered to humans in clinical trials. This form is available at the following: [www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf](http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf)
- ▶ A similar “Statement of the Investigator“ without reference to 21 CFR 312 is required by the FDA when an experimental **device** is used in humans [www.fda.gov/cdrh/devadvice/ide/responsibilities/shtml](http://www.fda.gov/cdrh/devadvice/ide/responsibilities/shtml)



# Statement of the Investigator

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Signing a **1572** is the PI's commitment in writing that she / he will be responsible for the study in question; responsible for everything. **312.53(c)(1)**

This means she / he agrees to follow:

- ✓ **21 CFR 50** - Protection of Human Subjects
- ✓ **21 CFR 56** - Institutional Review Boards
- ✓ **21 CFR 312** - Investigational New Drug Application
  - 21 CFR 312.64 - Investigator reports – AEs etc
  - 21 CFR 312.62 - Investigator record keeping
  - 21 CFR 312.68 - Inspection of Investigators R & R

# Statement of the Investigator

Signing a “**Statement of the Investigator**” is the PI’s commitment in writing that she / he will be responsible for the device study in question; **totally responsible** for everything **812.20(b)(4) & (5)**

This means she / he agrees to follow:

- ✓ **21 CFR 50** - Protection of Human Subjects
- ✓ **21 CFR 56** - Institutional Review Boards
- ✓ **21 CFR 812** - Investigational Device Exemptions
  - 21 CFR 812.43 - Selecting investigators & monitors
  - 21 CFR 812.110 - Responsibilities of investigators
  - 21 CFR 812.140 - Keeping Records
  - 21 CFR 812.150 - Reports

# Responsibility - A reminder



Investigator

**Study Participant Recruiting**

**System and Plan in Place**

Investigator

**On Time Study Start**

**Plan Well Executed**

Investigator

**Study Conduct**

**All SOP's Followed**

Investigator

**Subject Safety**

**Safety Nurse**

Investigator

**Study Completion**

**Rewarding**

# Commitments of the 1572

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- ▶ Personally conduct or supervise the investigation and in accordance with the protocol (to the letter)
  - ▶ Ensure that all associates, colleagues, and employees assisting in the study conduct know their obligations
  - ▶ Comply with all requirements / obligations including preparation and maintenance of study records
  - ▶ Inform the SP of the investigational nature of the study
  - ▶ Ensure that the IC process is clear and valid and all IRB requirements are met
  - ▶ Accurately report all AE's to the sponsor
  - ▶ Read and understand the Investigators Brochure (IB)
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# Commitments - Statement of ...

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- ▶ Conduct the investigation and in accordance with the investigational plan **Ref: 21 CFR 812.43(c)(4)(i)**
  - ▶ Supervise all testing of the device involving human subjects as defined in: **Ref: 21 CFR 812.43(c)(4)(ii)**
  - ▶ Ensure that the requirements for obtaining the IC are met as defined in: **Ref: 21 CFR 812.43(c)(4)(iii)**
  - ▶ Supply sufficient accurate financial disclosure information to allow the sponsor to submit the same as required in Part 54 **Ref: 21 CFR 812.43(c)(5)**
  - ▶ Permit an investigational device to be used only with subjects under PIs supervision **Ref: 21 CFR 812.110(c)**
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# Commitments - Statement of ...

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- ▶ Investigator must maintain accurate, complete, and current records relating to the investigators participation in the investigation **Ref: 21 CFR 812.140(a)**
- ▶ Investigator must permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect ... As defined in: **Ref: 21 CFR 812.145**
- ▶ Investigator must prepare and submit complete, accurate, and timely reports.. **Ref: 21 CFR 812.150(a)**

|                  |                          |
|------------------|--------------------------|
| UADE             | IRB approval withdrawal  |
| Progress reports | Protocol Deviations      |
| IC not prior ..  | Final report in 3 months |

# ICH and the Investigator

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## ▶ E6 - Good Clinical Practice

1. Glossary
2. Principles of ICH GCP
3. The IRB / IEC / REB
4. **The Investigator**
5. The Sponsor
6. The Trial Protocol and Amendments
7. The Investigators Brochure
8. Essential Documents

# Investigator Responsibilities

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## Medical Care of Study Participants

