CRC CERTIFICATION PREPARATION COURSE

SESSION 5
SPONSOR REQUIREMENTS

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SESSION 5 TOPICS

- Investigator and site qualifications
- Investigator brochure
- Site and investigator training
- Regulatory requirements for investigational products
- SOPs
- Regulatory requirements – regulatory documents
- Data Safety Monitoring Boards
- Regulatory requirements for electronic systems

SESSION 5 TOPICS (CON'T)

- Regulatory agency inspections
- Principles of Quality Assurance and CAPA (corrective and preventive action plans)

Investigator and Site Qualifications

- 21CFR 312 states: "A sponsor shall select only investigators qualified by training and experience as appropriate experts to investigate the drug."

General Sponsor Responsibilities

- Selecting qualified investigators
- Providing them with the information they need to conduct an investigation properly
- Ensuring proper monitoring of the investigation(s)
- Ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND
- Maintaining an effective IND with respect to the investigations
- Ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug

Transfer of Responsibility to CRO

21CFR 312 permits transfer of responsibility:

- A sponsor may transfer responsibility for any or all of the obligations set forth in this part to a contract research organization (CRO).
  - Any such transfer shall be described in writing.
  - If not all obligations are transferred, the writing is required to describe each of the obligations being assumed by the contract research organization
- A CRO that assumes any obligation of a sponsor shall comply with the specific 21CFR regulations applicable to this obligation and shall be subject to the same regulatory action as a sponsor for failure to comply with any obligation assumed under these regulations. Thus, all references to "sponsor" apply to a CRO to the extent that it assumes one or more obligations of the sponsor.

1572 FORM

- Every section of the 1572 form comes directly from the regulations:
  - Name
  - Address
  - Clinical facilities to be used
  - Laboratories to be used
  - IRB identified
  - All sub-investigators listed
  - Etc.

1572 – CONTRACT WITH THE SPONSOR / FDA

- The investigator is committing to the following:

(*a*) Will 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, the rights, or welfare of subjects;

(*b*) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;

(*c*) Will personally conduct or supervise the described investigation(s);

(*d*) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;

(*e*) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 312.64;

(*f*) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and

(*g*) Will 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.

INVESTIGATOR BROCHURE

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

IND Application

- Sections required by FDA
  - Cover sheet (Form 1571)
  - Table of contents
  - Introduction and general investigational plan
    - Human experience data summary
    - Previous use and status in other countries
    - Description of overall investigational plan and details about plan for first year of planned study
  - Investigator's brochure
  - Complete protocol for all planned phases of study
  - Chemistry, manufacturing and control information

Site and investigator training

- Human subject protection training
  - This is a general HHS requirement, with which the FDA complies
- Protocol training to assure understanding and compliance
  - On-site visit
  - Investigator/team training meeting
  - On-line resources / requirements
  - GCP training required
- Periodic retraining may be required

Regulatory requirements for investigational products

- An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a subinvestigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

Regulatory requirements for investigational products

- The sponsor shall assure the return of all unused supplies of the investigational drug from each individual investigator whose participation in the investigation is discontinued or terminated. The sponsor may authorize alternative disposition of unused supplies of the investigational drug provided this alternative disposition does not expose humans to risks from the drug. The sponsor shall maintain written records of any disposition of the drug in accordance with 312.57.

21CFR 312 – Drugs, Biologics

Components of 21CFR 312

- Subpart A – General Provisions
- Subpart B – IND Application
- Subpart C – Administrative Actions
- Subpart D – Responsibilities of Sponsors and Investigators
- Subpart E – Drugs Intended to Treat Life-Threatening and Severely Debilitating Illnesses
- Subpart F - Miscellaneous

312.2 Applicability

- Applies to all clinical investigations of products that fall under the Food, Drug and Cosmetic Act or the licensing provisions of the Public Health Service

