

# Clinical Research Overview for New Investigators

**For the University of Cincinnati**

**IND/IDE Assistance Program  
May 2011**

## Agenda

- Human Subjects Research
- Clinical Research Roles
- Sponsors and Corporate Partners
- Working with Sponsors
- The UC Sponsored Research Services Office
- Protocol Design of a Workable Study
- Good Clinical Practices in Research: Overview
- PI and Delegations to a Study Team
- Investigational Products
- Drug, Biologic and Medical Device
- Source Documentation
- Clinical (Medical) Records and Research Records
- Institutional Review Board Processes
- Timely Event Reporting and Documentation
- Proper Data Handling
- Document Retention
- AAHRPP Accreditation
- Follow-On Modules

2

## Human Subjects Research

- Human research subjects differ from medical patients in important ways.
- Animal research experience gives a head start on the record-keeping and record retention aspects of human subjects research.
- This series of modules is one of multiple supports that UC provides to researchers.
- Human Subject Protection training from the Collaborative Institutional Training Initiative (CITI).
- **Assumption: CITI training done before any of the remaining modules in this series.**

CITI, at [www.citiprogram.org](http://www.citiprogram.org)

3

## Some Clinical Research Roles

- Principal Investigator (PI) - For medical studies is often a physician, but does not have to be.
- Sub-Investigator (sub-I) – One, multiple sub-I's or none, depending on study complexity. If the PI is not a physician in medical studies there must be a physician sub-I.
- Study Coordinator (SC) – Often also a Study Nurse, but SCs are not required to be nurses.
- Sponsor – Can refer to the funding source but in research means the entity who:
  - Authors the protocol.
  - Is the eventual owner of the study data.
  - Is the source of investigational product under study (if any).
- Sponsor-Investigator - The Sponsor has self-selected to also be PI at his/her research site.

4

## Sponsors and Corporate Partners

- At UC, differing types of research relationships become established which power research studies. Examples:
  - A Corporate Sponsor firm. The UC researcher is the study PI (a PI for multi-site studies).
  - A UC researcher may initiate a study and has a corporate partner who provides support. The UC researcher is the study Sponsor or a Sponsor-Investigator.
  - A Corporate entity and a UC researcher may collaborate such that Sponsor functions are shared; formally shared is required. The UC researcher is a Sponsor or Sponsor-Investigator.
  - A UC researcher is developing his/her own invention with funding support from non-profit entities (and/or the University). The researcher is the Sponsor, **and should not become Sponsor-Investigator.**
  - Thoughtful construction of the contract or agreement between the researcher and partners is important.

5

## Working with Sponsors

- The PI-Sponsor axis is central to study conduct.
- A potential PI is initially approached by the Sponsor: **Are you interested?**
- Sponsor site selection activities occur: **Are you capable?**
- **Yes, let's do it:** PI submits the study to his/her IRB.
  - IRB is Local, Central (both in extreme instances).
- An Initiation visit occurs.
- IRB approves of the PI and the protocol: recruitment of participants, screening and enrolment of may begin.
- Documentation of IRB approval sent to Sponsor, so investigational product (if any) can be shipped to the site.
- Enrollment Start: Sponsor's routine (interim) study monitoring visits usually begin soon after and continue until the study closes at the site.

6

## Working with Sponsors

- PI should read contracts or agreements carefully.
  - Seek Legal department support sooner rather than later, if there's uncertainty.
- When a sponsor presents confusing, inappropriate or internally conflicting instructions, the site should speak up and secure resolution.
- “The Sponsor told me to” will not keep a site from compliance citations, if issues arise. Examples:
  - Protocol instructions are internally inconsistent.
  - Sponsor correspondence differs from protocol requirements.
  - Sponsor requests actions that are not allowed by the IRB.
  - Sponsor requests information but providing it would violate the participants' rights to confidentiality.

7

## The UC Sponsored Research Services Office

- Mission: to protect and minimize risk related to research for the institution.
- Provides a detailed review of proposal, budget, and subcontract information.
- Administers grants, contracts, and agreements, including signature authority for same.
  - Note: PIs cannot sign contracts and agreements on behalf of UC.
- Reviews for compliance and conflict of interest issues.
- Make sure that applications are complete and submitted for review at least 5 working days in advance of the deadline set by the potential funding source.

Cf. the Researcher's Gateway on the UC web,  
as linked from <http://www.uc.edu/ucResearch/>

8

## Protocol Design for a Workable Study

- Design is dependent on: study aims, the therapeutic area, available technologies, the standard of medical care, the measurements to be made and the tests to be performed.
- Getting the science right and preserving the capability of remaining in regulatory compliance are unrelated, but one needs both for successful regulated research.
- Care should be exercised in drafting the protocol that it stays workable.
- The physical and staff limitations of a site should be taken into account.
- Improvement suggestions: At the time the protocol is shared for site interest, or at a pre-study Investigator's meeting.

9

## Good Clinical Practices in Research: Overview

- Good Clinical Practices, or GCPs, is a term that reflects the sum of laws, guidelines and guidances for research on drugs, biologics and devices using human participants.
  - The term applies exclusively to research; there's "clinical" in the name, but GCPs are not meant to apply to medical care practices.
- In the United States, the Food and Drug Administration issued GCPs in 21 CFR Parts 11, 50, 54, 56, and: for drugs and biologics, also in 312, 314; for medical devices also in 812 and 814.
- The Common Rule, 45 CFR Part 46, applies to human research studies conducted or supported by the federal government that are outside the purview of the FDA.
- HIPAA or the Privacy Rule, a separate regulation at 45 CFR 160 and 164, is also applicable to human research studies.

10

## Good Clinical Practices in Research: Overview

- International GCPs have been put forth by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, or ICH.
- The original ICH was comprised of representatives from the regulatory authority and pharmaceutical industry in the United States, the European Union and Japan. Other interested parties, for instance Canada and the World Health Organization, sent observers.
- Since then other countries have adopted ICH GCPs as local law. FDA chose to make them guidance in the US.
- Note that ICH GCPs and ICH E6 are generally equivalent terms, however E6 is only one among multiple sets of set of requirements that ICH created. Others of interest:
  - ICH E2A, Clinical Safety Data Management Expedited Reporting.
  - ICH E3, Structure and Content of Clinical Study Reports.
  - ICH E11, Clinical Investigation of Medicinal Products in the Pediatric Population.

[www.ich.org](http://www.ich.org)

11

## PI and Delegations to a Study Team

- A lone PI can perform all study conduct tasks for an uncomplicated, brief in duration study with no investigational product.
- In more complex research a PI's study team varies, from a single coordinator/study nurse to a large team including sub-Investigators (medical, technical, biostatistical), study nurses, a regulatory coordinator, pharmacist, and a data manger.
- It is important for the PI to identify who on his/her team is authorized to perform what category(ies) of tasks on the study.
- Any task not delegated to anyone is retained by the PI and no one other than the PI should be doing them.
  - A Delegation of Duties log is used.

12

## Investigational Products (IPs)

*UC Research Policy VI.02. "Supplying and Handling Investigational Products in Human Subjects Research"*

- IP is a general term that refers to a study drug or medical device or biologic product.
  - There are also combination products.

13

## Drug

*Food, Drug and Cosmetics Act 201.(g) (1)*

The term "drug" means

- (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
- (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
- (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

14



## Biologic

[www.fda.gov](http://www.fda.gov)

- Biological products include a wide range of products such as:
  - Allergens
  - Vaccines
  - Blood and Blood Components
  - Cellular and Gene Therapy
  - Tissue and Tissue Products
  - Xenotransplants

15



## Medical Device

Device Advice  
at [www.fda.gov](http://www.fda.gov)

- If a product is labeled, promoted or used in a manner that meets the following definition in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act it will be regulated by the FDA as a medical device and is subject to premarketing and postmarketing regulatory controls.

16



## Medical Device

Device Advice  
at [www.fda.gov](http://www.fda.gov)

- A device is: "an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including a component part, or accessory which is:
  - recognized in the official National Formulary, or the United States Pharmacopoeia, 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 any of 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 any of its primary intended purposes."

17



## Investigational Products (IPs)

UC Research Policy VI.02.  
"Supplying and Handling  
Investigational Products in  
Human Subjects Research"

- Not all human subjects research studies use IPs.
- An IP, if used, may be a new, unapproved drug/biologic/device/combination, or it may be one from the trade (in commercial distribution) that is being studied for a new indication, new strength, or new dose form.
- IPs must be tightly controlled in distribution, storage at the research site, and in use. Sufficient records to allow for a complete accountability of the IP that comes to a site and leaves the site is required.
- At UC, per policy, drug and drug combination IPs must be held by the Investigative Pharmacy Service.

18

## Source Documentation

*Cf. UC Clinical research Template "Source Documentation" effective 14Feb05.*

- Source documents: the records of all original study data from participants. Includes the informed consent process, telephone contacts, screening and study procedures, diagnostic and study-related data, screening and study visits.
  - That these be documented is a matter of regulation, **but is also good scientific and medical practice.**
- Sufficient source documentation must exist for each study participant.
  - Potential participants who fail screening.
  - Participants who enter the study and complete it.
  - Participants who enter the study and do not complete it.
    - Due to withdrawal, being withdrawn, or dropping out.
- **How** the source is to be kept is not a matter of regulation, it is dependent on the institution's policies and procedures.

19

## Clinical (Medical) Records and Research Records

- Some study source documents may reside in patient (medical) charts.
- Research charts may also be where the first record of study-specific examinations, information gathering, or tests, are located.
- There are more extensive record-making requirements of research than for medical care. For instance:
  - Absence, or negative findings must be explicitly recorded. Charting by exception is not sufficient.
  - First person record-keeping is extremely important in making research records. Someone else recording what a study physician said or did, is not desirable in research.

20

## Institutional Review Board (IRB) Processes

- Human subjects research does not lawfully occur without the oversight of a properly constituted IRB.
- The mission of the IRB is to protect the rights, welfare and safety of the study participants.
- All UC studies involving humans must have IRB oversight.
- There are regulatory requirements for how many members minimum there must be, that include both scientific and non-scientific people, a member who is not affiliated with the institution, and members of both genders.

21

## Institutional Review Board (IRB) Processes

- UC has established 2 IRB panels. Both panels provide oversight for both medical studies and social/behavioral studies.
- Collectively, the UC IRB oversees research done at
  - University of Cincinnati
  - University Hospital
  - Cincinnati VA Medical Center
  - Shriners Hospital for Children Cincinnati
  - Drake Hospital
  - West Chester Medical Center
- For continuity, the panel which undertakes the initial review of a study is the one that the study is kept with throughout IRB oversight.
  - As a result, “the” IRB meets weekly, but “your” IRB meets twice per month.

22

## Institutional Review Board (IRB) Processes

- The IRB provides oversight that begins before the study starts at a PI's site.
  - The PI tells the IRB that the new study exists when PI applies for oversight.
- IRB oversight extends until after the last subject has completed or left the study and data analysis concludes.
  - The PI tells the IRB when oversight should be ending.
  - The IRB will let the PI know if the IRB disagrees.
- In between there is correspondence between the PI and IRB. Both keep all correspondence. **The PI may not rely on the existence of the IRB files and fail to retain a complete set of documents.**

23

## Institutional Review Board (IRB) Processes

- For some studies another IRB may have primary oversight responsibility though the PI is at UC.  
Examples: CCHMC IRB or a central IRB.
  - UC IRB must have and maintain awareness of the study as long as it is ongoing.
  - The study is submitted to the intended IRB of Record (the one to be supplying full oversight) and also to the UC IRB. UC IRB assesses and either elects to rely on the other IRB, or retain its own oversight.
  - With reliance on an external IRB (IRB external to UC), UC IRB receives notifications from the PI (**not from the other IRB**) but does not actively oversee the research.
  - Without reliance being declared by the UC IRB, the PI will have a full set of study notifications to, and correspondence with, two IRBs.

24

## Institutional Review Board (IRB) Processes

- For some studies another UC Committee in addition to (not instead of) the UC IRB may also be involved:
  - Radiation Safety Committee
  - Indemnification (contract lawyers)
  - Veteran's Affairs (R&D Committee)
  - Institutional Biosafety Committee
- If this is the case, get the other Committee's or Committees' approval of your study first.
- Show UC IRB documentation that the other approvals have already been secured *and not that they are pending at the time of application to the IRB*, for a shorter timeline through the entire required approval process.

25

## Institutional Review Board (IRB) Processes

- The study may not begin and IP, if any, may not be shipped to a site until the IRB (of Record) has approved:
  - The study (including the PI).
  - The protocol.
  - The informed consent form(s).
  - Compensation to be given to participants, if any: amount and schedule.
  - Study advertising to be used.
  - Any written materials to be given to participants.
  - Any other documentation the IRB requested to see.
    - Per GCPs, IRBs may ask for any information they want and the PI is held responsible to give them anything they ask for.
- Once full approval for the study is achieved, potential participants can be recruited and screened.

26

## Institutional Review Board (IRB) Processes

- The maximum length of approval an IRB is allowed to give for a study is one year.
- A study open for more than one year will need continuing review by the IRB.
  - Progress report documentation must be sent to the IRB 4-6 weeks before the expiration date to allow review time.
- If IRB reapproval is not obtained before the expiration date, all research-related activities must be stopped unless stopping would harm a participant.
- The IRB may require repeat review in less than one year if IRB decides that closer oversight is appropriate.

