

# PRINCIPAL INVESTIGATOR INITIATED CLINICAL STUDIES

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# OBJECTIVES

- ◉ Describe types of PI-initiated studies
- ◉ Discuss regulatory requirements of PI-initiated studies
- ◉ Define roles and responsibilities
- ◉ Discuss data management requirements
- ◉ Provide in-depth discussion regarding PI-initiated FDA-regulated studies



# DEFINITION OF CLINICAL RESEARCH

- Clinical research is research that either directly involves individual people or uses materials of human origin, such as behavior or tissue samples, that can be linked to a particular living person. The process of clinical research, however, protects personal data.
- Clinical research includes clinical trials and other types of research involving people.



# DEFINITION OF CLINICAL RESEARCH (CONT'D)

- The NIH defines “clinical research” as: Patient-oriented research: As explained above, this type of clinical research involves human subjects or materials from human subjects and can include:
  - > Studies of mechanisms of human disease
  - > Studies of therapeutic interventions
  - > Clinical trials
  - > Development of new technology



# DEFINITION OF CLINICAL RESEARCH (CONT'D)

- Epidemiological and behavioral studies: These types of studies examine the factors that affect health and health-related decisions.
- Outcomes and health services research: These studies seek to identify the most effective and most efficient interventions, treatments, and services.



# GENERAL CATEGORIES OF PI-INITIATED STUDIES

- ◉ Health Services / Outcomes Research
- ◉ Epidemiologic studies
- ◉ Behavioral / Social
- ◉ Physiology or Mechanisms of Action
- ◉ Off-label Use of Existing FDA Approved Drug



# “SPONSORS” OF RESEARCH

- ◉ Department / Institutional funds
- ◉ Foundations and other Not-for-Profit organizations
- ◉ Federal government
- ◉ Private industry (i.e. Pharma or Biotech)



# REGULATORY REQUIREMENTS

- General to all types of clinical research
  - > IRB review
  - > Hospital / Institutional approval
  - > Data management
  - > Reporting
  - > Fiscal management



# IRB APPROVAL

*Governed at 21 CFR part 56*

The IRB is an integral part of all clinical research. The FDA requires that an appropriately constituted IRB, as described in FDA regulations, review all the research documents and activities directly related to the rights and welfare of the subjects of any proposed clinical research. The FDA further requires the IRB to be sensitive to the composition and viewpoints of the community in which clinical research is to be conducted



# IRB RESPONSIBILITIES

- ◉ Reviews and approves the research protocol, questionnaires, patient informed consent (s) and all documentation provided to the subjects for teaching purposes
- ◉ Subsequent review of the study to ensure that the rights and welfare of the study subjects are being protected
- ◉ Approves the PI's qualifications to conduct the study



# IRB RESPONSIBILITIES (CONT'D)

- Approves the qualifications of any sub-I's or Co-PI's
- Approves all changes in the research protocol or patient informed consent form prior to the changes being implemented
- Reviews all safety reports, adverse events, and unexpected events occurring during the course of the study



# ADVERSE EVENT REPORTING

During the course of the study, the PI must keep the appropriate entities (e.g. FDA, Sponsor, IRB, etc.) informed of any adverse experiences associated with use of a drug, diagnostic, or device that is both serious and unexpected.

- Telephone **call within 3 days** of the occurrence of any **unexpected fatal or life threatening** event associated with use of a drug, diagnostic or device.
- 10 day written report to follow-up on telephone call or to report any other serious, unexpected adverse event associated with use of the drug.



# CLINICALTRIALS.GOV REGISTRATION

- Trials of drugs and biologics
  - ✓ Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation.
- Trials of devices
  - ✓ Controlled trials with health outcomes, other than small feasibility studies, and pediatric post market surveillance.
- If in doubt, register it!



# ROLES & RESPONSIBILITIES

- ◎ Principal Investigator
  - > Implementation of protocol
  - > Obtaining regulatory approvals
  - > Overseeing conduct of the research
  - > Meeting “sponsor” obligations
  - > Reporting
  - > Financial management



# ROLES AND RESPONSIBILITIES (CONT'D)

## ◎ Study Personnel

These individuals assist the PI with meeting the requirements of the protocol and perform the day to day activities. They also interact more frequently with study subjects. Study personnel may include:

- > Research Coordinator / Nurse Coordinator
- > Ancillary Research staff
- > Phlebotomist /Laboratory personnel
- > Co-PI or Sub-I
- > Financial personnel
- > Regulatory personnel
- > Screening / Recruitment personnel



# ROLES AND RESPONSIBILITIES (CONT'D)

Any task can be delegated to study personnel from the PI, however, the PI maintains responsibility for The delegated tasks.



# DATA MANAGEMENT REQUIREMENTS

## ◎ Study “Binder”

- › All IRB correspondence
- › Copy of protocol / amendments
- › Copy of surveys / questionnaires
- › Original approved Informed Consent and all subsequent IFC's
- › Log of all screened /consented subjects (de-identified)
- › Log of adverse events
- › PI delegation log
- › Lab certifications



# DATA MANAGEMENT REQUIREMENTS (CONT'D)

## ◎ Subject “Binder”

- › Signed / Dated informed consent (s)
- › Patient demographics
- › Case report forms
- › Study visit tracking form (best practice)
- › Study Drug dispensing log (best practice)
- › Lab results
- › Completed surveys / diaries
- › Results for any tests / procedures performed



ALWAYS REMEMBER.....

If it is not documented, it  
did not happen.....