Exemptions

- Studies that are exempt from IND;
  - Study involves a drug that is lawfully marketed in the U.S. and…… (all criteria must apply)
    - Not intended to be reported to FDA in support of a new indication or to support change in labeling
    - Not intended to support a significant change in advertising for the drug
    - Does not involve a route of administration or dosage level in a patient population that increases risk of the drug
    - Investigation is conducted under IRB review and with informed consent requirements
    - Must adhere to section 312.7
  - IRB applies these criteria to decide if investigator needs an IND

Charging for Investigational Drugs (21CFR 312.7)

- Drug cannot be promoted as safe and effective until approved
- No commercial distribution or test marketing until approval
- Investigations cannot be unnecessarily prolonged
- Charging for investigational drug
  - Must be adequately justified by sponsor
  - Must be pre-approved by FDA as part of IND

Subpart B: IND

- IND shall be submitted by a sponsor for an intended clinical investigation with an investigational new drug that falls under the Food, Drug and Cosmetic Act
- Investigation shall not begin until IND is in effect
- FDA shall respond to IND application in 30 days or sooner

IND Content and Format

- Cover sheet – form 1571 – (let's review)
- Table of contents
- Introductory statement and general investigational plan
- Investigator's Brochure
- Protocols
- Chemistry, manufacturing and control information
- Pharmacology and toxicology information
- Previous human experience with drug
- Additional Information

Investigator's Brochure

- Description of drug substance, formulation, structure
- Summary of pharmacological and toxicology data in animals and humans
- Summary of pharmacokinetics and biological disposition in animals and humans
- Safety and effectiveness data in humans
- Possible risks and side effects
- ** Updated with new information – basic and clinical

Protocols

- One protocol for each planned study
- Phase 1
  - May be less detailed and more flexible
  - Provide outline of investigation, number of subjects, safety exclusions, dosing plan and duration
  - Details that are pertinent to safety (monitoring parameters)
- Phase 2 and 3
  - Detailed protocols of all aspects of study
  - Deviations, contingencies should be built into protocol
    - Cross-over for non-responders
    - Dose reduction for intolerance (side effects)

Protocol Components

- Objectives and purpose
- Investigator qualifications (1572) – who signs this document?
- Patient selection criteria, numbers
- Design of study
  - Use of control group, if included
  - Means to minimize bias
- Dosing plan (determination, max dose, duration)
- Observations and measurements to be made to fulfill the study objectives
- Monitoring procedures
  - Procedures, laboratory tests

What does it mean to sign the 1572?

- The investigator is signing a "contract" with the FDA to do everything right for the study:
  - Conduct the study as per the protocol, no deviations except to avoid apparent harm; reporting AEs in a timely way
  - Assure that only qualified personnel are involved with the study
  - Ensure informed consent (21CFR 50) and IRB review (21CFR 56) are met
  - Maintaining accurate records, available for inspection
  - Obtain initial IRB approval and continuing approval, as specified
  - Inform subjects that drug is being used for investigational purpose

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Additional Information

- Address special topics, if indicated
  - Drug dependence and abuse potential
  - Radioactive drugs
  - Pediatric studies
- Relevant information
  - Always submit original plus two copies
  - Submissions on same IND must have consecutive numbering system 001 (on the 1571 form)

IND Amendments

- All amendments are submitted with sequential numbering versions of Form 1571
- Protocol Amendments
  - New Protocol
  - Changes to existing protocol that significantly affect safety of subjects
  - Addition of a new investigator (new 1572)
  - Require IRB approval and FDA submission before implementation
- Information Amendments
  - New toxicology, chemistry data
  - New information for investigator's brochure

IND Safety Reports

- Written notification of FDA required for
  - Adverse events associated with the use of the drug that are both serious and unexpected
  - Any new finding in animal data that suggests an change in risk for humans including reports of mutagenicity, teratogenicity and carcinogenicity
- Notifications are to be made ASAP, within 15 days of awareness
- FDA may change this time frame at will
- Local reporting requirement at UCI is 5 days to the IRB