27

## Institutional Review Board (IRB) Processes

- If any of the IRB-approved study documents need revision, amendments are submitted to the IRB.
  - **HOWEVER**, change needed to prevent immediate harm to a participant should be made and the IRB notified **within 48 hours after, if change involves temporary or permanent interruption of study activities**. If study activities are not interrupted, notify IRB within **10 calendar days**.
- The PI is required to submit reports to the IRB as the study progresses and when the study is completed.
- The IRB may request additional information at any time.

28

## Institutional Review Board (IRB) Processes

- IRB oversight must continue until the data analysis phase is finished. The PI may submit a report to the IRB indicating that the study is completed if the only activity remaining is writing/publishing the results.
- In multi-center studies a Sponsor will notify the PI when the site's closure notification should be sent to the IRB.

UC IRB web address:

<http://researchcompliance.uc.edu/irb/>

29

## Timely Event Reporting and Documentation

*Cf. UC Policy II.02 "Reporting to the IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems"*

- The IRB must be informed in a timely manner when new information comes to the PI concerning the risks of the study to the participants.
  - If the risk-benefit ratio shifts too much toward increased risk, the IRB must stop the study.
- Serious adverse events (SAEs), adverse drug reactions (ADRs), unanticipated problems (UPs) and, for device studies, unanticipated adverse device effects (UADEs) are to have more rapid reporting than in the next routine progress report.
  - Non-serious, or "ordinary" Adverse Events (AEs) and anticipated adverse device effects can be reported in aggregate at the time of next progress report.

30

## Timely Event Reporting and Documentation

*Cf. UC Policy II.02 "Reporting to the IRB: Unanticipated Problems Involving risk to Participants or Others, Adverse Events, and Other Problems"*

- Noncompliance in general, particularly if continuing, is also to be reported in a timely manner.
- Time lines for rapid reporting are provided in UC research policies and SOPs.

31

## Proper Data Handling

- Data Handling comes between the source records and the report and/or publication made of the study results.
  - May involve transcription of data and information onto a Case Report Form.
    - **CRF use is optional unless your Department has made mandatory.**
    - **If a CRF is to be used** the Sponsor provides it, site personnel fill it out and the study monitor checks it against the source records.
  - May involve transcription of data and information into a study database, with or without unit conversion of numerical data:
    - From a completed case report form.
    - Directly from the source documents.
  - May include only tabulated summary tables with averages
    - With or without the calculation of standard deviations.
  - May include statistical analysis
    - Performed as defined in the study design, *i.e.* as described in the study protocol.

32

## Proper Data Handling

- Done only by properly delegated persons who are trained in:
  - Regulatory requirements.
  - The systems they are to use.
  - How to make corrections of inadvertent errors.
- Includes a document trail sufficient to reconstruct how the processes worked including:
  - When any conversion that occurred was made.
  - What conversion factors were used.
- The processes of data handling should include:
  - Control over access to the study data.
  - Prevention of inadvertent alteration of any entries.
  - Maintenance of participant confidentiality.
- If electronic systems are to be involved appropriate attention to controls, accesses and validation that contribute to data integrity is needed.

33

## Document Retention

- The PI is held accountable to properly retain the documents of her/his study.
  - Under secure, limited access conditions.
  - Protected against loss.
  - Readily retrievable for review such as an audit or inspection by a Regulatory authority.
  - For as long as necessary.
- Retention and retrievability of: the source data, copy of the case report form (if used), and related supporting records such as training records of the study team.
- If supporting records are not kept in your study's binders:
  - Know where else they are and for how long they will be kept.
  - Place cross-references to these other locations in your study's binders.

34

## AAHRPP Accreditation



- Association for the Accreditation of Human Research Protection Programs
  - Ensure that human research protection programs meet rigorous standards for quality and protection.
  - UC holds full AAHRPP accreditation (there are other types).
  - UC values the accreditation that the University holds.
- AAHRPP divides its standards into three areas
  - The Organization
  - Institutional Review Board or Ethics Committee
  - Researcher and Research Staff

*The AAHRPP Standards are available on the AAHRPP web-site*  
<http://www.aahrpp.org/www.aspx?PageID=316>

35

## Follow-on Modules

This orientation is the first of a series of human subject research-specific topics.

- Responsibilities and Obligations of Clinical Research Investigators
  - In two parts.
- How to Avoid Protocol Deviations and Violations in Clinical Research Conduct
- Informed Consent for Human Research Studies at UC
- Adverse and Other Events in Human Research Studies

36



## Follow-on Modules

- Case Report Forms: From Source Records to Data(base) Entry
- Drug Accountability in Human Research Studies
- Device Accountability in Human Research Studies
- Sponsor Responsibilities and Obligations in Clinical Research Studies with Sponsor-Investigators
- Submissions and Reports per Federal Authority
  - For Sponsor-Investigators

37



## We're Here to Assist You

- The IND/IDE Assistance Program, Office of Research Compliance and Regulatory Affairs, the IRB and the Sponsored Research Office are here to help and support your human subject research efforts.
- The UC web-site <http://researchcompliance.uc.edu/> contains helpful links to compliance training, the IRB, and the Human Subject Protection web-site.
- UC Policies and procedures for the conduct of research are available on the UC Human Research Protection site.
- There's also a Compliance Handbook and a helpful newsletter, "Compliance Matters" also linked from <http://researchcompliance.uc.edu/> .

38

## Getting You Credit

**We appreciate your review of this module.**

To achieve credit for having done so, please complete the corresponding quiz provided in the CPD system.

**You will receive a certificate of completion when your quiz is satisfactorily passed (score >80%).**

# Responsibilities and Obligations of Clinical Research Investigators Part 1 of 2

**For the University of Cincinnati**

**IND/IDE Assistance Program  
May 2011**



2

## Agenda: Part 1

- Research or Regulated Research?
- Investigator-Initiated Research – when the PI is also the Sponsor
- Compliance and Science
- Responsibilities of Investigators
- UC PI Rights
- Human Research Study and Conduct
- Ethical Considerations – Vulnerable Subjects
- Delegation of Duties
- The Study Site



## When is it a Regulated Research Study?

- It is a systematic investigation, including study development, testing and evaluation, designed to develop or contribute to generalizable knowledge. DHHS
- It is an experiment that involves a Test Article and one or more human subjects. US FDA
  - Test Article could be a drug, a device, a biologic or combination product
- It is any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of (an) investigational product(s), and/or to study product(s) with the object of ascertaining its safety and/or efficacy. ICH

***If any of the above is applicable,  
the study is regulated research.***



## Some Research Roles

- Investigator
  - Principal Investigator
  - Co-Principal Investigator
  - Sub-Investigator
- Clinical Research Coordinator
  - Often called Study Coordinator
- Other Study Staff
  - Regulatory Coordinator
  - Biostatistician
- Study Sponsor
  - In the Regulatory sense, as described further on.



## Principal Investigator (PI) of a Research Study:

- Leads the team of people who conduct the study
  - Delegates study tasks to team members
- Holds total responsibility for the overall conduct of the study
  - *Responsibility* cannot be delegated to study team members.
  - Team members are accountable to the PI, however.
- Can also be the sponsor of the study, even when not the funding source, **in which case the study is referred to as Investigator-Initiated** (more on slide #7).



## Other Investigators: Co-Principal and Sub-

- At UC, a Co-Principal Investigator (abbreviated Co-PI) is a second study team leader who may have the same rights and responsibilities as does the Principal Investigator.
- A sub-Investigator is a member of the PI's (and Co-PI's, if any) study team and has study tasks delegated to him or her by the PI and/or Co-PI.
  - Most sub-Investigators have a sub-set of study tasks delegated to them, however a sub-Investigator may be enabled to perform the complete list of tasks that the PI has.
  - **The difference is in leadership role and responsibility.**



## A PI is Also the Study Sponsor When:

7

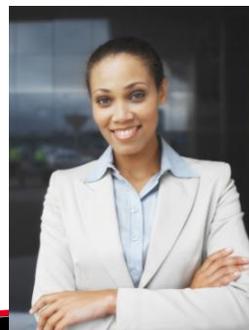
- The PI designed the (whole) study.
- The PI wrote the protocol.
- The PI allocated duties and functions and selected the Investigator(s) (self-selection included).
- Someone the PI assigned to do it is the manager of study conduct.
- Someone the PI assigned to do it is making needed notifications to regulatory authorities.
- Someone the PI assigned to do it is confirming that IRB notifications and reviews occur as needed.
- The PI engaged the person who is monitoring the study.
- The PI “owns” the study data.
- ✓ Sponsor-Investigators have defined obligations in regards to a research study which go beyond those of an individual PI.
  - ✓ The companion training module "Sponsor Responsibilities and Obligations of Clinical Research Sponsor-Investigators" provides more information.



## You Are the Clinical Research Sponsor Whether or Not also the Investigator If:

8

- You hold the IND or IDE under which the research is conducted.
  - Especially if you select someone else to be the PI or Co-PI.
  - Even when you yourself are also the Principal Investigator or Co-PI.
  - No matter where your funding for the study comes from.
- ✓ As the Sponsor you have defined obligations in regards to your study.



## Compliance and Good Science

- UC needs human research studies to involve both compliance and good science, each to a sufficient degree.
- The two are achieved by different, independent means.
- Compliance is with respect to requirements described in:
  - Organizational Human Research Protection Program Policies.
  - Organizational SOPs.
  - The study protocol.
  - Prevailing regulations and guidelines.
  - Accreditation standards (such as AAHRPP).



## At UC, the PI and any Co-PI are each fully responsible for:

From UC HRPP Policy IV.01  
*“Rights and Responsibilities of  
Principal Investigators in Human  
Subjects Research”*

1. Conducting the research study in a manner that will protect the safety and welfare of participants in the study and that conforms to the protocol approved by the IRB.
2. Ensuring that research studies employ a sound study design that develops or contributes to generalizable knowledge that uses research methods that minimize risks to participants, and that recruits participants in a fair and equitable manner that adequately reflects the population being studied and protects participants from coercion or undue influence.
3. Ensuring that federal (FDA and HHS), state and local laws and regulations **and the policies and procedures of the University of Cincinnati** are followed in the conduct of research.
4. For externally sponsored studies, reading and understanding all the information in the grant documents, the investigator’s brochure, the informed consent, the protocol and all other study related materials.



At UC, the PI and Co-PI are each fully responsible for:

<sup>11</sup>  
From UC HRPP Policy IV.01  
"Rights and responsibilities of  
Principal Investigators in Human  
Subjects Research"

5. Informing all participants of all the elements of the research and following all requirements relating to obtaining their informed consent. See UC Research Policy II.01, *Obtaining Informed Consent in Human Subjects Research*. *[This includes securing an IRB waiver of consent when warranted.]*
6. Preparing and submitting documents for initial review, and, timely submission of documents for continuing IRB review and approval.
7. Conducting study activities only after IRB approval and in accordance with the approved protocol, and assuring that all IRB requirements are met.
8. Implementing modifications in approved research only after review and approval of the modification by the IRB, except where necessary to eliminate apparent immediate hazards to participants.
9. Appropriate control, inventory, administration, storage, record keeping and destruction or return of test articles *[(the study drug(s), devices, biologics),*
10. Reporting to the IRB unforeseen events that may present risks or affect the safety or welfare of subjects or others, or that may affect the integrity of the research. See Research Policy II.02 Reporting Unanticipated Problems in Human Subjects Research.



At UC, the PI and Co-PI are each fully responsible for:

<sup>12</sup>  
From UC HRPP Policy IV.01  
"Rights and responsibilities of  
Principal Investigators in Human  
Subjects Research"

11. Reporting any interim analysis or other study findings to the IRB and study participants, when they may affect the health or welfare of study participants. *[Example, DSMB evaluations]*
12. Formally delegating responsibilities to other members of the research team for appropriate tasks, such as delegation of obtaining informed consent. The PI will provide appropriate training to such individuals for whom the tasks have been delegated. *[The Delegation of Responsibilities Form (filed in the PI's regulatory binder) will indicate the tasks that were delegated and to whom the stated tasks were delegated.]*
13. Adequately supervising members of the research team and ensuring that all members of the research team have appropriate training, expertise, and any required current licenses, certifications, or other credentials, to conduct the study.
14. Assuring that the facilities and equipment for conducting the research are adequate, and that provisions exist to protect the health and safety of participants.



## At UC, the PI and Co-PI are each fully responsible for:

From UC HRPP Policy IV.01  
*"Rights and responsibilities of Principal Investigators in Human Subjects Research"*

15. For clinical research, assuring that all study drug(s), device(s), equipment and supplies are distributed and stored in accordance with the protocol, FDA and OHRP regulations and institutional policy.
16. Ensuring that all blood, tissue and other samples are collected, processed, and stored in accordance with the protocol, Good Laboratory Practices, and Good Clinical Practices.
17. If research is conducted by *[a PI who is]* a person in-training such as a student, fellow, or resident, the research protocol must have a faculty member designated as the Co-PI *[who will be expected to mentor and supervise the PI]*.
18. Assuring that key personnel have reported any financial conflict of interest in accordance with Research Policy IV.02 *Investigator Conflict of Interest in Human Subjects Research*.
19. Maintaining adequate and accurate records.
20. Assuring full cooperation with both external and internal monitoring, reviews, investigations, and audits of the research.