- ▶ All medical decisions are made, and medical acts are performed, by qualified physicians
- ▶ The primary doc of the SP is notified regarding the participation of their patient on the or a study
- ▶ The Study Physician knows when and why a Study Participant leaves a study - all SP are accounted for at all times
- ▶ The Investigator is responsible for the medical care of SP's when there are Adverse Events\*

Ref: **ICH E6 GCP: 4.3**



# FDA and the Investigator

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## The 1572 - item # 9. COMMITMENTS:

- ▶ On page 2 of 2 of the “**FORM FDA 1572**” is a listing of 9 statements.
- ▶ Seven begin with the words: “**I agree ...**”, one with “**I have read ...**”, and one with “**I will ensure ...**”.
- ▶ By signing the Form FDA 1572, the Investigator acknowledges her / his legal responsibility and obligation to comply with the law
- ▶ To not take this responsibility and obligation seriously is folly

# 1 - Adhering to the Protocol

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**“I agree** to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.”

Ref: **21 CFR 312.53(c)(1)(vi)(a)**

# Application

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**Investigator is required by law to conduct the study according to:**

All applicable regulations - National / Federal / State  
Good Clinical Practice - ICH Guidelines  
The Study Protocol / Investigational plan  
Institutional requirements

- ▶ Any deviations from the protocol should be documented and the sponsor consulted in advance if a deviation is requested
  - ▶ Unauthorized deviations are usually considered protocol violations and may result in the investigator ....
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## 2 - Personally Supervise Investigation

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**“I agree to personally conduct and supervise the described investigation(s).”**

**Ref: 21 CFR 312.53(c)(1)(vi)(c)**

## 3- Obtaining IC and IRB Approval

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**“I agree** to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and **I will ensure** that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.”

Ref: **21 CFR 312.53(c)(1)(vi)(d)**

# Application - Informed Consent

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**The “Informed Consent” is a process, not a signature.**

- ▶ “Except as provided in § 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject’s legally authorized representative.” \*
- ▶ NB: Subjects need sufficient time to understand what participation in the study involves and to consider whether or not to participate.

**\*Ref: 21 CFR 50.20**

# Application - IRB Approval

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- ▶ “Except as provided in § 56.104 and 56.105, any clinical investigation ...shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.” \*
  
- ▶ IRB approval is required for, but not limited to, the following documents:
  - ✓ Protocol and any amendments
  - ✓ Informed consent form and any translations
  - ✓ Any other information given to the subject (e.g., call center screening scripts, information sheets, etc.)
  - ✓ Advertisements

\*Ref: **21 CFR 56.103**

# 4 - Reporting Adverse Experiences

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**“I agree** to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.”

Ref: **21 CFR 312.53(c)(1)(vi)(e)**



# Adverse Event Reporting

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## **AE handling (safety) is a key function of the PI**

- ▶ “An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug”.
- ▶ “If the adverse effect is alarming or (by definition) serious, the investigator shall report the effect immediately.”

**Ref: 21 CFR Part 312.64(b)**

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# Application

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- ▶ The protocol will contain directions for adverse events and serious adverse events: definitions, when to collect, and how to report events to the sponsor.
    - Events are documented in the subject's medical records.
    - Events are recorded in the Case Report Form (CRF).
  - ▶ Serious adverse events (SAEs) require additional reporting within short time frames to both the sponsor and IRB.
  - ▶ Additional adverse events (e.g., unexpected events, specific events being monitored) may also require expedited reporting to the sponsor and/or IRB.
  - ▶ Adverse events are followed to resolution, stabilization (if persistent) or until the patient is lost to follow-up.
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# 5 - Understanding Information in the IB

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**“I have read and understand the information in the investigator’s brochure, including the potential risks and side effects of the drug.”**

Ref: **21 CFR 312.53(c)(1)(vi)(f)**

# Application

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**An Investigator Brochure (IB) contains the following information:**

- ▶ “A brief description of the drug substance and its formulation...”
- ▶ “A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.
- ▶ “A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

**Ref: 21 CFR 312.23(a)(5)**

# Application

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**An Investigator Brochure (IB) contains the following information:** continued

- ▶ “...safety and effectiveness in humans obtained from prior clinical studies...”
- ▶ “...possible risks and side effects to be anticipated...and of precautions or special monitoring to be done...”

The Investigator Brochure is usually revised periodically through the clinical development process as more information is learned.

**Ref: 21 CFR 312.23(a)(5)**

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## 6 - Training of Site Personnel

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**“I agree** to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.”