Clinical Holds

- FDA can impose clinical holds at or prior to 30-days after IND receipt
- Grounds for clinical holds
  - Risk to subjects is unreasonable
  - Clinical investigators are not qualified by training and experience
  - I.B. is misleading, erroneous or incomplete
  - Insufficient data to assess risk potential
  - (Not enough time to review the IND application)

Clinical Holds

- Grounds for clinical hold
  - Design is not adequate and well-controlled enough to achieve objectives of study
  - Not enough investigational drug exists
  - Lack of efficacy has been demonstrated
  - Another drug has demonstrated better potential risk/benefit ratio
  - Lack of due diligence of sponsor to pursue marketing approval of drug

Clinical Holds

- Imposition of hold
  - By phone or other means of rapid communication
  - (communication often arrives by e-mail)
- Discussion of deficiency
- Response by sponsor to FDA – starts 30-day clock again for removal of hold
- If unacceptable – regulatory hearing may be proposed
- If acceptable, resumption of plan for clinical investigations occurs after FDA approval

Meetings with FDA

- Pre-IND meeting
- End-of-Phase 2 meeting
  - Encouraged by FDA
  - Purpose: determine the safety of proceeding to Phase 3
  - Purpose: evaluate Phase 3 proposed plan
  - Should be held prior to major commitments to Phase 3 protocols
- Pre-NDA meeting
  - Uncover major unresolved issues that might delay approval for marketing

Case Study

- Your PI tells you that he has just agreed to join a multi-center pharma-sponsored study for an approved drug that is attempting to extend the indications to a new patient population.
- You begin to review the paperwork (sponsor protocol, etc.) as the first step to initiate the IRB approval process, what are your concerns?

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21CFR 812 – Medical Devices

Criteria for Medical Device Determination

- A medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—
  - Recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
  - Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  - Intended to affect the structure or any function of the body of man or other animals, and
- which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

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Medical Devices

- Medical devices include, among other things:
  - surgical lasers, intraocular lenses
  - wheelchairs, vascular grafts
  - sutures, orthopedic pins
  - pacemakers, diagnostic aids such as reagents
  - test kits for in vitro diagnosis (IVD) of disease and other medical conditions such as pregnancy.

Clinical Investigations of Medical Devices

- Must comply with the FDA informed consent and Institutional Review Board (IRB) regulations [21CFR parts 50 and 56, respectively]
- Federal requirements governing investigations involving medical devices were enacted as part of
  - Medical Device Amendments of 1976, and the
  - Safe Medical Devices Act of 1990
- These amendments to the Federal Food, Drug, and Cosmetic Act (the Act) define the regulatory framework for medical device development, testing, approval, and marketing.

Premarket Notification

- Is the device substantially equivalent to a "pre-amendments" device?
  - If equivalent, the device can be marketed immediately (510 k devices)
  - If not equivalent, the device must undergo clinical testing and premarket approval before it can be marketed

Investigational Device Exemption (IDE)

- An investigational device is a medical device which is the subject of a clinical study designed to evaluate the effectiveness and/or safety of the device.
- Must be conducted according to regulations - [21 CFR part 812]
- Certain studies of lawfully marketed devices may be exempt from the IDE regulations [21 CFR 812.2(c)]

Non-Exempt Studies

- Must be categorized as either
  - "significant risk" (SR) or
  - "non-significant risk" (NSR)
- The determination that a device presents a non-significant or significant risk is initially made by the sponsor.
- Then the proposed study is submitted either to
  - FDA (for SR studies) or
  - IRB (for NSR studies) [IRB makes determination]

SR Device Studies

- Must be conducted in full accordance with 21 CFR 812
- Cannot commence until 30 days after filing of the IDE application
  - Enables FDA to review information about the technical characteristics of the device
  - The results of any prior studies (laboratory, animal and human) involving the device
  - The proposed study protocol and consent documents.