## For Some Studies, there are Additional Responsibilities

- Statements made for a study, which may be in the protocol, declare under which regulations and guidelines the study is to be conducted. For instance, studies with external Sponsors specify ICH-GCPs, the International Conference on Harmonization guidelines for good clinical practices, in addition to compliance with U.S. FDA GCPs.
  - UC does not require ICH GCP compliance for all human subject research conducted at UC or by UC Investigators at affiliated institutions.
- If the study Sponsor, external or internal, specifies ICH GCPs for a study then ICH E6 applies and the UC PI has 24 additional specific responsibilities for that study.



## ICH-GCP Specific PI Responsibilities

15

From UC HRPP Policy IV.01  
"Rights and responsibilities of  
Principal Investigators in Human  
Subjects Research"

21. When appropriate, the investigator informs the participant's primary physician about the participant's participation in the clinical trial if the participant has a primary physician and if the participant agrees to the primary physician being informed. [Document the Subject's agreement for the notification, in appropriate relative temporal order.]
22. [If a participant withdraws from study participation:] Although a participant is not obliged to give his or her reasons for withdrawing prematurely from the clinical trial, the investigator should make a reasonable effort to ascertain the reason, while fully respecting the participant's rights. [To be able to declare lost to follow-up, there must be documented phone calls followed with a certified letter to the Subject that is returned. Keep any certified letter that is returned to sender in the Subject's file (research chart/binder).]
23. A qualified **physician** provides the medical care given to, and medical decisions made on behalf of, participants.
24. The investigator provides evidence of such qualifications through up-to-date curriculum vitae or other relevant documentation requested by the sponsor, the IRB, or the regulatory authority.



## Additional ICH-GCP Specific PI Responsibilities

16

From UC HRPP Policy IV.01  
"Rights and responsibilities of  
Principal Investigators in Human  
Subjects Research"

25. The investigator is familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.
26. The investigator is aware of and follows GCP and the applicable regulatory requirements.
27. The investigator permits monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority.
28. A qualified **physician** (or **dentist, when appropriate**), who is an investigator or a co-investigator for the clinical trial, is responsible for all trial-related medical (or dental) decisions.
29. During and following a participant's participation in a trial, the investigator ensures that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial.



## Additional ICH-GCP Specific PI Responsibilities

17  
From UC HRPP Policy IV.01  
*"Rights and responsibilities of  
Principal Investigators in Human  
Subjects Research"*

30. The investigator informs a participant when medical care is needed for illnesses of which the investigator becomes aware.
31. Responsibility for accountability of the investigational product at the clinical trial site rests with the investigator.
32. The investigator ensures that the investigational product is used only in accordance with the approved product.
33. The investigator ensures the accuracy, completeness, legibility, and timeliness of the data reports to the sponsor.
34. The investigator maintains the clinical trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements.
35. Essential documents are retained until at least two years after the last approval of a marketing application in an ICH region and there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. *[This could be a very long time.]*



## Additional ICH-GCP Specific PI Responsibilities

18  
From UC HRPP Policy IV.01  
*"Rights and responsibilities of  
Principal Investigators in Human  
Subjects Research"*

36. If the investigator terminates or suspends a clinical trial without prior agreement of the sponsor, the investigator informs the IRB and the sponsor.
37. If the sponsor terminates or suspends a clinical trial, the investigator informs the IRB.
38. If the IRB terminates or suspends its approval of the clinical trial, the investigator should promptly notify the sponsor.
39. Upon completion of the trial, the investigator informs the IRB with a summary of the trial's outcome, and the regulatory authority with any reports required.
40. The investigator provides written reports to the sponsor and the IRB on any changes significantly affecting the conduct of a clinical trial or increasing risk to participants.
41. The investigator maintains a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.



## Additional ICH-GCP Specific PI Responsibilities

19  
From UC HRPP Policy IV.01  
*"Rights and responsibilities of  
Principal Investigators in Human  
Subjects Research"*

42. The investigator reports all serious adverse events (SAEs) to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The investigator follows regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and the IRB.
43. Investigators report adverse events or laboratory abnormalities identified in the protocol as critical to safety evaluations to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
44. For reports of deaths, the investigator supplies the sponsor and the IRB with any additional information (e.g., autopsy reports and terminal medical reports).



## UC PI Rights

20  
From UC HRPP Policy IV.01  
*"Rights and responsibilities of  
Principal Investigators in Human  
Subjects Research"*

A UC PI has the following Rights:

1. To a review of their submissions to the IRB in a reasonably prompt manner.
2. To a reasonable notice of internal monitoring reviews, investigations, or audits of the research and to actively participate during the course of any such review.
3. To receive notice of disapprovals, suspensions, or terminations of research in writing with the reason for the action.
4. To address concerns with the IRB on any matter of concern, either in person or in writing, and to have concerns addressed.
5. To a reasonably prompt rehearing by the IRB on any research proposal or modification which has been disapproved, or any research which has been suspended or terminated.
6. To bring any question or concern regarding the functioning of the IRB to the attention of the Office of Research Compliance and Regulatory Affairs, and if the concerns are not adequately addressed, to the Vice President for Research or the Institutional Official or to the Office of General Counsel.



## A Human Research Study:

- Is defined by a written plan, often called a protocol.
  - Written and scientifically approved *before* the study begins.
  - Reviewed and approved by an IRB *before* any enrollment of subjects
  - For FDA regulated research, includes details of the statistics to be used.
- The protocol can be written by the study sponsor, or the funding/initiating organization/agency.

A thoughtfully written protocol results in a study that is more straightforward and easier for the team to conduct. The companion training module “How to Avoid Protocol Deviations and Violations” provides more information.



## Study Conduct:

- A research study begins when the PI signs the protocol and ends when the PI signs the final report.
- Study conduct is thoroughly documented before, during and after the participant visits.
  - The study, the Investigator, the protocol, the informed consent form(s), any advertising to be used any written materials to be given to subjects, gifts or other compensation to be given to subjects are approved by the IRB
    - Prior to enrollment start.
    - Throughout the study, as revisions occur. *Appropriate Quality measures throughout.*
  - Subjects are recruited and enrolled.
  - Source data are generated.
  - Periodic updates to the IRB are made.
    - The IRB will decide how often they want to hear from the PI on a study-by-study basis.
  - Subject Safety review occurs (if required, reports to Medical Monitor or DSMB).



## Study Conduct:

- Study conduct is thoroughly documented.
  - Participants complete their portion of the study.
  - Use of case report forms (CRFs) to move data and information from the source records to study database entry is *optional*.
    - CRFs could be hard copy or electronic
    - If used, a copy is to be retained at the study site.
  - A study database is populated.
    - The database is checked.
      - If needed, queries are generated and resolved.
    - Data analysis occurs.
  - A study final report is generated.
    - There may also be interim analysis(es) with report(s) such as to a DSMB (if the study has one).

Appropriate  
Quality measures  
throughout.



## Ethical Considerations: Research with Vulnerable Subjects

From UC Research Policy V.01  
"Vulnerable Populations  
in Human Subjects Research"

- Research Ethics includes equitable choosing of subjects among those who express interest in participation, and full and uncoerced informed consent.
- The normal safeguards are insufficient when the study draws subjects from vulnerable populations. Additional care, often additional documentation is needed when offering a study to a subject or legally authorized representative on behalf of a subject, when the subject is vulnerable.
- Vulnerability is found due to condition of the person and/or hierarchical structures which lead to undue influence (**whether or not justified**) of either:
  - Benefits from study participation
  - Retaliatory response from senior members of one's hierarchy upon refusal to participate.



## Ethical Considerations: Research Studies with Vulnerable Subjects

- Examples of vulnerable populations include [ICH E6 1.61]

Patients with incurable conditions	Medical, dental, pharmacy and nursing students
Patients in emergency situations	Wards
Children and aged adults	Members of the armed forces
Persons living in nursing homes	Unemployed or impoverished persons
Persons incapable of giving consent	Ethnic and minority groups
Prisoners	Nomads
Subordinate hospital and laboratory personnel	Refugees

- The IRB will want to see that the protocol includes how undue influence will be avoided or minimized, when a study involves participants who are noted as vulnerable per UC Policy V.01, "*Vulnerable Populations in Human Subjects Research*".



## Who is Conducting the Study: Delegation of Duties

- The PI agrees to personally conduct the study or have it conducted by others under the PI's supervision, or both.
- Unless research study duties are delegated to someone else, the PI retains them and to maintain compliance, no one else may do those duties the PI has retained for him/herself.
- The delegations have a start and end date which correspond to when each individual staff person joins and/or leaves the study team, and at the end of the study all delegations conclude.
- The delegations that a PI makes are documented on a log that is kept current and retained in the Regulatory Binder.
- **Over-delegation is to be avoided.** If tasks delegated require certain (e.g. medical) licensure be held by the person doing those tasks, then assure the proper licensing and as necessary privileges are in place, prior to making the delegation for the study.



## Where the Study is Conducted : The PI's Study Site

- A PI leads the team who is conducting a study; the PI and his/her team do their work at the PI's site.
- The term "site" is variable, from study to study.
- "The site" is the collection of facilities where the PI is directing and has responsibility for the study activities that happen there.
- The site could be composed of various facilities which may be at the same or at differing physical buildings or street addresses.
- A study may involve other locations as well, such as central labs or central reading facilities with whom the Sponsor has contracted that are not under that PI's direction or control, thus outside of the PI's site.
- Some PIs set up a main site and "satellite" sites, such as multiple office locations in the same city, at all of which the study is to be conducted. Special care is to be taken with satellite sites, to have the subjects seen at each satellite be provided with the same degree of oversight and care that the subjects at the main site experience.



## End of Part 1

You have completed Part 1 of a two-part module on Investigator Responsibilities and Obligations.

**Please review both parts.**

There are separate quizzes for Parts 1 and 2.



## Getting You Credit

**We appreciate your review of this module.**

To achieve credit for having done so, please complete the corresponding quiz in the CPD system.

You will receive a certificate of completion for this module when your quiz is satisfactorily passed (score >80%).

# Responsibilities and Obligations of Clinical Research Investigators Part 2 of 2

**For the University of Cincinnati**

IND/IDE Assistance Program, UC  
May 2011



## Start of Part 2

This module is Part 2 of 2 on the topic of Investigator Responsibilities and Obligations.

**Please complete Part 1 before embarking on Part 2.**



## Agenda: Part 2

- Study Events
- Adverse Events and Unanticipated Problems
- Source Data and the Medical Record
- Study Files
- Study Quality Control and Quality Assurance
- Protocol Compliance and Deviations
- Human Subject or Participant, not Patient
- Human Subject Protection
- Regulations and Guidelines Governing Human Research Studies
- UC Policies and Standard Operating Procedures for Human Subjects Research
- AAHRPP Accreditation
- Form FDA 1572 and Commitments the PI Makes
- Parting Thoughts



## Study Events

- Things happen to people while they are research participants in a study.
  - The investigational product or study interventions may have desirable effects on the participants, and/or improve the participant's condition or quality of life. These events may be:
    - Anticipated, the effects hoped-for by the study designers (e.g., efficacy).
    - Unanticipated, surprises that have a positive impact on the health and well-being of the participants who incur them.  
 [Example: Viagra was not being tested for its currently marketed indication when the effect was first reported that is now the reason for that drug to be on the market.]
  - The investigational product or study interventions may have undesirable or adverse effects on the participants, such as those issues colloquially termed “side effects”.
    - Anticipated effects, from the developmental history of the drug, both preclinical work and previous clinical studies.
    - Unanticipated effects, surprises that have a negative impact on the health or well-being of the participants who incur them.



## Study Events

- For proper research study conduct it is important to:
  - Identify, capture and classify each event that study participants incur.
  - Recognize the unanticipated.
  - Recognize the adverse: at what level of severity and how serious.
  - Report events in an appropriately timely manner.



## Adverse Event Definitions

*Cf. UC HRPP Policy II.02 "Reporting to the IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems"*

- Adverse Event (AE): any untoward occurrence (physical, psychological, social, or economic) in a human subject who is participating in research.
- Adverse Event: any unfavorable or unintended sign, symptom, or disease temporally associated with the use of an investigational product that does not necessarily have a causal relationship with the investigational product.
- More information on the detection, documentation and reporting of Adverse Events is presented in the companion training module "Adverse and Other Events in Human Research Studies".



## Recent FDA Additions to Event Definitions

21 CFR 312.32(a),  
March 2011

- Adverse Event (AE)
  - Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
- Adverse Reaction (AR)
  - Any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.
- Suspected Adverse Reaction (SAR)
  - Any adverse event for which there is reasonable possibility that the drug caused the adverse event. For IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the event. With a lesser degree of certainty of causality than for an AR.



## Unanticipated Problems

8

Cf. UC HRPP Policy II.02 “Reporting to the IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems”

- Events that are anticipated are those in the Investigator’s Brochure (drug products) or device information (devices) and the study informed consent form. Anticipated problems (including events) are often also expressed in the study protocol.
- **Un**anticipated problems in human subjects research are, per UC Policy, always in connection with to an IRB-approved study (either ongoing or closed) and are to be reported to the IRB.
- An incident is classified as an unanticipated problem involving risk to participants or others when it is:
  - Unexpected in nature, severity or frequency
  - Related or possibly related to participation in the research.
  - Suggests that the research places the participants or others at greater risk of harm than was previously known or recognized.