Ref: **21 CFR 312.53(c)(1)(vi)(g)**

# 7 - Adequate and Accurate Records

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**“I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.”**

Ref: **21 CFR 312.62(a-c)**

Ref: **21 CFR 312.68**

# Test Agent Accountability

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**“An investigator is required to maintain adequate *records* of the disposition of the drug, including dates, quantity, and use by subjects.”**

- ▶ **“If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under Part 312.59.”**

**Ref: 21 CFR 312.62(a)**

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# Source Documentation

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- ▶ “An investigator is required to prepare and maintain ***adequate and accurate case histories / source docs*** that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation”.

Ref: **21 CFR 312.62(b)**

**If it is not written, it does not exist**

# Record Retention

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- ▶ “An investigator shall retain records required to be maintained under this part 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.”

Ref: **21 CFR 312.62(c)**

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## 8 - Ensuring IRB is Compliant

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**“I will ensure** that an IRB that complies with the requirements of 21 CFR 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree ...”

Ref: **21 CFR 312.53(c)(1)(vii)**

# What is the Purpose of an IRB

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- ▶ An “*Institutional Review Board (IRB)* means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects.”
- ▶ “The primary purpose of such review is to assure the protection of the rights and welfare of human subjects.”

Ref: **21 CFR 56.102(g)**

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## 8 - Reporting Changes / Problems

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**“I also agree.. to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, ...”**

Ref: **21 CFR 312.53(c)(1)(vii)**

# IRB Continuing Review

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**The Principal Investigator is responsible for keeping the IRB apprised of:**

- ▶ Study progress (interim progress reports)
- ▶ Reportable adverse experiences from the investigative site and any Safety Reports received from the sponsor
- ▶ Any changes to the protocol, informed consent form, Investigator Brochure and/or package insert for study products, safety amendments and updates, etc.
- ▶ Protocol deviations and violations
- ▶ The final study report

## 8 - Changing the Protocol

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“Additionally.. I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.”

Ref: **21 CFR 312.53(c)(1)(vii)**

# Protocol Changes

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**Any protocol amendment and / or modification to the ICF cannot be implemented / used prior to obtaining IRB approval.**

- ▶ For minor changes (no risk to subjects) an ‘expedited’ review may be obtained. **21 CFR 56.110**
- ▶ Only one exception to not following the protocol: If immediate implementation of a change is required to eliminate an apparent immediate hazard to safety and well being of the subject(s)



## 9 - Complying with Part 312

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**“I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.”**

**Ref: 21 CFR 312.53(c)(1)(vi)(b)**

# 21 CFR Part 312:

## Investigational New Drug Application (Subparts)

- ▶ A - General Provisions (.1-.10)
- ▶ B - Investigational New Drug Application (.20-.38)
- ▶ C - Administrative Actions (.40-.48)
- ▶ D - Responsibilities of Sponsors & Investigators (.50-.70)
- ▶ E - Drugs Intended to Treat Life Threatening and Severely Debilitating Illnesses (.80-.88)

Ref: **21 CFR 312.1 - .160**

# 21 CFR Part 812:

## Investigational Device Exemptions (Subparts)

- ▶ A - General Provisions (.1-.19)
- ▶ B - Application and Administrative Action (.20-.38)
- ▶ C - Responsibilities of Sponsors (.40-.47)
- ▶ D - IRB Review and Approval (.60-.66)
- ▶ E - Responsibilities of Investigators (.100-.119)
- ▶ G - Records and Reports (.140-.150)

Ref: **21 CFR 812.1 - .150**

# Additional PI Responsibilities

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## **Financial Conflicts of Interest / Disclosure**

- ▶ [21 CFR Part 54](#) - Financial Disclosure by Clinical Investigators. This Includes
  - Certification and disclosure requirements (.4),
  - Agency evaluation of financial Interests (.5)
  - Recordkeeping and record retention (.6)

## **Informed Consent Process for adults and kids**

- ▶ [21 CFR Part 50](#) - Protection of Human Subjects
    - Subpart B - Informed Consent of Human Subjects
    - Subpart D - Additional Safeguards for Children in Clinical Investigations ..
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# Additional PI Responsibilities

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## **The functions and actions of the IRB**

- ▶ [21 CFR Part 56](#) Institutional Review Boards
  - Subpart A - General Provisions
  - Subpart B - Organization and Personnel
  - Subpart C - IRB Functions and Operations
  - Subpart D - Records and Reports
  - Subpart E - Administrative Actions ...