SR Device Studies

- A study of a device that presents a potential for serious risk to the health, safety, or welfare of a subject and
  - (1) is intended as an implant; or
  - (2) is used in supporting or sustaining human life; or
  - (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or
  - (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- IRB approval is required before initiation of study

NSR Device Studies

- One that does not meet the definition for a significant risk study.
- NSR device studies, however, should not be confused with the concept of "minimal risk"
- IRB approval is still required before initiation of study

SR Device Studies

- FDA may impose restrictions on the study
  - to ensure that risks to subjects are minimized
  - to ensure that the risks do not outweigh the anticipated benefits to the subjects and the importance of the knowledge to be gained.
- The study may not commence until FDA has approved the IDE application and the IRB has approved the study.
- All SR studies must be reviewed by a full IRB committee; assumed that greater than minimal risk is involved

NSR Device Studies

- Do not require submission of an IDE application to the FDA
- Sponsor is required to conduct the study in accordance with the "abbreviated requirements" of the IDE regulations [21 CFR 812.2(b)]
- May commence immediately following IRB approval

NSR Device Studies

- NSR study is considered to have an approved IDE if the sponsor fulfills the abbreviated requirements.
- Abbreviated requirements address
  - requirements for IRB approval
  - requirements for informed consent, recordkeeping, labeling, promotion, and study monitoring.

NSR Studies

- Once NSR determination has been made by IRB, the study is reviewed by the IRB using the same criteria as all other studies of an FDA-regulated product [21 CFR 56.111]
- Some NSR studies can qualify as minimal risk – may be expedited by IRB

Class Distinction for Devices

- Class I, II, and III
- Distinction is made primarily on the level of risk to users/patients and, therefore, the level of FDA oversight needed to ensure that the device is safe and effective as labeled.

Class, Controls, Products

Class	Controls	Products
Class I	General Controls	Crutches Bandaids
Class II	Special Controls	Wheelchairs Tampons
Class III	Pre-market Approval	Heart Valves

Class III Description

- Known to present hazards requiring clinical demonstration of safety and effectiveness
  - or
- Not enough known about safety or effectiveness to assign to Class I or II

510 (k) versus PMA

510 (k)	PMA
New device is substantially equivalent to another device that is legally on the market without a PMA	New device is not substantially equivalent to existing device
If FDA agrees, the device can be marketed	Clinical data are required; to be conducted in compliance with IDE regs and IRB regs

SR or NSR – who decides?

- Sponsor makes initial decision / recommendation
- If NSR, submitted to IRB, not to FDA
- If IRB agrees, IRB reviews and approves study
- If IRB disagrees, sponsor notifies FDA who then requires an IDE application
- Study then begins after IDE and IRB approvals are obtained

SR OR NSR – WHO DECIDES?

- If study is SR
  - IDE application must be filed with FDA
  - FDA reviews application; questions or approval in 30 days
  - IRB review can then proceed
  - Risk determination should be based on the proposed use of the device, not just on the device alone; what is the nature of the harm that may result from use of the device?

SR TRIGGERS

- Potential harm to subjects could be life-threatening
- Permanent impairment could result
- Medical or surgical intervention could be necessary to preclude impairment
- If subject must undergo a procedure as part of the study, potential harm of procedure must be considered along with potential harm from the device

SR EXAMPLE

- Study of a pacemaker
  - A modification of a commercially-available pacemaker
  - Still considered a SR study
  - Use of any pacemaker poses potential for serious harm to subjects, even it is less harm than other similar devices

SR Example

- Study of extended wear contact lenses
- A SR study because wearing the lenses overnight presents potential for injury not normally seen with daily wear lenses (which are considered NSR)

Emergency Use of Unapproved Medical Device

- Requirements for emergency use
  - Life-threatening situation exists requiring immediate treatment
  - No generally acceptable alternative exists
  - Because of immediacy of need, there is no time to seek FDA approval for the use
  - Physician must justify these criteria after the fact

Emergency Use of Unapproved Medical Device

- FDA expects physician to follow as many subject protection procedures as possible:
  - Independent assessment by uninvolved MD
  - Obtaining informed consent from subject or LAR
  - Notification of institutional officials
  - Notification of IRB
  - Obtaining authorization from holder of IDE