## Expedited Event Reporting to the IRB

9  
UC HRPP Policy II.02, "Reporting To The IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems"

- The UC IRB requires PIs to report certain Adverse Events to the IRB in an expedited manner. *In addition* to those, there are other types of events that require expedited reporting:
  - Significant protocol deviations (or other accidental or unintentional changes to the protocol or procedures) involving safety or integrity risks OR with the potential to reoccur.
  - Complaints made by research participants indicating an unanticipated event, OR complaints that cannot be resolved by the research staff.
  - Unapproved changes made to the research to eliminate an apparent immediate hazard to a research participant.
  - Data and Safety Monitoring Board (DSMB) reports, interim analyses, or other oversight committee/monitoring reports/recommendations altering the risk/benefit profile.



## Expedited Event Reporting to the IRB (continued)

10

- Events that require expedited reporting:
  - New information indicating an unexpected change in risks or potential benefits (e.g. literature/scientific reports or other published findings).
  - Investigator's Brochure updates or revisions to safety information.
  - Other problem or finding (e.g. breach of confidentiality, loss of study data or forms, *etc.* that an Investigator or research staff member believes could influence the safe conduct of the research).
  - All internal or external events that may represent unanticipated problems involving risks to participants or others.
    - Regardless of whether the events occur during or after the study, or to a participant who has withdrawn from study participation.

After the study, here, means after subject participation and before final close-out with the IRB.



## Immediate Report Events: To IRB within 48 Hours

11

Cf. UC HRPP Policy II.02, "Reporting To The IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems"

The UC IRB has defined prompt reporting as 10 calendar days of site knowledge of an event (VA: 5 business days). For one category of events this is not fast enough, and within 48 hours reporting is required for:

- Events resulting in temporary or permanent interruption of study activities by the Investigator or Sponsor, to avoid potential harm to participants.

Site knowledge of events that require expedited reporting "starts the clock" that the study team will be judged against in regard to was the reporting timely.

Having a protocol say that reporting would occur within 48 hours or 10 days **of the event itself** is not recommended, and is practical only for studies that are of hospitalized persons. With participants at home between visits, the participants may not inform the study team until after an event has resolved.



## Research (Source) Data and the Medical Record

12

- There are medical records used for research, and research-only records. A study may use both. It is important to understand when a record is a medical record used for research, and when a record is research only.
- When the actions/data being recorded are for/from standard of medical care, it's a medical record and will be retained in the medical chart.
  - Such records may be reviewed and/or copied or transcribed for research later, but when made, were for medical care.



## Research (Source) Data and the Medical Record

- When the actions/data are protocol prescribed and are not needed for medical care of the participant, it's a research record, and is retained in a research binder or chart.
  - Medical care teams do not need and do not directly access research charts.
  - Labs done for the research tend to be exceptions, as in e-charting systems all labs are visible to both the research and medical teams.
- When the medical chart will be drawn upon, and for what data separate records in a research chart will be made should be kept in mind as the protocol is written.

Ask your monitor, your audit group or Regulatory support person, if there is uncertainty.



## The Regulatory Binder

- The term refers to one or a set of multiple physical ring binders or alternatively, a set of designated file folders. At informal communication levels the term 'Regulatory Binder' is often shortened to 'Reg Binder'.
- Whatever its physical form, the Reg Binder for each research study contains many of the documents in the Investigator's Site File (ISF), which is owned by the study PI.
- At UC, PAMP provides on request a sample regulatory binder structure to guide Investigators as to what documents are to be filed in which section of the Binder.
- What records are to be kept are conveniently listed in ICH GCPs Section 8 and are also presented in UC SOP ADM 002.
  - The listing in the ICH GCPs is divided into subsections:
    - Those documents that are to be on file before the enrollment of participants at the site,
    - Those that are generated or become updated during the time participant visits are occurring, and
    - Those documents that are to be on file after the last participant has completed study involvement and prior to site closure.



## Investigator's Site File and the Sponsor's Trial Master File

- When an Investigator is a Sponsor-Investigator, then a second set of files, the Sponsor's files, are also to be kept, by the Sponsor and his/her employees.
  - These could be the same people as are on the Investigator's study team.
- The Sponsor keeps the Trial Master File (TMF), which for a multi-site study includes a sub-section that is the central file for each PI site involved with the study.
- ICH GCP Section 8 and UC SOP ADM 002 also include what documents the Sponsor should have in the central file for each PI site.
  - There is overlap between the ICF and the TMF, according to the lists of Essential Documents. However there are some document types to be in the TMF are not also expected to be in the ISF.



## Quality Control (QC ) and Quality Assurance (QA)

QC and QA often sound, and at times feel, much the same. But the two differ in scope and objectives.

### QC

- Is a part of study conduct.
- Assesses everything that's going on in study conduct.
- Identifies issues and gets them fixed.
- Involves multiple review events (visits).
- Is a primary level of support to the PI and the study team.

### QA

- Is not study conduct.
- Assesses key areas of study conduct (and sometimes also the ongoing QC efforts).
- Identifies issues not yet found in QC and those found in QC but not fixed yet. Flags them for others to address.
- Often involves only one visit.
- Is a secondary level of support of the PI and study team.



## Quality Control (QC ) for a Research Study:

- QC: Quality Control that is internal to the study team
  - Completeness of the research records.
  - Accuracy of any transcriptions into summaries and reports.
  - Activities are documented in the study conduct records.
  - Accuracy of case report forms or database entries made directly from the source records.
- QC: Study Conduct Monitoring by a qualified person who is not on the study staff delegation log.
  - Defined and arranged for by the study Sponsor.
    - By the Sponsor-Investigator, if that is who is in total charge of the study.
  - Correspondence and a signed log in the PI's regulatory binder, and separate reports of visits in the Sponsor's Trial Master File.



## Quality Assurance (QA) for a Research Study:

- QA: Internal Audit by and for UC
  - Done by a qualified individual who is independent of the study team and study conduct.
- QA: Sponsor audit at their discretion, done by someone other than the Monitor, is also Quality Assurance.



## Protocol Adherence is at the Heart of Compliance

- When the study that is done is the one that was approved
- When the visits, tests, measures and treatment that occur are those that were defined in the protocol and were IRB-approved
  - And if revisions, extras become indicated?
    - Amend them into the protocol and get them approved **before they are implemented**, for full compliance.
    - Please refer to the separate module “How to Avoid Protocol Deviations and Violations”, for more information.
- The data gathered are those defined in the protocol and were approved.
  - Additional data indicated? Or the PI finds that some data being gathered have become demonstrated as not useful?
  - Amend the revisions into the protocol and get them approved **before you acquire** and additional data **or cease acquiring** the data that the has decided is not needed.



## Deviations from the Protocol, SOPs, or from Regulatory Requirements

- Deviations happen in the course of even well-controlled and monitored human subjects research.
  - Some are discovered by the study team members themselves, and are corrected prior to the Monitor seeing them.
  - Some are discovered by the study Monitor, and are reported to the PI for resolution. The sponsor is copied on the report.
  - Some are discovered by internal institutional or external Auditors, who report them to the PI with a request for both correction and a prevention plan to block reoccurrence of the deviations noted. Deviations noted on Internal audit reports go to UC Sponsor-Investigators but are not sent out to external sponsors. External (sponsor) auditors report deviations to the external sponsor.
  - Those discovered by a Regulatory Agency inspector are shared with the PI and reported to the Regulator.
  - Some are caused by the participants themselves, and all the site can do is document and react to them appropriately.



## PI Reports of Deviations

*Cf. UC HRPP Policy II.02 "Reporting to the IRB: Unanticipated Problems Involving risks to Participants or Others, Adverse Events, and Other Problems"*

- The PI is to report deviations to the IRB which is providing him/her with study oversight.
  - As soon as possible for those deviations made to avoid immediate hazard to participants
  - On the timelines for reporting as "Other Problems" as per UC Policy II.02: within 48 hours when study activities become interrupted, within 10 working days when not.
  - At next continuing review for deviations or violations:
    - Not involving risks to participants.
    - That are unlikely to recur.



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Directories
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### Institutional Review Board

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Post Approval Activities  
IRB Contacts  
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**Miscellaneous Reporting/Information**

**Miscellaneous Reporting/Information**

- Event Reporting Form - [Word](#)
- [Deviation Report](#) - for minor events
- Investigator Brochure Information Sheet [Word](#)
- [Conflict of Interest Form & Instructions](#)
- [HIPAA](#)
- [CITI Training Instructions](#)

Which form depends on the significance of the deviation being reported.

[http://researchcompliance.uc.edu/irb/Miscellaneous\\_Reporting\\_Information.html](http://researchcompliance.uc.edu/irb/Miscellaneous_Reporting_Information.html)

## Dealing with Deviations

- Deviations happen, in a research study.
- Identification, documenting the discovery and reporting the deviation are important, but there is more the PI and team should do about deviations.
  - If applicable, the Investigator(s) and team should put any needed supporting measures in place in support of and for the participant(s) affected by the deviation.
  - The PI should assess the impact of the deviation on the study data.
  - The PI and team should devise a corrective means to prevent reoccurrence.
- If a deviation is assessed as something that should be permanent for the study for all participants going forward, then a protocol deficiency has been identified and a corresponding amendment should be initiated.
  - Once the Amendment is approved by the IRB, further instances of the situation will not be deviations any longer.



## Routine Study Status Updates to the IRB

- The IRB must be kept aware of the study overall, so they may provide appropriate oversight of the work.
- Annual reports often termed continuing review, give the IRB a summary of the study activities and status.
- Each IRB indicates what it wants for continuing review and whether the frequency for routine reporting is annual or on a shorter cycle.
- Continuing review reports typically cover events and status since the last study review provided to the IRB and include:
  - An enrollment status update.
  - Summary of adverse events and list of protocol deviations that occurred during the interval including those that did not need to be promptly reported.
  - Information on any participant who ceased study enrollment for reasons other than completion.
  - Whether there has been a sponsor audit or Regulatory Agency inspection during the interval.



## Why do We Say Human Subject or Participant, and not Patient?

- Patients receive medical care, human subjects volunteer to participate in research studies.
- Participants may have been the Investigator's or a colleague's patients before they enter a research study, and may go back to being just patients afterwards. During the study, their becoming research participants places additional obligations on the Investigators, towards them.
- The regulations and guidelines by which human research studies are done define "human subject" as a living individual about whom an investigator (whether professional or student) conducting research obtains:
  - (1) data through intervention or interaction with the individual, or
  - (2) identifiable private information.

45 CFR § 46.102(f) [DHHS]



## Human Subject or Participant, not Patient

- Human subject means an individual who is or becomes a participant in research, either as a recipient of a test article or as a control.
  - A subject may be either a healthy human or a patient.
  - In device studies, also someone whose specimen an investigational device is used on, or used as a control.
- Subject/Trial Subject: An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

21 CFR 50 §3(g), 21 CFR 812 §3(p) [US FDA]

ICH E6 1.57



## Human Subject Protection Includes Confidentiality

- Confidentiality of participant identity
  - Before the study (prescreening).
  - During the study.
  - After the study.
  - In publications.
- Confidentiality of the records and data
  - Participant PHI (HIPAA).
  - Assuring a sufficiently de-identified data set.
    - When you need one.



## Regulations Applicable to Human Subjects Research

- U.S. Food and Drug Administration (FDA GCP)
  - IND (New Drug Entities), IDE (Medical Devices)
  - 21 CFR parts 11, 50, 54, 56,  
21 CFR Part 312 (Drug) or Part 812 (Device)
- Department of Health and Human Services (Office of Human Research Protection, OHRP)
  - 45 CFR Part 46
- Health Information Portability and Accountability Act (HIPAA)
  - 45 CFR Parts 160 and 164
- Ohio State law concerning research involving humans which indicates that the Federal regulation is to be followed (some States add their own specifics).



## Guidelines Applicable to Human Subjects Research

- ICH E-6 (ICH GCPs)
  - Law in some countries of the world
  - Guidance in the USA
    - US FDA heavily involved in producing the ICH Guideline
    - *It is policy at UC that ICH GCPs be followed when the study protocol so indicates.*
- FDA “Guidance for Industry” Documents. Examples:
  - Collection of Race and Ethnicity Data in Clinical Trials
  - Bioanalytical Method Validation
  - Computerized Systems Used in Clinical Investigations



## UC Policies on Human Subjects Research

- UC has made the University’s research policies available in the Human Research Protection area of the University web site, at  
[http://ahc-sharepoint.uc.edu/hrp\\_policies/HRP%20Policies/Forms/AllItems.aspx](http://ahc-sharepoint.uc.edu/hrp_policies/HRP%20Policies/Forms/AllItems.aspx)
- To the left on the UC home page, choose Research, then again to the left under Research Offices, choose Research Compliance. That will take you to the ORCRA page. Choose HRP, then from that main menu choose Research Policies.
- The policies are grouped topically into seven electronic folders as illustrated on the next slide.



HRP\_Policies

Home

HRP\_Policies > HRP Policies

**HRP Policies**

View All Site Content

**Documents**

- Shared Documents
- HRP Policies**
- IRB Procedures
- Good Clinical Practice SOP Templates
- Sponsor-Investigator SOPs

**Pictures**

**Lists**

Type	Name
Folder	I - AUTHORITY AND INSTITUTIONAL COMMITMENT
Folder	II - CONDUCT OF RESEARCH
Folder	III - IRB REVIEW
Folder	IV - INVESTIGATOR RESPONSIBILITIES
Folder	V - VULNERABLE POPULATION
Folder	VI - CLINICAL RESEARCH
Folder	VII - QUALITY ASSURANCE, LEGAL AND COMPLIANCE

Each folder contains a group of individual Policy documents.