## **Use of Computers for handling of data**

- ▶ [21 CFR Part 11](#) Electronic Records and Signatures
  - Subpart B - Electronic Records;
  - Subpart C - Electronic Signatures

## **Principals of Laboratory consistency and validation ...**

- ▶ [21 CFR Part 58](#) - Good Laboratory Practice ...
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# Additional PI Responsibilities

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**If the investigator is involved in federally funded studies there must also be compliance with the DHHS Common Rule**

- ▶ **45 CFR Part 46** - Protection of Human Subjects
    - Subpart A - Basic Policy or Common Rule
    - Subpart B - Protection for the vulnerable  
(neonate, fetus or pregnant women)
    - Subpart C - Protection for prisoners
    - Subpart D - Protection for Children
  - ▶ 45 CFR 46.103 is the key institutional “Assurance of Compliance”
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# When an Investigator does Not...

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- ▶ “If the FDA has information that an 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 sponsor false information in any required report the CDER or CBER 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”.

Ref: **21 CFR 312.70(a)**

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# Investigator Disqualification...

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- ▶ “If an explanation is offered but not accepted by CDER or CBER, 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”.

Ref: **21 CFR 312.70(a)**

- ▶ An investigator who has been determined to be ineligible to receive investigational drug may be reinstated as eligible when the commissioner is assured that the investigator will comply with all applicable regulations.

Ref: **21 CFR 312.70(f)**



# Investigator Disqualification.

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## **21 CFR 812 Investigational Device Exemptions**

- ▶ Disqualification of a clinical investigator - the wording is very similar to that of the last two examples except it is the Center for Devices and Radiological Health (CDRH) that receives the reports and may act on it and there is no reference to Part 312.

**Ref: 21 CFR 812.119**

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# Investigator Disqualification.

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## **21 CFR 812 Investigational Device Exemptions**

- ▶ If FDA has information indicating that an investigator has repeatedly or deliberately failed to comply with the requirements of this part, part 50, or part 56 of this chapter, or has repeatedly or deliberately submitted false information either to the sponsor or in any required report, the CDRH will furnish the investigator written notice of the matter and offer the investigator an opportunity to explain ....

**Ref: 21 CFR 812.119(a)**

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# What is the FDA Inspection Policy

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- ▶ It is called the Bioresearch Monitoring (BIMO) Program and it covers on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research
  - ▶ The BIMO program covers all aspects of food and drug research, manufacture and testing of new chemical entities and, as well post marketing surveillance
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# Fraud in Bioresearch Monitoring

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**defined as the deliberate reporting of false or misleading data or the withholding of reportable data.**

- ▶ **Altered data** - generating biased data or changing data that is legitimately obtained. E.g. changing laboratory data, altering weights, breaking the blind and/or randomization
  - ▶ **Omitted data** - not reporting data that has an impact on study outcome. E.g. removing subjects from a study for bogus reasons, disguising AEs, and replacing subjects
  - ▶ **Manufactured data** - Fabricating information or creating results without performing the work. E.g. filling in values (BP, lab values, x-ray reports) for which no data were obtained, photocopying data from one patient for another, and creating fictitious patients
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# Investigator Orientated Audits

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**A particular event or circumstance is the trigger:**

- ▶ PI is doing a large number of studies
- ▶ PI / site has most subjects entered in study
- ▶ The study is pivotal to product development
- ▶ There are too few Adverse Events
- ▶ Sponsor reports a problem
- ▶ Study Subject complaints
- ▶ Data inconsistent or too good to be true
- ▶ Studies are outside of field of her / his expertise

# BIMO Audit Findings

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**Most common is rights and welfare of Subjects vs. Integrity and validity of the data:**

- ▶ Failure of oversight
  - ▶ Inappropriate delegation of authority
  - ▶ Inadequate or improperly executed consent process
  - ▶ Excessive protocol deviations and violations
  - ▶ Poor investigational product accountability
  - ▶ Inadequate / inaccurate case histories
  - ▶ Inaccurate / fraudulent data on CRF's or reports
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# Questions to expect from FDA

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**There are a number of questions which the study conduct team should expect to discuss:**

- ▶ What is the Informed Consent *process*?
- ▶ What is your SP / Patient recruitment *process*?
- ▶ What PI responsibilities have been delegated?
- ▶ How are CRF's completed? The *process*?
- ▶ What is your SAE reporting *process*?
- ▶ What is the Sponsor / Monitor interaction like?
- ▶ Where is the bathroom?