After Emergency Use of Unapproved Medical Device

- Physician reports to IRB within 5 days
- Physician evaluates likelihood that another instance of emergency need may occur
  - Initiate IDE and IRB approval for future use
- If IDE exists, notify sponsor immediately
- If IDE does not exist, notify FDA of emergency use and provide written summary

FDA Form 483

- Issued to an institution when an FDA inspection finds conditions that may constitute violations of the FD&C
  - Form 482 is issued upon arrival – notice of inspection and request for records
- Institution responds in writing with a corrective action plan to correct deficiencies
- What happens next?
  - All inspection data is collated
  - Institution's response is reviewed
  - Then, FDA determines next steps
  - If the study under inspection is funded by the federal government, then OHRP is also notified
  - Sponsors may ask, as part of site screening for studies, "Has your institution been issued a 483 within the past 5 years?"

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CFR Sections to Memorize

- 45CFR 46
  - Subpart A – Basic HRP
  - Subpart B – Pregnant women and fetuses
  - Subpart C - Prisoners
  - Subpart D – Children (minors)
- 21CFR 50 (Basic HRP) & 56 (IRBs)
- 21CFR 312 – IND (drugs, biologics)
- 21CFR 812 – IDE (medical devices)
- 21CFR 11 – electronic signatures
- 21CFR 54 – financial disclosures

Question 1

1. What FDA document must be signed prior to participating in a drug clinical trial?
   a) FDA 1571
   b) FDA 483
   c) FDA 1572
2. Who signs this form?
   a) Anyone who is co-researcher on the team
   b) Anyone who is sub-investigator on the team
   c) The lead investigator of the team

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Question 2

- What do the following abbreviations stand for?
  - CFR
  - GCP
  - CRO
  - ICH
  - FD&C
  - IB
  - IDE / IND
  - PMA
  - OHRP
  - NSR

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SOPs

- All research teams should have specific SOPs:
  - Demonstrates division of responsibility
  - Delineates lines of authority / delegation / roles as approved by the IRB
  - Standardizes all processes done by the team members
    - This is how we conduct informed consent
    - This is how specimens are acquired and processed
    - This is how data is entered / transferred

Regulatory Documents

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.4.1	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	Documentation of investigational product(s) destruction	To document destruction of unused investigational product(s) by sponsor or at site	X (if destroyed at site)	X
8.4.3	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	

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Study Documentation

- Keeping accurate and complete protocol records is the responsibility of the Lead Researcher.
- The Office of Research maintains an official protocol file for each study.

Reference: Lead Researcher Recordkeeping Responsibilities

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Study Documentation

- Download the UCI IRB Approval Letter, Protocol Narrative, Consent Form or Study Information Sheet, Recruitment Material and Data Abstraction Sheet from the IRB Document Depot.
- Save a copy of each IRB approved document for your records.
- Save a copy of any application that is formally submitted to the IRB.

Reference: IRB Document Depot

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Study Documentation

Study Closure:

- Submit a closing report to the IRB when:
  - Recruitment and enrollment complete
  - All specimens, records, data obtained
  - No contact with subjects is necessary
  - Analysis of subject ID data, specimens complete
  - Review of source documents complete

Reference: UCI Closing Report

Study Documentation

Record Retention: OHRP: 3 Years (minimum):

- The HHS protection of human subjects regulations require institutions to retain records of IRB activities and certain other records frequently held by investigators for **at least three years** after completion of the research (45 CFR 46.115(b)).

Reference: (45 CFR 46.115(b))

Study Documentation

Record Retention: Other Considerations:

- PHI: 6 years
- Minors in research: 7 years after age 18

- In-vitro fertilization studies or pregnant women: 25 years

Reference: Lead Researcher Recordkeeping Responsibilities

Study Documentation

Record Retention: FDA: 2 Years (minimum)

- Drugs: marketing application approved: 2 years after FDA approval.
- Drugs: no application is filed or the application is not approved: 2 years after the investigation is discontinued and FDA is notified.
- Contractual obligations may require records to be maintained per the agreement with the trial sponsor.