UC

32

## UC's Policies on Human Subject Research

- Be aware of them.
- Decide how your study will be conducted in accordance with them.
- Ask ORCRA if any questions arise as you read them.  
Contact:
  - Jane E. Strasser, Ph.D.
  - Associate Vice President and Director
  - Office of Research Compliance and Regulatory Affairs
  - 51 Goodman Street
  - University Hall Room 510
  - P.O. Box 2100567
  - Cincinnati, OH 45221-0567
  - Tel: 513.558.5034
  - Fax: 513.558.0549

UC

## Standard Operating Procedures for Human Subjects Research: It is Policy that PIs Have SOPs for Research Conduct

UC has established HRPP Policy VI.01: *“Research Unit Standard Operating Procedures in Clinical Human Subjects Research”*

- A Research Unit is Department, Division, unit or clinical practice affiliated with the University of Cincinnati. Research Unit includes all personnel, including Sponsor-Investigators, involved in the implementation and coordination of investigations involving human subjects by all departments.
- Per the above policy all Research Units that engage in clinical research will develop Standard Operating Procedures (SOPs) similar to the template provided by the Office of Research Compliance and Regulatory Affairs at UC (ORCRA).
  - Each set of SOPs will be reviewed for currency and updated as needed, at least annually.



## Clinical Research SOPs

- Some UC Departments have already taken the ORCRA templates and from them have created SOPs by which human research studies are to be done.
  - A PI doing human subjects research needs to have SOPs.
  - If his/her Department has not made research SOPs at the Departmental level, the PI becomes the Research Unit, and is to take the template SOPs and create SOPs from them, for his/her program or study.
  - The ORCRA SOP templates can be accessed from the Human Research Protection area of the UC website, at [http://ahc-sharepoint.uc.edu/hrp\\_policies/default.aspx](http://ahc-sharepoint.uc.edu/hrp_policies/default.aspx).



# Clinical Research SOPs

35

**HRP\_Policies**

Home

View All Site Content

**Documents**

- Shared Documents
- HRP Policies
- IRB Procedures
- Good Clinical Practice SOP Templates**
- Sponsor-Investigator SOPs

**Pictures**

**Lists**

**HRP Policies**

Type	Name
Folder	VII - QUALITY ASSURANCE, LEGAL AND COMPLIANCE
Folder	VI - CLINICAL RESEARCH
Folder	IV - INVESTIGATOR RESPONSIBILITIES
Folder	III - IRB REVIEW
Folder	II - CONDUCT OF RESEARCH
Folder	I - AUTHORITY AND INSTITUTIONAL COMMITMENT
Folder	V - VULNERABLE POPULATION



# Clinical Research SOPs

36

**HRP\_Policies**

Home

HRP\_Policies > Good Clinical Practice SOP Templates

**Good Clinical Practice SOP Templates**

View All Site Content

**Documents**

- Shared Documents
- HRP Policies
- IRB Procedures
- Good Clinical Practice SOP Templates**
- Sponsor-Investigator SOPs

**Pictures**

**Lists**

Type	Name
Folder	1 - Responsibilities of the Research Team
Folder	2 - Working with Research Participants
Folder	3 - Unanticipated Problems
Folder	4 - Record Keeping

Each folder contains template documents pertinent to PIs and their teams.



37

## Clinical Research SOPs

HRP\_Policies

Home

HRP\_Policies > Sponsor-Investigator SOPs

### Sponsor-Investigator SOPs

Type	Name
Folder	Administration
Folder	FDA
Folder	FORMS FOR MONITORING
Folder	Monitoring
Folder	Regulatory

Each folder contains additional template documents pertinent when the PI is also the study Sponsor.

38

## Financial Disclosure, Agreements, and Conflict of Interest

- A key person may work on a study even with a financial or conflict of interest in the study. The interests and conflicts must however be documented in detail and shared with the Sponsor, FDA and the IRB.
  - The conflicts will be weighed by the US FDA in their assessment of the reliability of the study (21 CFR 54.5).
  - The IRB considers the impact when they review and evaluate the research study.
- Conflicts that arise during the research are also to be reported.
- Records of the interests and conflicts will be held in Sponsor's files, with copies retained by the PI in the study regulatory binder.
- Sponsors are to secure signed and dated conflict of interest forms at specified intervals, from each Investigator (PI, Co-PI and sub-I).

## AAHRPP Accreditation

- Association for the Accreditation of Human Research Protection Programs
  - UC holds full accreditation (there are other types)
  - UC values the accreditation that the University holds.
- AAHRPP divides its standards into three areas
  - Researcher and Research Staff
  - The Organization
  - Institutional Review Board or Ethics Committee



## AAHRPP on the Researcher and Staff

III-1 In addition to following applicable laws and regulations, Researchers and Research Staff adhere to ethical principles and standards appropriate for their discipline. In designing and conducting research studies, Researchers and Research Staff have the protection of the rights and welfare of research participants as a primary concern.

*[With 7 specific elements under this Standard, on next slide.]*



## AAHRPP Element III-1: Standards

- A. Know which of the activities they conduct are overseen by the HRPP and seek guidance when appropriate.
- B. Identify and disclose financial Interests, manage, minimize or eliminate financial conflict of interest.
- C. Employ sound study design in accordance with standard of the discipline. Study design minimizes participant risk.
- D. Have necessary resources present before start of study conduct (necessary for protection of participants).
- E. Recruit participants in a fair and equitable manner.
- F. Appropriate consent processes and methods, emphasize comprehension, voluntariness, participant informed decision making.
- G. Have a process to address participants' concerns, complaints, or info requests.



## AAHRPP on the Researcher and Staff



III-2 Researchers and Research Staff meet requirements for conducting research with participants and comply with all applicable laws, regulations, codes, and guidance; the Organization's policies and procedures for protecting research participants; and the IRB's or EC's determinations. [EC is Ethics Committee, analogous to IRB]

*[With 4 specific elements under this Standard, next slide.]*



## AAHRPP Element III-2: Standards

- A. Researcher and Staff are qualified by training & experience for research roles, know applicable laws, regulations, codes and guidance, professional standards and Organization's policies and procedures regarding participant protections.
- B. Researchers maintain appropriate study oversight, including of staff and trainees, and delegate functions appropriately.
- C. Follow the protocol/plan and adhere to policies and procedures of the Organization, and the IRB's determinations and requirements.
- D. Follow reporting requirements in accordance with laws, regulations, codes, guidance, Organization's policies and procedures, and IRB's determinations and requirements.



## For PIs of FDA-Regulated Drug Studies: Form FDA 1572

44

This Form functions as the PI's contract with the U.S. Government. On the front side, the PI:

- Self-identifies and presents documentation of education, training and experience that qualified him/her to be a PI.
- Defines where the study is occurring.
- Identifies what clinical laboratories are participating.
- Identifies which IRB(s) will be providing study oversight.
- Defines who his/her sub-Investigators are, if any.
  - Study coordinators considered to be sub-Investigators must be listed here.
- Identifies the study: protocol name and if any, code number.

⇒ Information can be supplied in the form of attachments (such as a curriculum vitae) rather than entering that information directly onto the Form, and this should be so noted on the Form in the relevant numbered block.



## Form FDA 1572

On the back side of the Form

- The PI identifies the study as Phase I, or as Phase II or III.
  - Protocol titles do not always indicate Phase, and authors are not required to include Phase in the study title.
  - **Note: Phase IV (postmarketing) studies don't require this Form to be executed.**
  - **Note: Device studies don't require this Form to be executed.**
- There is a list of commitments the PI is taking on by signing the Form, in Form section 9.
  - These commitments are often referred to as the Investigator's obligations.



## Form FDA 1572 Commitments the PI Makes

- To conduct the study in accordance with the relevant, current protocol
- Only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- To personally conduct or supervise the described investigation(s)
- To inform any patients and any persons used as controls, that the drugs are being used for investigational purposes and 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.

The drug being for investigational purposes is usually incorporated into the informed consent form (ICF) text and is also verbally explained during an appropriate IC process. The labeling should say so also.

The informed consent form must have IRB Approval before the ICF is used. An IRB-approvable ICF will contain all the required elements in it as each applies to the particular study.



## Form FDA 1572 Commitments

- To report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.
- To read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.
- 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.
- 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.

21 CFR 312.62 refers to case histories [which are the sum of the source records plus any case report forms], drug disposition, and proper retention of study records.

Available for inspection means at the request of any properly authorized officer or employee of the FDA, at reasonable times, the FDA inspector will have access to, and have the ability to copy and verify any records or reports made in pursuant of §312.62.



## Form FDA 1572 Commitments

- Ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.
- Promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others.
- Make no changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- To comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

Note it is a PI responsibility to assure that the IRB was properly constituted to do their work on his/her study. Have documentation of that in the regulatory binder.

Note it was in a different obligation above that no changes in the research without the Sponsor being notified, here the IRB is to be notified in advance as well, unless there is immediate hazard to Subjects that is being avoided (in which case, promptly report once the hazard-avoiding actions have been taken).



## Form FDA 1572

- When a Study has multiple PIs (such as a multi-site study) each PI fills out his/her own Form FDA 1572. Sponsor receives the original, PI keeps a copy.
- Form FDA 1572 can be revised and UC prefers that it be revised, whenever the information on the front side changes during the study.
  - *Examples:* new or departing sub-Investigators, change of lab or new study conduct location added.
  - All of the older copies are retained in the regulatory binder behind the current version.
- The Form with the commitments thereon is to be taken seriously. Just below blocks 10 and 11, where the Investigator signs and personally dates the Form, is the following:
 

**(WARNING:** A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)
- The Form FDA 1572 is printed as a one page 2-sided document, then signed and personally dated by the signatory. Hard copy reproductions of the Form that are made, are best done as 2-sided copies.



## High Quality Research

- Results from both study design and study conduct.
- Includes a high level of compliance.
- Produces the most useful data.
- Preserves the assurances given to potential participants when they sign up, by:
  - Maintaining acceptable risk-benefit ratio.
  - Generating data of a sufficient quality to be used in answering the questions posed by the study design.
  - Generating data that are useful towards furthering medical science.



## Parting Thoughts

- Conducting successful human subjects research differs from successful practice of medicine.
- The PI, as leader, guide, director, trainer and source of study decisions, controls the study conduct at his or her site.
- The PI as protector of the participants rights, safety and well-being, fulfills the promises made to the volunteers who are participating in the study.
- Fulfillment of the PI's regulatory and policy responsibilities and obligations results in research of maximum utility for the study Sponsor.



## Getting You Credit

**We appreciate your review of this module.**

To achieve credit for having done so, please complete the corresponding quiz provided in the CPD system.

You will receive a certificate of completion for this module when your quiz is satisfactorily passed (score >80%).



# Adverse and Other Events in Human Research Studies

**For the University of Cincinnati**

**IND/IDE Assistance Program**

**May 2011**

## Agenda

- Adverse Events: Definition, Discovery, and Documentation
- Serious, Severe and Significant Adverse Events
- Adverse Drug Reactions
- Adverse Event Reporting
- Immediate Report Events
- Post-Reporting Reclassification of Adverse Events
- Unanticipated Problems
- Other Reportable Events
- Regulatory and Guideline References
- UC Policies and Standard Operating Procedures Concerning Events
- Safety Letters from the Study Sponsor
- Parting Thoughts



## Adverse Event Definitions

*Cf. UC HRPP Policy II.02 "Reporting to the IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems"; ICH E6 1.2, ICH E2A Guideline for Clinical Safety Data Management*

- Adverse Event (AE): any untoward occurrence (physical, psychological, social, or economic) in a human subject who is participating in research.
- Adverse Event: any unfavorable or unintended sign (including a laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
- "Adverse Experience" is a term considered to be synonymous with Adverse Event
- The identification, capture and classification of each event that study subjects incur, the recognition of those adverse events that are serious and those events that are unanticipated, and timely event reporting **are all important to proper research study conduct.**

3



## Adverse Event Discovery

- AEs are identified in varying ways:
  - During physical exam of the subject.
  - In review of laboratory test results.
  - On medical chart review e.g., X-rays, scans, specialist reports.
  - While hearing a verbal report from a study participant (or about a participant by a family member or care provider).
    - Spontaneous phone call.
    - During interviews at study visits (in-person and telephone visits).
  - In an e-mail from a participant.
  - From follow-up on entries in a study diary or answers a participant gave on a study questionnaire.
- All adverse events are captured in study source records.

4

## Adverse Event Documentation

- Each event is documented by the study team, assessed, reported to the IRB in summary at least annually, and is included in the final study report that is eventually written.
- Each adverse event:
  - Is anticipated or unanticipated.
  - Is related to the participant's participation in the research (definitely, probably or possibly), or is unrelated to the research.
  - Is serious or not serious.
  - Is internal or external.
    - Internal means the event was incurred by a participant at UC or at an Investigator site that receives oversight from the UC IRB.
    - External means the event occurred at a study site receiving oversight from another IRB, not the UC IRB.
  - Has a severity (intensity): mild, moderate or severe.
    - Whether both initial intensity and maximal intensity of each event are to be separately captured in study records is according to the study sponsor, as indicated in the study protocol.