# What will be expected - Staff

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## **The Inspector will query the study staff regarding:**

- ▶ How and where was the data recorded?
  - ▶ How were the research duties assigned?
  - ▶ How was study conduct performance monitored?
  - ▶ What were your IRB/IEC reporting requirements?
  - ▶ Are there any concurrent studies?
  - ▶ And, most importantly, were the rights, welfare and safety of the Study Participants protected.
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# What will be expected - PI

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## Did the PI carry out her/his responsibilities?

- ▶ Did the **PI** meet her / his regulatory obligations?
- ▶ Did the **PI** brief the study staff regarding the study?
- ▶ Did the **PI** appropriately delegate tasks?
- ▶ Did the **PI** hold any 'in-service' sessions?
- ▶ Was the **PI** Available to answer questions?
- ▶ What was the **PI's** involvement in recruiting?
- ▶ Did the **PI** know the qualifications of all of the co-investigators and sub-investigators?

# Deficiencies noted at Inspection

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- ▶ 23% - Failure to adequately monitor the study
- ▶ 21% - Failure to document monitoring visits
- ▶ 18% - Failure to have or follow SOPs

## Other commonly observed deficiencies

- ▶ Failure to follow the protocol
  - Violation of inclusion / exclusion criteria
  - Failure to perform required tests
- ▶ Failure to maintain adequate / accurate records
  - Absent, inaccurate or incomplete supporting source documents