# PI-INITIATED, FDA- REGULATED STUDIES



# STUDY AS FDA- REGULATED

- Drug, device, or diagnostic developed locally and being submitted through the FDA for approval
- Off-label use of an already FDA approved drug, device or diagnostic



# IND vs. NON-IND DETERMINATION

- ◉ In general a study requires an IND if it is intended to support a:
  - > New indication
  - > Change in the approved route of administration or dosage level
  - > Change in the approved patient population (pediatric) or a population at greater or increase of risk (elderly, HIV positive, immunocompromised)
  - > Significant change in the promotion of an approved drug



# IND SUBMISSION REQUIREMENTS

- ◉ Statement of the PI Form FDA 1572  
[www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf](http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1572.pdf)
- ◉ Form FDA 1571 [www.fda.gov/opacom/morechoices/fdaforms/FDA-1571.pdf](http://www.fda.gov/opacom/morechoices/fdaforms/FDA-1571.pdf)
- ◉ Study protocol
- ◉ Curriculum vitae for the PI ,and all other personnel listed on the form FDA 1572
- ◉ Notification of the IRB approval to FDA: a copy of the IRB letter stating both protocol and patient informed consent have been approved
- ◉ Copy of the IRB approval for any announcement used to patients recruit patents for the study



# DETERMINATION PROCESS

The FDA determines exemption status, i.e., IND or Non-IND, after the PI submission of the FDA form 1571. The PI can use the FDA Investigational New Drug (IND) Guidance document for additional information.

Information on animal and previous human studies can be obtained by seeking permission from the original pharmaceutical or device company. A company generally allows a PI to cross reference the company's IND/NDA.



# ADDED RESPONSIBILITY

Person / Institution who submits and receives approval to hold an IND takes on the role of the Sponsor



# SPONSOR RESPONSIBILITIES

- ◉ When acting as the sponsor the PI is held to the same standards and obligations as any other individual or organization, that takes responsibility for and initiates a clinical investigation. These responsibilities include:
  - > Writing the protocol and designing the Case Report Form
  - > Monitoring the study and reviewing the source documents for compliance/accuracy
  - > Drug/Product accountability
  - > Submitting safety reports to the FDA
  - > Complying with all applicable FDA regulations



# PI RESPONSIBILITIES

- ⦿ Identification of potential study subjects
- ⦿ Medical responsibility for all study subjects
- ⦿ Active involvement during all aspects of the study
- ⦿ Resource management
- ⦿ Accurate and timely reporting of all data and adverse drug events
- ⦿ Directly overseeing the administration /compliance of study drug/product
- ⦿ Directly overseeing study personnel and financial accountability of the study



# PI RESPONSIBILITIES (CONT'D)

The PI is responsible for **EVERY** aspect of the study. He or she may delegate the roles but **can not** delegate the responsibility. He/She remains ultimately responsible for all study related activity regardless of who performs the tasks



# STUDY PERSONNEL: LEAD COORDINATOR / NURSE

- Oversight and delegation of duties to additional study personnel
- Patient recruitment, retention and scheduling within the protocol guidelines
- Historical and current medical data collection
- Completion of Case Report Forms /Electronic Data Entry



## STUDY PERSONNEL: LEAD COORDINATOR / NURSE (CONT'D)

- Processing/storage of specimens and drug/product accountability
- Regulatory and financial adherence and compliance
- Day to Day problem solving
- Compliance of the Protocol



# FDA REGULATIONS

There are well-defined regulations and guidelines from the FDA that govern the conduct of clinical investigations in the United States. These include Institutional Board Review (IRB) approval and informed consent; it is the PI's responsibility to comply with all stated requirements. In addition, if the study requires an IND, the PI must also follow a number of other regulations. For example, it will be the PI's responsibility to communicate with the FDA and to provide, among other things, complete information regarding the PI's protocol, the conduct of the PI's study, and the experiences of subjects exposed to study drug over the entire study course.



# FDA STUDY REQUIREMENTS: INFORMED CONSENT - 21 CFR PART 50

- The most current IRB approved Informed consent must be obtained from the study participants before any screening, treatment or study procedure required by the protocol are performed
- All subjects who have signed a consent form must be provided a copy of the IFC and the process of obtaining IFC should be documented in the subjects study record
- Consent forms are legal documents, and must be kept as part of the permanent study records
- The IFC must be written in wording that is easy to understand and preferably in the subjects first language
- The principal PI is the person responsible for fully informing the potential study subjects about the trial. The written informed consent is helpful in this process, but it should not replace the principal PI's responsibility (or that of any sub-PI) to directly inform potential study subjects about all aspects of the trial



## FDA STUDY REQUIREMENTS: CASE REPORT FORMS (I.E. DATA MANAGEMENT) – 21 CFR PART 312.62B

- Complete documentation is essential to the conduct of the clinical study.
- FDA regulations clearly state that the PI is required to prepare and maintain adequate and accurate case histories for each patient, containing all observations and other data pertaining to the trial.
- Each case report form should contain information consistent with each patient's medical record.



# ADDITIONAL FDA STUDY REQUIREMENTS

- ◉ **Study Drug Dispensation:** PIs are additionally required to store study drug (s) as recommended on the label in a secured area.
- ◉ **Collecting Data and Retaining Records:** PIs must identify who will be responsible for the documentation of all data entered into a patients' medical record.
- ◉ **Completing Case Report Forms:** PIs must also identify who will complete the Case Report Forms. This process can be somewhat time consuming, because data transcription must be legible, complete, up to date and accurate.
- ◉ The FDA requires that the PI **retain study documents for at least two years** after the application is approved for the indication for which the drug is being investigated, or two years after the investigation is discontinued and the FDA has been notified.



# AN ENDING THOUGHT....

Clinical research involving human beings is a moral, scientific, and humanistic endeavor.

It is premised on two fundamental commitments:

- 1) to improve human welfare by advancing scientific knowledge and understanding of disease and illness; and
- 2) to preserve and protect the dignity and health-related interests of those who participate in it as subjects.