5

## Adverse Event Documentation

- Each adverse event:
  - Has a date (and time) of onset.
  - Has a date the site finds out about it. This date:
    - Is when any member of the study team learns of the event, whether or not that person is able to assess event relatedness.
    - Is the start point for events that have defined reporting timelines.
    - May be later than the onset date, and for studies with non-hospitalized participants may also occur after the resolution date.
  - Has an outcome.
    - May resolve completely (has a resolution date and time) or
    - May stabilize and become chronic (and have a date when this assessment was made).
      - May have associated long-term effects.
  - Could result in a temporary or permanent change in how the investigational product is administered.
  - Could result in concomitant, supportive treatments being given to the participant, or additional laboratory testing.

6

## Event Documentation

- It matters who is making the assessments of relatedness and intensity of adverse events. To be eligible, the assessor needs to be a study team member with sufficient medical background.
  - PIs who lack medical background should not be making these assessments.
- Documentation of events being AEs is made in each subject's research record.
- Documentation of AE reporting is held in the PI's regulatory binder.
  - The reporting does not include Subject names. Inclusion of the Subject's study ID is recommended for reports to the IRB and Sponsor.
  - Timelines for reporting are as prescribed by regulations but the Sponsor and the IRB can ask for shorter timelines than are required by regulators.
  - Being timely in event recognition, of documentation and of reporting demonstrates Investigator involvement and active PI oversight of the study.
- To be timely an initial report may be incomplete, such as for a serious adverse event which takes multiple days or weeks to resolve.
  - One or more follow-up reports would be filed, the first promptly after a definable event end date is reached or promptly once the event is classified as chronic/ongoing, with possibly others especially if there are sequelae from the event.

7

## Unanticipated Problems

Cf. UC HRPP Policy II.02 "Reporting to the IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems"

- To be considered as unanticipated problems, events are always related to an IRB-approved study (either ongoing or closed).  
All unanticipated problems are to be reported to the IRB.
- An incident is classified as an unanticipated problem involving risk to subjects or others when it is:
  - Unexpected in nature, severity or frequency, given:
    - The research procedures in the protocol-related documents and the informed consent form, or in the Investigator's Brochure.
    - The characteristics of the subject population.
  - Suggesting that the research places the subjects or others at greater risk of harm than was previously known or recognized.
    - Here "harm" includes physical, psychological, economic, or social harm.

8



## Unanticipated Problems

Cf. UC HRPP Policy II.02 "Reporting to the IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems"

- Events that are anticipated are identified in the Investigator's Brochure (drug products) or device information (devices) and in the study informed consent form.
  - Anticipated adverse events are also to be expressed in the study protocol, when the UC PI is a Sponsor-Investigator.
- Unanticipated adverse drug/device effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death:
  - Caused by, or associated with a drug/device.
  - If that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application).
  - Associated with a drug/device and is related to the rights, safety, or welfare of subjects.

9



## Unanticipated Problems

Cf. UC HRPP Policy II.02 "Reporting to the IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems"

- A UC Sponsor/Investigator shall immediately conduct an evaluation of any UADE.
- Should the Sponsor/Investigator determine that a UADE presents an unreasonable risk to subjects, the Sponsor/Investigator should terminate all investigations or parts of investigations presenting that risk as soon as possible.
  - Not later than 5 working days after making this determination and not later than 15 working days after the event.

10



## Serious Adverse Events

Cf. UC HRPP Policy II.02 "Reporting to the IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems"

- Definition of when an adverse event is or becomes serious is given in FDA Guidance, ICH E6 GCPs, and in ICH E2A on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. As expressed in UC Human Research Protection Program Policy II.02:
  - Event resulted in the subject's death, whether related to an investigational agent or not related.
  - Event is life-threatening.
  - The participant became a hospital in-patient because of the event, or an existing hospitalization for other causes became prolonged. (Elective hospitalization for a condition unrelated to the research study excepted).
  - Event results in persistent or significant disability/incapacity.
  - The event is a congenital anomaly/birth defect in the offspring of a participant who was pregnant during the research study, regardless of how long after the study the defect is diagnosed.
  - Any intervention required to prevent one of the above outcomes.

**The Policy notes that drug overdose and cancer are not automatically characterized as SAEs *per se*, but will be if these criteria are met.**

11



## Severe Adverse Events, Serious Adverse Events, and Significant Adverse Events

- It is important to distinguish between severity and seriousness of adverse events as the terms are not synonymous.
  - An 'ordinary' AE (a non-SAE) can have an intensity of severe, but if the event does not meet the definition of SAE, the event remains an AE and is reported out as such.
- Confusingly, some protocols introduce a third "S" in regard to AEs: Significant. These are events that do not meet the regulatory definitions of S(erious)AE, but the study Sponsor has written into the protocol, that non-SAEs of specified kinds, usually termed significant adverse events, are to have expedited reporting by the study sites to said Sponsor.
  - Since Sig(nificant)AEs are not SAEs, they do not receive expedited reporting to the IRB unless the Sponsor has so specified.
  - **If the Sponsor does instruct PIs to expedite non-SAEs of any specified kind, the UC IRB expects the PI to use expedited reporting to the IRB as well as to the Sponsor.**
  - "Significant" AEs are Sponsor-driven, and do not have to be included in the study protocol.

12



## Adverse Drug Reactions

Cf. ICH E2A; Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, II.A.

- Adverse Drug Reactions (ADRs) that occur in the pre-approval clinical experience with a new medicinal product or its new usages are defined by ICH as: all noxious and unintended responses to the product related to any dose.
- For ADRs that occur in marketed products, the ICH draws on the definition put forth by the World Health Organization: A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.
- Unexpected Adverse Drug Reaction (UADR) is also defined by ICH: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved medicinal product).

13



## Definitions from the US FDA for IND Drugs

- Adverse Event (AE) [new 21 CFR 312.32(a)]
  - Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
- Adverse Reaction (AR)
  - Any adverse event caused by a drug.
- Life-threatening adverse event (AE) or life-threatening suspected adverse reaction (SAR)
  - An AE or SAR is considered “life threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death.
  - It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.

14

## Definitions from the US FDA for IND Drugs

- Serious Adverse Event (SAE) or Serious Suspected Adverse Drug Reaction [new 21 CFR 312.32(a)]
  - An AE or SAR is considered serious if, in the view of either the Investigator or the Sponsor it results in any of the following outcomes:
    - Death
    - A life-threatening adverse event
    - Inpatient hospitalization
    - Prolongation of existing hospitalization
    - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
    - A congenital anomaly/birth defect.

15

## Definitions from the US FDA for IND Drugs

- Serious Adverse Event (SAE) or Serious Suspected Adverse Drug Reaction [new 21 CFR 312.32(a)]
  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes in this definition.
- Suspected Adverse Reaction (SAR)
  - Any adverse event for which there is reasonable possibility that the drug caused the adverse event.  
For IND safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the event.  
With a lesser degree of certainty of causality than for an AR.

16

## Definitions from the US FDA for IND Drugs

- Unexpected Adverse Event or Unexpected Suspected Adverse Reaction
  - An AE or SAR is considered “unexpected”:
    - If it is not listed in the IB.
    - If it is not listed at the specificity or severity that has been observed, or if an IB is not required or not available, is not consistent with the risk information in the investigational plan or elsewhere in the current application as amended.
  - “Unexpected” also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from pharmacological properties, but are not specifically mentioned for the particular drug under investigation.

17

## Adverse Event Reporting

*Cf. UC Research SOPs 3-1 “Promptly Reportable Events” and 3-2 “Adverse Event Reporting” and UC HRPP Policy II.02 “Reporting to the IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems”*

- PIs report AEs to the Sponsor and to the IRB.
- Categories of adverse events that are to be expedited (reported promptly to the IRB within 10 calendar days of the site's knowledge of the event) are:
  - Internal SAEs that are unexpected AND related to study participation.
  - Unanticipated related adverse events/device effects, both internal and external.
  - Events that the Sponsor has defined as needing prompt reporting to the Sponsor (sometimes Sponsors will also specify prompt to the IRB).
- For expedited (timed) event reporting, the clock starts with site knowledge of the event and not the event onset date.
- Adverse events that are not severe, and SAEs that protocol has defined that do not need prompt reporting, are summarized for the IRB and the summary reported at continuing review of the study.
  - For studies with a Data and Safety Management Board, summary reports of events go to them on the DSMB's desired timing.

18

## Adverse Event Reporting

- Both SAEs and unanticipated problems should be reported to the UC IRB on the “Event Reporting Form for Unanticipated Problems Involving Risks to Participants or Others, Adverse Events and Other Problems” form provided by the IRB.  
**Include a corrective action plan for the unanticipated events.**
  - Exception: unanticipated problems that pose an immediate threat to the participant or others are to be reported by telephone or email to the IRB within 1 business day, with a follow-up in writing.
- Sponsors may accept the same form, or may prefer to have PIs report events on a Sponsor-supplied form.
- It is the Sponsor, not the PI, who sends reportable adverse events to an applicable Regulatory Agency (e.g., FDA). The Sponsor has defined timelines to adhere to, for that reporting.

Additional information on reporting requirements can be found in the separate module “Submissions and Reports per Federal Authority”.

19

## Events to Be Reported To IRB within 48 Hours

Cf. UC HRPP Policy II.02, “Reporting To The IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems”

- UC IRB expedited reporting is within 10 calendar days of site knowledge of an event, for most reportable events.
- For one category of events this is not fast enough. Within 48 hours reporting is required for events resulting in temporary or permanent interruption of study activities to avoid potential harm to participants, interruption made by the Investigator or the Sponsor.
  - Within 48 hours of the decision being made by the PI to interrupt the study activities to avoid harm.
    - The decision is to be documented and include the time the decision was made.

20



## Events to Be Reported To IRB within 48 Hours

Cf. UC HRPP Policy II.02, "Reporting To The IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems"

- Within 48 hours reporting (continued)
  - Within 48 hours of the site receiving a communication from the Sponsor of such study activity interruption.
    - Sponsor communication arriving on a Friday at 6 pm cannot wait until Monday. The Investigator's report to the IRB is to be made over the week-end.
    - The transmittal time of Sponsor Fax communication is also time of arrival at a site, but for email the time on the printed message is time transmitted. A site will need to document when the email was opened and read.
  - Within 48 hours means hour by hour, not within the next 2 days. Example: a Fax that arrives at 9 am on Tuesday has a report due to the IRB by 9 am on Thursday. If not sent until 2 pm on Thursday, the report is late.

21



## Post-Reporting Reclassification of Adverse Events

- Events initially determined to be SAEs can on follow-up and further reflection, become re-classified as (downgraded to) AEs (non-SAEs).
  - The status change should be documented and communicated to the recipients of the initial SAE reports.
- The reverse also occasionally occurs: an event a site thought was not an SAE can be later elevated to SAE status (typically by the Sponsor).

22

## Post-Reporting Reclassification of Adverse Events

- When an Investigator reports an SAE and the study Sponsor re-classifies the event as an AE, then Sponsor and Investigator are viewing the event differently.
  - As long as the PI has reported the event to the IRB and Sponsor according to the established timeline for an SAE, regulatory repercussions from the re-classification, if any, belong to the Sponsor.
  - Note also, newly revised FDA regulation declares Sponsor OR Investigator as determiner of what is an SAE: PI-Sponsor agreement is not required and the Sponsor should report the events to FDA even when they disagree with an Investigator.

23

## Post-Reporting Reclassification of Events

- When an event initially thought to be an AE is upgraded to SAE, the event reporting becomes expedited.
  - At the time of event status change, it may already be too late to report the event out on the timeline that applies if the event had been classified as SAE at the time of its discovery.
  - For upgraded adverse events, the prompt reporting timeline starts on the date the event was upgraded to SAE.
  - The assessment that upgraded the event must be documented in the study records.
- Reclassification of events should be rare occurrences.
  - If not, additional training may be in order.
    - Repeated event reclassification after the initial report to the IRB is made signals a possible training need in regards to AEs and their assessment by site personnel.
    - Event reclassification by the Sponsor happening too often may need to be addressed with additional training of both site personnel and the assigned monitor.

24



## Other Reportable Events

Cf. UC HRPP Policy II.02, "Reporting To The IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems"

- There are additional types of study events that at UC are to be reported to the IRB more rapidly than at next continuing review:
    - Complaint of a participant when the complaint indicates unexpected risks or when the complaint cannot be resolved by the research team.
    - Violation, meaning an accidental or unintended change to the IRB approved protocol that places one or more participants at increased risk, or has the potential to occur again.
    - Breach of confidentiality.
    - Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the participant to remain in the study.
- Subpart C: research involving prisoners. Additional review and safeguards are to be in place to conduct such research.

25



## Other Reportable Events

Cf. UC HRPP Policy II.02, "Reporting To The IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems"

- There will be times when it is not clear whether an event is "reportable" to the IRB or not. The IRB wants to help and support PIs who encounter such events; uncertain events should be reported.  
Per UC Policy II.02:
  - The UC IRB will accept other reports when the investigator is unsure whether the event should be reported, and the IRB will review such reports to determine whether the event meets the threshold for an unanticipated event representing risk to the participant.