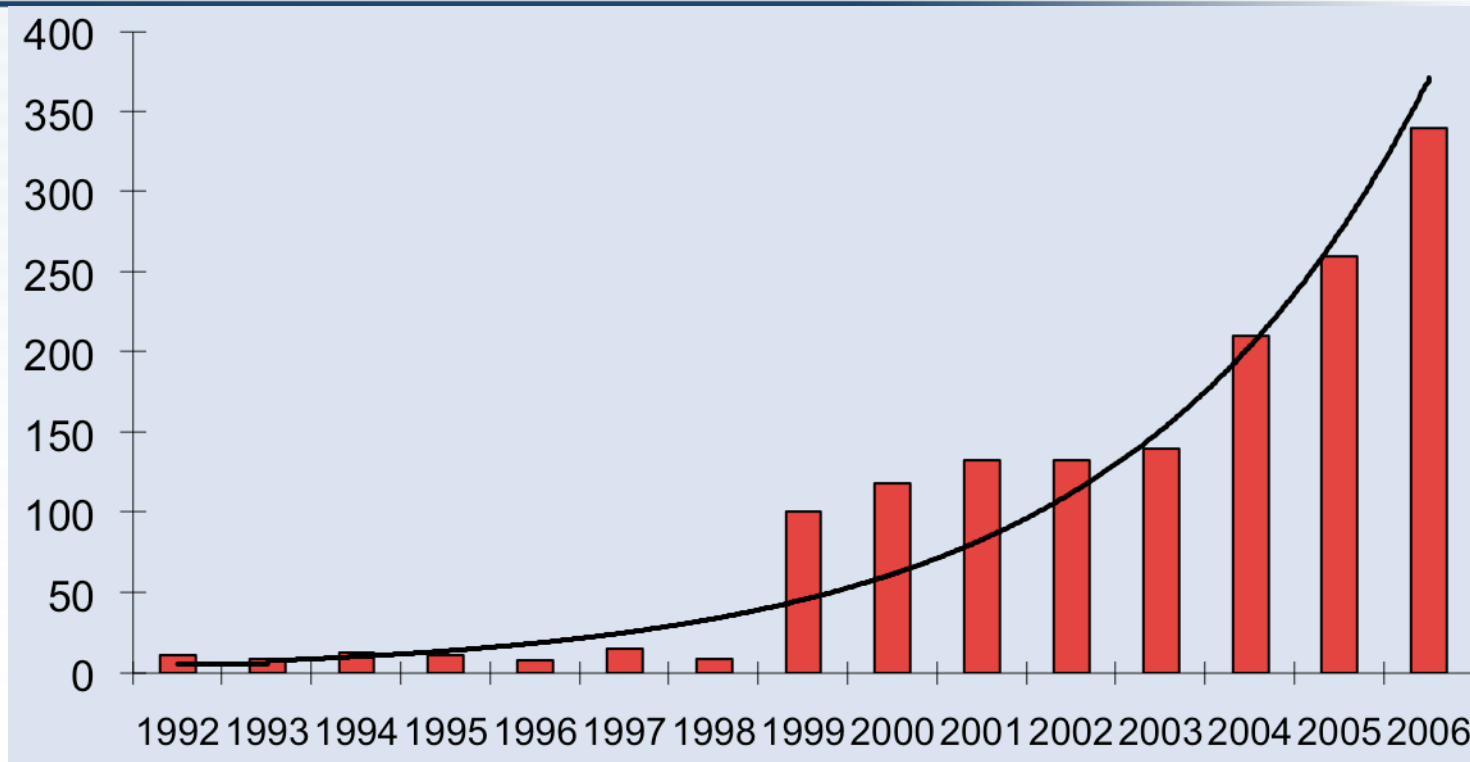
# Classification of Inspection

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**The FDA Classification of the Inspections is according to the following:**

- ▶ **NAI** - No Action Indicated
- ▶ **VAI** - Voluntary Action Indicated
- ▶ **OAI** - Official Action Indicated
  - ✓ Recommend that Study Data be Disqualified
  - ✓ Recommend Restrictions placed on the **PI**
  - ✓ Recommend Disqualification of the **PI**
  - ✓ Recommend that the **PI** be prosecuted

# Complaints to FDA



Among the most frequent complaints:

Informed Consent issues

Qualification of staff performing physicals

# What Happened in 1999?

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## **1999 may have been a watershed year for public awareness of chinks in the clinical research industry**

- ▶ May 1999: Duke University failed to respond to requests for proper monitoring of human volunteer subjects – federal regulators temporarily suspended research;
- ▶ Sept. 1999: Univ. of Pennsylvania; an 18 year old died from drugs given as part of gene vector therapy study; Understated risks, protocol not followed and Conflict of Interest not disclosed
- ▶ June 2001: Johns Hopkins Univ.; a 24 year old died

# BIMO Inspection Results

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|                              | <u>2007</u> | <u>2006</u> |
|------------------------------|-------------|-------------|
| % OAI in BIMO Inspections    | 14%         | 11%         |
| % OAI to Sponsors            | 33%         | 11%         |
| Warning Letters              | 29          | 24          |
| Clinical Investigators (183) | 16          |             |
| IRBs (92)                    | 5           |             |
| Sponsors (40)                | 8           | 3           |

**Ref: The Gray Sheet - 07 Jan 08**

# Detecting Misconduct - FDA

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**Do not 'shoot the messenger'** - believe monitors as the burden of proof should be on the PI

**Be Suspicious of blame shifting** - Let the PI know the she / he is 'totally responsible' for study conduct

**Expect Fraud** - Start from the assumption that the records are bogus and the study is fraud

**Cultivate Whistleblowers** - establish rapport with study staff, be approachable and available, listen, observe

**Be Prepared** - Have a system in place to capture, document and deal with complaints. SOPs?

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# Investigator Misconduct

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**Fortunately not common but one can check an FDA web site for a listing of:**

- ▶ FDA Debarment

[www.fda.gov/ora/compliance\\_ref/debar/](http://www.fda.gov/ora/compliance_ref/debar/)

- ▶ FDA Disqualified / Restricted

[www.fda.gov/ora/compliance\\_ref/bimo/dis\\_res\\_assur.htm](http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm)

- ▶ FDA Warning letters

[www.fda.gov/foi/warning.htm](http://www.fda.gov/foi/warning.htm)