Reference:
Drugs 21 CFR 312.62.
Devices 21 CFR 812.140

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Study Documentation

Record Retention: National & International

- National record retention requirements may be different.
- Canada requires retention for 25 years.

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Data and Safety Monitoring Committees

- Data and Safety Monitoring Committees (DSMCs, also referred to as Boards) are groups of individuals with pertinent expertise that review on a regular basis accumulating data from one or more ongoing clinical trials

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DSMC

- Data and Safety Monitoring Committees are responsible to
  - Advise the Sponsor-Investigator regarding the continuing and prospective safety of trial subjects
  - Advise the Sponsor-Investigator regarding the continuing validity and scientific merit of the trial
  - Objectively appraise a study's progress
  - Assess data quality via a formal and planned process
  - Provide analytical expertise and rigor
  - Determine the statistical significance of efficacy and/or risk-benefit ratio

DSMCs: When are they required?

- Large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome
- Generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity
- To verify or validate efficacy and/or safety information significant to a novel therapy
- To gauge data quality to confirm the research question/ hypothesis in developing treatments
- To assess efficacy and safety when "lives and wellbeing depend on valid results"
- When mandated by an IRB

FDA recommendations for DSMCs

- The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion
- There are *a priori* reasons for a particular safety concern, as, for example, if the procedure for administering the treatment is particularly invasive;
- There is prior information suggesting the possibility of serious toxicity with the study treatment;
- The study is being performed in a potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity;
- The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint;
- The study is large, of long duration, and multi-center.

Condensed from http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm

DSMC Charters and Standard Operating Procedures

- May be drafted by Sponsor and presented to the Committee for concurrence, or the Committee can draft the charter for concurrence from the Sponsor
- Schedule/format of meetings
- Format for presentation of data
- Procedure for assessing conflicts of interest from potential Committee members
- Timing of interim reports submitted to Committee
- Other relevant Committee operations issues

Regulatory requirements for electronic systems – 21CFR11

- Applies to signatures as well as data entry and submission systems
- Must be equivalent to handwritten systems
- Closed system
  - Ensure authenticity, integrity and confidentiality of records
  - Validation practices to assure accuracy, reliability and consistent performance
  - Must be able to retrieve and print all data
  - Limited access to intended individuals
  - Audit trail must support all access and entries
- Signature protections must be in place

Electronic Records

- Open systems
  - Require same protections as closed system
  - Must have additional elements (e.g., encryption) to assure integrity of records

Regulatory Agency Inspections

- Which regulatory agencies can audit our research records?
  - FDA
  - OHRP

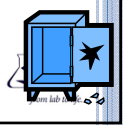
Audits and Inspections

- Research must stand up to inspection
- Documentation is key
- If not documented, it didn't happen

Audits and Inspections

- If not documented, researchers may open themselves to fraud allegations
- Scientific misconduct is rare
  - Affects public confidence in the clinical trial process
  - Raises questions about effectiveness of trial monitoring and its follow up by sponsors

Reference: ORI



Audits and Inspections

Common Goals:

- Assure human research subject protections are in place
- Assure data is accurate and reliable
- Assess compliance
- Detect fraud and misconduct

Audits and Inspections

More Goals:

- Process improvement
- Educational needs
- Assure quality control
- Prepare for inspection

Audits and Inspections

More Goals:

- Are actions needed for organization to come into compliance?
- Are regulatory sanctions required?

Audits and Inspections

At UCI:

UCI Office of Research
5171 California Avenue, Suite 150, Irvine, CA 92697-7600

EQUIP
Education & Quality Improvement Program

- Office of Research Compliance

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Audits and Inspections

The **FDA** can inspect:

- Clinical Researchers
- IRBs
- Sponsors
- Clinical Research Organizations
- Other Agencies

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Audits and Inspections

FDA Good Clinical Practice Inspections of Sponsors:

- Were the SOPs followed?
- How were monitors & investigators selected?
  - Were they qualified?
- Were periodic site visits conducted?