26

## Regulatory References

### U.S. Food and Drug Administration (FDA GCP)

IND (New Drug Entities), IDE (Medical Devices)

21 CFR parts 11, 50, 54, 56, AND either  
21 CFR Part 312 (Drug) or Part 812 (Device)

- From newly revised 21 CFR 312.64 (b):  
Safety Reports.

An investigator **must immediately** report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or IB and must include an assessment of whether there is a possibility that the drug caused the event.

Study endpoints that are SAEs must be reported in accordance with protocol unless there is evidence suggesting a causal relationship between the drug and the event. In that case, the Investigator must immediately report the event to the Sponsor.

27

## Regulatory References

### U.S. Food and Drug Administration (FDA GCP)

IND (New Drug Entities), IDE (Medical Devices)

21 CFR parts 11, 50, 54, 56, AND either  
21 CFR Part 312 (Drug) or Part 812 (Device)

- From newly revised 21 CFR 312.64 (b): Safety Reports.

The investigator must record nonserious adverse events and report them to the Sponsor according to the timetable for reporting specified in the protocol.

- From 21 CFR 312.66: Assurance of IRB review.

An investigator shall also assure that he or she will promptly report to the IRB ... all unanticipated problems involving risk to human subjects or others...

28

## Regulatory References

- From 21 CFR 812.150 Reports, (a) Investigator reports:

An investigator shall prepare and submit the following complete, accurate and timely reports:

(1) Unanticipated adverse device effects: An investigator shall submit **to the sponsor and to the reviewing IRB** a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

...

(7) Other. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

29

## Regulatory References

Department of Health and Human Services  
(Office of Human Research Protection, OHRP)  
45 CFR Part 46

- From 45 CFR 46.103(b)(5); [the organization shall have] written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of
  - (i) any unanticipated problems involving risks to subjects or others ...

30

## Guidelines

- ICH E-6 (ICH GCPs)
  - 4.11 Safety Reporting
    - 4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs which the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports...
    - 4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
    - 4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g. autopsy reports and terminal medical reports).

31

## Guidelines : ICH E-2A (ICH Expedited Reporting)

- ICH E-2A (ICH Expedited Reporting)
  - Section III.A. What should be reported?
    - III.A.1. Single cases of serious, unexpected ADRs.
    - III.A.2. Other Observations:
      - Increase in rate or occurrence of an expected ADR which is judged to be clinically important.
      - Significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.
      - A major safety finding from a newly completed animal study (such as carcinogenicity).

32

## UC Policies Concerning Adverse and Other Events

- UC has made the University’s research policies available in the Human Research Protection area of the University web site, at [http://ahc-sharepoint.uc.edu/hrp\\_policies/HRP%20Policies/Forms/AllItems.aspx](http://ahc-sharepoint.uc.edu/hrp_policies/HRP%20Policies/Forms/AllItems.aspx)
- Start at the UC Home page ([www.uc.edu](http://www.uc.edu))
- On the left on the UC home page, click Research.
- Again to the left of that next page under Research Offices, click Research Compliance. That will take you to the ORCRA page.
- Click HRP
- From that main menu click Research Policies.

33

## UC Policies Concerning Adverse and Other Events

- The policies are grouped topically into seven electronic folders, as illustrated on the next slide.
- The policies most central to adverse and other events are:
  - UC HRPP Policy II.02 “Reporting to the IRB: Unanticipated Problems Involving Risk to Participants or Others, Adverse Events, and Other Problems”
  - UC HRPP Policy VII.02 “Reporting of Unanticipated Problems, Non- Compliance, Suspensions and Terminations to the Appropriate Institutional Officials Departments and Agencies”
- Be aware of these policies and decide how your study will be conducted in accordance with them.
- **Ask ORCRA if any questions arise as you read them.**

34

UC

## UC Policies: Adverse and Other Events

Academic Health Center > HRP\_Policies

**HRP\_Policies**

Home

HRP\_Policies > HRP Policies

### HRP Policies

Type	Name
Folder	I - AUTHORITY AND INSTITUTIONAL COMMITMENT
Folder	II - CONDUCT OF RESEARCH
Folder	III - IRB REVIEW
Folder	IV - INVESTIGATOR RESPONSIBILITIES
Folder	V - VULNERABLE POPULATION
Folder	VI - CLINICAL RESEARCH
Folder	VII - QUALITY ASSURANCE, LEGAL AND COMPLIANCE

View All Site Content

**Documents**

- Shared Documents
- HRP Policies**
- IRB Procedures
- Good Clinical Practice SOP Templates
- Sponsor-Investigator SOPs

**Pictures**

**Lists**

- Contacts

35

UC

## UC Policy Requires PIs to Have SOPs for the Performance of Research

UC has an established HRPP Policy: VI.01 *“Research Unit Standard Operating Procedures in Clinical Human Subjects Research”* Adverse Events are reflected in several of the SOP templates.

- A Research Unit is a Department, Division, unit *or clinical practice affiliated with* the University of Cincinnati. Research Unit includes all personnel involved in the implementation and coordination of investigations (studies) that involve human subjects by all departments.
- Per the above policy all Research Units that engage in clinical research will develop Standard Operating Procedures (SOPs) similar to the template provided by the Office of Research Compliance and Regulatory Affairs at UC (ORCRA). (Template location is illustrated on the next few slides.)
- Each set of SOPs used by PIs will be reviewed for currency and updated as needed, at least annually.

36



## Clinical Research SOP Templates

Academic Health Center > HRP\_Policies

 **HRP\_Policies**

**Home**

View All Site Content

**Documents**

- Shared Documents
- HRP Policies
- IRB Procedures
- **Good Clinical Practice SOP Templates**
- Sponsor-Investigator SOPs

**Pictures**

### HRP Policies

Type	Name
	VII - QUALITY ASSURANCE, LEGAL AND COMPLIANCE
	VI - CLINICAL RESEARCH
	IV - INVESTIGATOR RESPONSIBILITIES
	III - IRB REVIEW
	II - CONDUCT OF RESEARCH
	I - AUTHORITY AND INSTITUTIONAL COMMITMENT
	V - VULNERABLE POPULATION

37



## Clinical Research SOP Templates

Academic Health Center > HRP\_Policies

 **HRP\_Policies**

**Home**

View All Site Content

**Documents**

- Shared Documents
- HRP Policies
- IRB Procedures
- **Good Clinical Practice SOP Templates**
- Sponsor-Investigator SOPs

**Pictures**

**Lists**

- Contacts

HRP\_Policies > Good Clinical Practice SOP Templates

### Good Clinical Practice SOP Templates

Type	Name
	1 - Responsibilities of the Research Team
	2 - Working with Research Participants
	3 - Unanticipated Problems
	4 - Record Keeping

The Unanticipated Problems folder includes Adverse Events.



## Clinical Research SOP Templates

Academic Health Center > HRP\_Policies

 **HRP\_Policies**

[Home](#)

HRP\_Policies > Sponsor-Investigator SOPs

### Sponsor-Investigator SOPs

View All Site Content

**Documents**

- Shared Documents
- HRP Policies
- IRB Procedures
- Good Clinical Practice SOP Templates
- **Sponsor-Investigator SOPs**

**Pictures**

**Lists**

- Contacts

**Actions** ▾

Type	Name
Folder	Administration
Folder	FDA
Folder	FORMS FOR MONITORING
Folder	Monitoring
Folder	<b>Regulatory</b>

The Regulatory folder includes Adverse Event Reporting.

39



## Human Subject Research SOP Templates Concerning Events

- Adverse events are addressed in several of the SOP templates, including:
  - SOP 1-1 *“Responsibilities of the Research Team”*
  - SOP 3-1 *“Promptly Reportable Events”*
  - SOP 3-2 *“Adverse Event Reporting”*
  - REG 001 *“Sponsor Required Reports”*
  - REG 003 *“Adverse Event Reporting”*
  - REG 004 *“Unanticipated Adverse Drug-Device Effect” Reporting (UADE)*
- Note that some UC Departments have already created Departmental SOPs from these ORCRA templates by which human research studies are to be done. PIs in those Departments will be adopting their Departmental SOPs. PIs in Departments which have not created Departmental SOPs, are still expected to have SOPs by which to do research.
  - Adoption or adaptation of the UC templates is strongly encouraged.
  - **Please ask ORCRA if any questions arise from the assessment of these templates for adoption.**

40

## Safety Letters from the Study Sponsor

- When a Sponsor has an obligation to inform all PIs of events that may have occurred anywhere in the world, on any concurrent study of the drug or device, the Sponsor has options as to how to do the communication.
  - A common means is to have PIs receive letters from the Sponsor *via* Fax or, after rendering a signed copy into pdf form, by e-mail.
- There could be a few to a few hundred events that the Sponsor reports to a PI during a given study, depending on study length and the investigational product under study.
- PIs are to read the letters promptly after their arrival (document when each arrived and was read by the PI).
- It is the PIs who are to decide which letters need to be promptly forwarded to their IRB, and which letters do not need prompt forwarding.

41

## Safety Letters from the Study Sponsor

- When there is a central IRB (such as in a multi-site study) the Sponsor may elect to forward the letters to the IRB on behalf of all PIs. In these cases, the Sponsor so informs each PI, so the PIs have documentation that their reporting requirement has been met.
- When a local IRB provides oversight it the PI's responsibility to forward those safety letters received from a Sponsor that are to be reported to the IRB. The UC IRB should receive letters for events that are
  - Serious.
  - Unanticipated.
  - Were judged related or probably related to study participation.

42

## Safety Letters from the Study Sponsor

- Documentation to be held in the site's Regulatory Binder:
  - All safety letters a PI receives (printed copy if received electronically).
  - Documentation of PI review and assessment (whether to report to the IRB or not), and
  - Documentation of reporting to the IRB, of those letters that were reportable.
- When the PI is a Sponsor-Investigator with a Corporate Pharma collaborator, the collaborator may supply safety letters to the Sponsor-Investigator for information, evaluation and reporting to his/her IRB.

43

## Parting Thoughts

- Adverse and other study events are central to the evaluation of an investigational product's safety profile.
- Complete capture and timely reporting of events is crucial to maintaining the support and care of study participants.
  - Investigators, coordinators and study nurses alike should be on the alert for events that are occurring during their studies.
- The assessment of both local and external events by the PI and the IRB allow both to confirm whether participants at UC may continue to be exposed to the investigational product through to the end of the study, or whether emerging risks have become too great.
- Timely assessment of local events and of safety letters from the Sponsor/collaborator are aspects that demonstrate the active involvement of the PI in study conduct.

44

## Getting You Credit

**We appreciate your review of this module.**

To achieve credit for having done so, please complete the associated knowledge check (quiz) that is in the CPD system.

You will receive a certificate of completion for this module when your quiz is satisfactorily passed (score >80%).

# Informed Consent for Human Research Studies at UC

**For the University of Cincinnati**

**IND/IDE Assistance Program, UC  
May 2011**



## Agenda

- Informed Consent (IC) for Research
- The IC Process and its Documentation
- The Informed Consent Form
- Special Situation: Participant or Representative not Fluent in English
- Special Situation: Cultural Issues
- Special Situation: Participant or Representative Not Physically Present
- Special Situations: Illiterate and Non-Competent Persons
- Emergency Situations: Exception From Informed Consent
- Updates of the Informed Consent Form: When to Re-Consent
- Required Elements of the Informed Consent Form
- HIPAA Authorization Alongside of Informed Consent
- Assent of Participants When Consent Comes from Someone Else
- The Special Case of Emancipated Minors
- Informed Consent in AAHRPP Accreditation Standards
- Common Problems with Informed Consent

2



## Informed Consent (IC) in Research

- Informed consent for research must be freely given.
- Informed consent for research must be uncoerced.
- Informed consent is how the PI and study team show respect to research participants, and it is mandated by the **\*Code of Federal Regulations (CFR)** to:
  - Protect human subjects/volunteers.
  - Ensure that potential study subjects clearly understand the benefits and risks associated with their participation in a study.
  - Provide the potential study subjects with all information needed to reach a decision on whether or not to participate in a research study.
  - Safeguard potential subjects who are vulnerable to coercion, as they consider becoming study subjects.

21 CFR 50  
45 CFR 46



## Informed Consent (IC) for Research

Cf. CITI GCP optional  
module on Informed  
Consent.

- It is important to understand that informed consent is a process that begins with the recruitment and screening of a study participant, includes the signing of the consent document, continues throughout the participant's involvement in the research, and possibly beyond study termination.
- IC includes: providing specific information about the study in ways that are understandable to the potential participants; giving participants the opportunity to have their questions answered; and adequate time to consider participation.
- Obtaining the voluntary agreement of participants to take part in the study is a requirement. Although the participant is agreeing to participate in the entire study, participants may also withdraw at any time. Part of the ongoing nature of the consent process is verifying the participant's continued interest in continuing in the study as it progresses.
- Provision of new information to be shared with former participants, as applicable even after the study ends, is also part of IC.



## The IC Process and its Documentation

- Informed consent must be obtained prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from medication (wash-out).
  - Here procedures includes labs, vital signs or screening questionnaires that are done/asked only for the research.
- Procedures performed as part of the practice of medicine (that would be done whether or not study entry was contemplated), may be performed without first obtaining informed consent and the results used for study eligibility after informed consent is obtained.