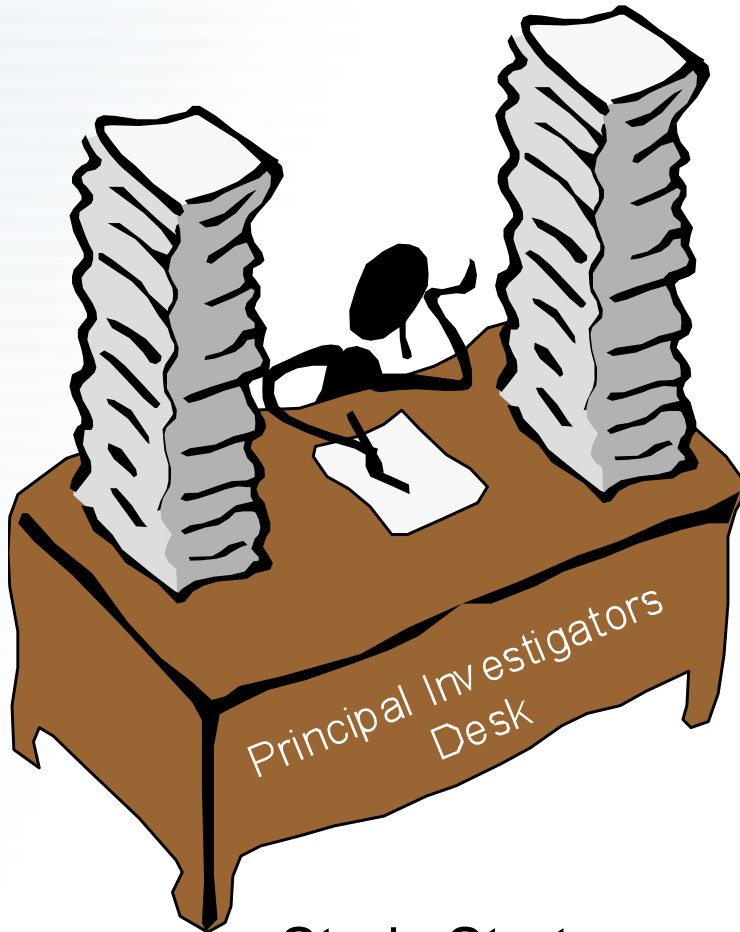


# In the End ...

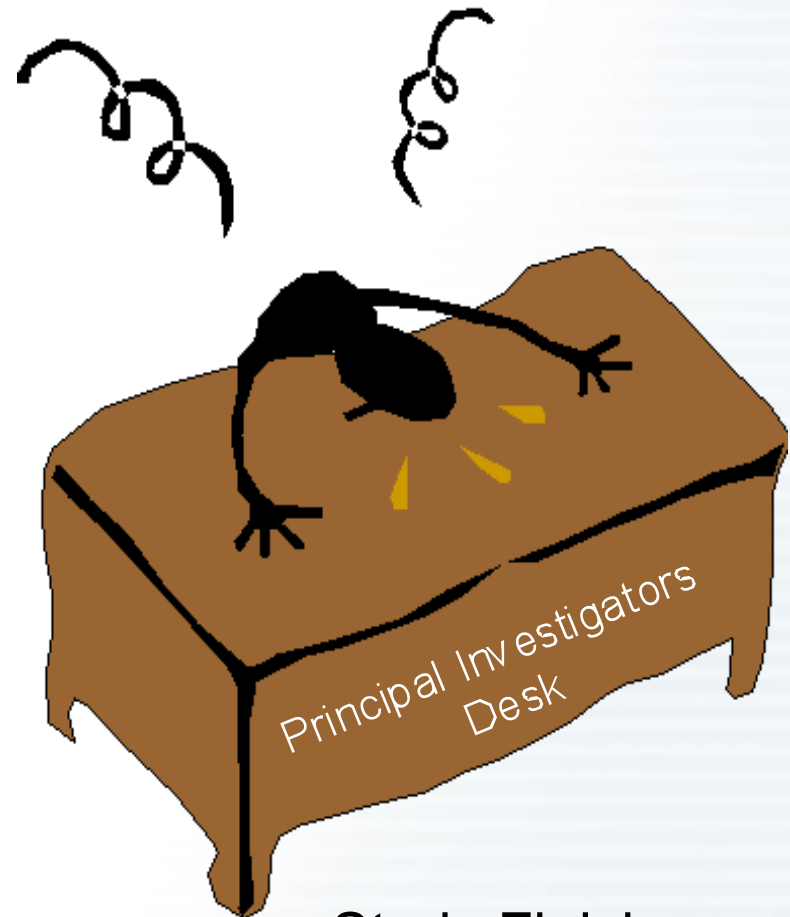
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- ▶ A physician remains the key to safety of human subjects & ethical drug development
- ▶ A Physician investigator doing clinical research is still a physician with all that this entails like taking great care in all aspects of the care of those with whom they have been entrusted to care for.
- ▶ This care includes patient safety first but also accurate record keeping and clear documentation of one though processes.
- ▶ A “certified” competent investigator is the key.

# In the end - illustrated ....



Study Start



Study Finish

**Thank you.**



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