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Audits and Inspections

FDA Good Clinical Practice Inspections of Sponsors:

- Were sufficient monitoring resources allocated to the project for on site monitors and medical monitors?
- Were corrective actions taken when deviations, violations, errors occurred?
- Did the monitor assess drug storage and accountability routinely?

Audits and Inspections

FDA Good Clinical Practice Inspections of Sponsors:

- How was data quality assured?
- Were statisticians qualified?
- Was the statistical analysis plan followed?

Audits and Inspections

Types of FDA Investigator Inspections:

- Prescription Drug User Fee Act (PDUFA)-related inspections
  - Routine inspections
  - Triggered by a New Drug Application (NDA)
    - New Molecular Entities (NME)
    - Foreign data – pivotal studies not in the US

AUDITS AND INSPECTIONS

Types of FDA Investigator Inspections:

- Directed Inspection
  - For cause
  - Other "triggers"

AUDITS AND INSPECTIONS

What an FDA Audit Looks Like:

1. Investigator notified and date chosen
2. FDA auditor shows up – notice of audit is served officially
3. Preliminary meeting with Investigator

AUDITS AND INSPECTIONS

What an FDA Audit Looks Like: During the Visit:

1. Key personnel interviewed
2. Study records inspected
3. Exit interview
   1. Form FDA 483

AUDITS AND INSPECTIONS

What an FDA Audit Looks Like: Report

1. Form FDA 483
   1. Respond in person
   2. Respond in writing
   3. Form FDA 483
2. FDA Report Prepared & Evaluated

AUDITS AND INSPECTIONS

What an FDA Audit Looks Like: Letter

Investigator, sponsor & IRB receives letter

- NO ACTION needed
- VOLUNTARY ACTION needed
- OFFICIAL ACTION needed

AUDITS AND INSPECTIONS

What an FDA Audit Looks Like: IRB!

- Interview Staff
- Ask about policies and procedures
- Follow 1 or more studies through regulatory review process Reference: FDA 2014 Warning Letters

AUDITS AND INSPECTIONS

What an FDA Audit Looks Like: IRB!

- IRB membership
- Procedures
- Minutes of meetings
- Materials submitted to IRB

AUDITS AND INSPECTIONS

What an FDA Audit Looks Like: IRB!

Results:

- IRB noncompliance

AUDITS AND INSPECTIONS

What an FDA Audit Looks Like: IRB!

Measures:

- Withhold authority to approve
- Cease enrollment of subjects
- Terminate ongoing research

Audits and Inspections

What an FDA Audit Looks Like: IRB!

Measures (if *really* noncompliant):

- Notify state and federal authorities
- Disqualification

Forms

- MedWatch 3500 – form for voluntary submission by a health care professional with concerns about FDA-regulated product
- MedWatch 3500B – form for voluntary reporting by a consumer
- MedWatch 3500A – form for mandatory reporting of product problems
- MedWatch reports are then compiled as a tool to allow monitoring of human medical products

Quality Assurance

- **The planned and systematic activities implemented in a quality system so that quality requirements for a product or service will be fulfilled.**
- You can think of quality assurance as the activities and management processes that are done to ensure that the products and services the project delivers are at the required quality level. It is process driven and focused on the development of the product or delivery of the service.

CAPA (Corrective And Preventive Action)

- The purpose of the corrective and preventive action subsystem is to collect information, analyze information, identify and investigate product and quality problems, and take appropriate and effective corrective and/or preventive action to prevent their recurrence. Verifying or validating corrective and preventive actions, communicating corrective and preventive action activities to responsible people, providing relevant information for management review, and documenting these activities are essential in dealing effectively with product and quality problems, preventing their recurrence, and preventing or minimizing device failures.