## The IC Process and its Documentation

- Dialogue is fundamental. Written consent is supplemental to face-to-face (sometimes voice-to-voice) communication. The participant should be given the chance to ask questions in a private setting.
- The process of obtaining informed consent meets the investigator's ethical obligations. Documenting the process used meets legal and regulatory requirements.
- During the IC process the participant's name is recorded in full, and sometimes also their date of birth. Both are PHI, thus the IC documents are to be protected and retained in a confidential manner.
- The informed consent form (ICF) is a key part of IC process documentation.
  - ICFs are provided by the study Sponsor as model or template documents. Site PIs may need to customize some of the details for their own institutions.
  - The ICFs are submitted to the IRB which is providing oversight, for approval, prior to being used with potential subjects.
  - IRBs may ask for revisions to or additions to the ICFs they receive. In cases of conflict, it is what the IRB wanted not what the Sponsor indicated in the template, that governs.



## The IC Process and its Documentation

- The original signed ICFs will be held in each participant's research binder that is kept by the Investigator.
  - Original signed ICFs are retained as long as the regulatory binder of a study is retained.
- For drug trials a copy of the ICF is provided to the Pharmacy.
  - The Pharmacy copy of the ICF is archived by the Pharmacy and is retained as long as the Pharmacy file for the study exists.
- A copy of the consent form will also reside in the participant's medical record but with restricted review rights.
  - Example: an insurance company audit would not include review of the consent form.
  - The copy in the medical record is retained as long as the medical record is retained.



## The IC Process and its Documentation

- For some studies it is convenient to have two IC processes, with separate forms for screening and participation.
  - In such studies the first informed consent includes study screening only and is administered to all potential participants. Then there is a second, separate IC process for participation and a second ICF that is administered only to those potential participants who qualify for the study.
  - All consent forms must be reviewed and approved by the IRB before use, both for screening and for participation.
- Multiple informed consent forms for different study groups or arms are permitted, with IRB approval.
  - Example: in a study of persons with a disease that involves a control group of matched healthy normal participants, it gives clarity and greater simplicity to the IC processes to write separate ICFs for each group.
    - This is especially true when the controls will not be undergoing every study procedure or having any or every specimen(s) taken from them that will be asked from the participants who have the disease being studied.



## The IC Process and its Documentation

9

- It matters, that every individual who is to sign an ICF do so him- or herself, and hand-date his or her own signature.
  - When anyone dates for anyone else it casts doubt on whether the overall process was done correctly.
  - Different involved persons' dates that are not all on the same day casts great doubt on the appropriateness of the IC process when study records indicate the IC process was conducted in person.
- The fully signed ICF is the source of the copy that is to be given to the participant/LAR.
- Documentation of the IC process means more than keep the original signed ICF. At UC a progress note or some other source document record is to exist that is to include:
  - A brief description of the process as it occurred, on what date.
  - Who was present.
  - Who administered.
  - Who translated or witnessed (if applicable).
  - Relationship, or where the signature authority came from, when an LAR signs for a participant.



## Documenting the Process Regulations and Guidelines

10

- 21 CFR 312.62 - Investigator Record Keeping & Record Retention
  - Case histories... The case history for each individual shall document that Informed Consent was obtained prior to participation in the study.
    - Progress note or equivalent in addition to the signed ICF.
- 21 CFR 812.100 – An Investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR 50.



## Documenting the Process Regulations and Guidelines

11

- ICH 4.8 – Informed Consent of Trial Subjects
  - Subject should be provided with ample time to ask questions and make a decision on whether or not to participate in the trial
  - Written informed consent form should be signed and dated by participant and by the individual obtaining consent.
    - The participant or the participant's legal representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation (e.g., revised Investigator's Brochure, IND or IDE safety reports).
  - A copy of the signed form is to be given to the participant or LAR, and the research record will indicate when and by whom the signed copy was given.



## Who May Administer IC: Delegation of Duties

12

- The PI agrees to personally conduct the study or have it conducted by others under the PI's supervision (or both).
- The Informed Consent process can be delegated to a staff member. That delegation is proper when the designee:
  - Has an appropriate combination of training, education and experience for the task.
  - Has received training on the protocol and ICF that pre-dates the first time the individual administers the informed consent to a potential study participant or representative.
- There should be no one involved in the IC process who is not the PI or someone who has IC for that study delegated to him/her.



## The Informed Consent Form

13

- Contains all the required elements indicated in 21 CFR Part 50 and ICH 4.8.10.
- Compensation payments if any, must be disclosed in the ICF and must be prorated and not contingent upon completion of the study so as not to appear coercive.
- The ICF is to be approved by IRB/IEC prior to utilization.
- Each participant is to have the most recent applicable version signed and in a timely manner.
- The informed consent should follow the protocol and also contain additional descriptions when appropriate.
- FDA regulations require the participant's signature and date.
  - ICH requires that and also the dated signature of the person who conducted the informed consent discussion.
- IRB/IEC, institutional policy or a study Sponsor may require other signatures in addition to those required by regulations and guidelines.
  - There will be other signatures at UC and also another document, when the IC process is witnessed or a short-form consent process is used such as to address language issues.



VA-funded Investigators will use VA-approved ICF formats to document informed consent.

## Special Situation: Participant or Authorized Representative is not Fluent in English

14

- Unless the researchers are fluent in the participant's language a qualified translator must be included in the consent process and the translator will sign the ICF.
  - A participant's family members may **not** serve as translators for the informed consent process. Medical translation capability is needed.
- For non-acute therapeutic trials, the study-related information must be translated into the participant's language at a level readable by the participant/representative.
  - This could be the entire ICF with the translation approved by the IRB before use. OR
  - This could also be a verbal presentation of the study with a short-form written document that itself is translated. Both the translated and English versions of the short-form document must be approved by the IRB before use.
    - The short-form consent document is accompanied by a written summary of the oral presentation. The English-language full ICF may be used as the summary.

*UC Research  
Policy II.01 "Obtaining  
Informed Consent in  
Human Participants  
Research"*



## Special Situation: Participant or Authorized Representative is not Fluent in English

15

- The English-language summary of oral presentation document is signed by the administrator of the consent.
- Both the short-form document and the summary document (the ICF if used as the summary) are signed by a witness.
  - The witness is to be an uninvolved third party, not a family member.
  - The translator may also serve as the witness.
- When ‘the’ signed copy of the ICF is given to the participant both the short form and summary document are given.
- The study team should assure the presence of appropriate language support for this participant throughout the study.
  - When the participant returns for study visits.
  - During protocol-required telephone contacts.
  - Study questionnaires may have to be obtained in translation or translated, in addition to the study ICF(s).



## Special Situation: Cultural Issues

16

*Cf. UC Research Policy V.01  
“Protecting Vulnerable Populations  
in Human Participants Research”*

- Cultural differences may prevent full understanding of the proposed research. Individuals whose values are shaped by a culture other than the researcher’s may make decisions on assumptions that are not valid.
- The presence of the PI in the IC discussion may represent undue influence, with a culture that predisposes persons to defer to physicians and respond favorably to a perceived request for a favor.
  - It may be preferable for a qualified study coordinator to administer informed consent to such persons.
- If the researcher is also the potential participant’s primary care physician, the IRB may require that another physician advise the person or the person be transferred to another physician for primary care.
- When the IRB reviews research which includes participants who are vulnerable (culturally and otherwise), the IRB Chair will ensure that one or more individuals who are knowledgeable about or experienced in working with such participants are present at the convened meeting of the IRB when this study is being deliberated.



## Special Situation: When the Participant or Authorized Representative is Not Physically Present

17

- Telephone consent is verbal, which alone is insufficient for research.
- An e-mail string of messages between the IC administrator and the participant or representative is not acceptable.
- A phone conversation with the ICF previously mailed or delivered to the individual is acceptable when the participant can Fax the signed form to the site on the same day. The other needed ICF signatory(ies) should sign and date on the same day as the call, on the Faxed ICF copy received.
- IRB approval in advance is required when a study involves persons who do not have Fax machine access and the PI decides a telephone consent process using a mailed-in and not Faxed signed ICF is needed for her/his study.
- Per UC Research Policy II.01, "*Obtaining Informed Consent in Human participants Research*", the IC process is to be included in the study protocol, thus the intended IC approach becomes IRB approved when the protocol and ICF are approved.



## Special Situation: Illiterate but Competent Persons

18

- If the person from whom informed consent is to be obtained is unable to read then the following steps are to be taken:
- An impartial witness is present.
  - No one on the study team, no subordinate of the PI (even if not assigned to work on that particular study) and no family member would be considered impartial for this purpose. A translator, if used, may serve as the witness but no one in the family may translate.
- In the presence of the witness the entire IRB-approved consent form is read to the person whose consent is being obtained. The reader can be the PI or anyone delegated by the PI to administer IC.
- The witness signs the ICF as a witness, and dates his/her signature.
- The person to whom the form was read makes his/her mark on the signature line.



## Special Situation: Illiterate but Competent Persons

19

- Participants are to be encouraged to take the consent form home and discuss it with other family members, and return to complete the IC process on another day.
- When a study is expected to involve illiterate participants, the PI will present a description of how the IC process will be carried out to the IRB in their initial review of the study.
  - The UC SOP allows for a short-form process to be used in these instances. The PI must submit the short-form for approval prior to its use.
- A **visual impairment** does not in all cases mean an individual may be considered illiterate for the purpose of IC. Potential participants (or their legally authorized representatives) who have visual impairments, who are competent to give informed consent and who are not otherwise illiterate should be offered the ICF in large type if enlargement will allow them to read the document for themselves.



## Special Situation: Illiterate and Non-competent Persons

20

- In acute disease or injury situations **and when the study is non-therapeutic**, the ICF is presented to the illiterate person and to any and all family present. At UC, family signatory priority for non-competent participants is as follows:
  - Spouse, then family designated adult child, then adult sibling.
  - Document the non-existence or unavailability of higher-level kin, before admitting a non-competent person to a study *via* the consent of kin lower in level, in the above hierarchy.
  - Other family members who wish to sign must be allowed to do so, however they are **additional** and do not stand in for the primary consent signatory (highest priority individual).
  - **If no family member or power of attorney holder is present, the person is not to be enrolled into the research.**



## Special Situation: Illiterate and Non-Competent Persons

21

- **In acute therapeutic research studies**, the ICF is presented to the illiterate person and to any and all family present. If the potential participant is married and the spouse is living, every effort to locate and discuss the trial with the spouse is to be made.
- If the PI is made aware that a power of attorney holder or court-appointed guardian exists, every effort must be made to locate and discuss with that individual.
- If the above efforts result in multiple contacts (including adult children and siblings), they will be asked to all confer and render a consensus decision.
- If consensus is not reached, then the spouse and power of attorney holder's/guardian's consensus will be used, **and if those two are not in agreement the potential participant will not be enrolled into the research.**



## Special Situation: Illiterate and Non-Competent Persons

22

- Signature on the consent document, in order: if competent, the participants signs. If not competent, the spouse; if no spouse, the family designated adult child of the participant; if no adult children, the family designated adult sibling signs.
  - Document the non-existence or unavailability of higher-level kin, before admitting a non-competent person to a study *via* the consent of kin in a lower hierarchical level.
  - Other family members who wish to sign must be allowed to so do however they are **additional**, and do not stand in for the primary consent signatory.



## Emergency Situations: Exception from Informed Consent

23

*Cf. 21 CFR 50.24 "Exception from informed consent requirements for emergency research", ICH E6 4.8.15 regarding emergency situations, prior consent of the participant not possible, and 45 CFR 46. Sponsors also see 21 CFR 312.54.*

- Research study conduct in emergency medicine is complex.
- There are Investigational Products or other interventions that are designed to be life-saving if they are deployed soon enough after emergency onset.
- The situation is often encountered when the investigational drug, device or intervention must be given/applied to the participant without taking the time for a proper IC process to occur.
  - The participant may not be coherent enough for the IC process to occur.
  - The intended participant may be unconscious and cannot be consented until after the IP is used.
  - The absolute amount of time between presentation and "too late to treat" may be too short for an IC process, even when an appropriate LAR comes in with the potential participant.
    - The participant may also be alone in the ER thus no spouse or kin present, and too little time to locate either.



## Emergency Situations Exception From Informed Consent

24

- GCP regulations and guidelines recognize research in emergency situations as involving exceptions from informed consent prior to treatment with an investigational product (**applies also to non-IP emergency research interventions**).
- There are stringent requirements for a study to qualify for an exception from IC, and safeguards for the participants are expected.
- The IRB must agree that the research could not be practicably carried out with a normal IC process in place, and agree to waive the requirement for IC prior to research participation.
- Eventual IC administration to the participant (when conscious and coherent) or to the LAR is to occur.
- The PI must take different approaches to:
  - 1) Research done in the ER, when informed consent in advance of treatment is possible, and
  - 2) Emergency research where, due to emergency situation, an exception from IC is proper.
    - In 2) above, the study protocol is written with the exception built into it, and IRB approval of the exception to IC being in advance of study procedures is secured before the study begins.



## Emergency Situations Exception from Informed Consent

25

- Only studies that offer prospect for direct benefit to the participants can be considered for waiver of informed consent [cf. 21 CFR 50.24 (a) (3)].
- From 21 CFR 50.24 (a) (7), additional safeguards to be put into place for such studies include:
  - Consultation
  - Establishment of a DSMB (independent data monitoring committee who will provide oversight during the study)
  - Public disclosure to the communities from which the participants will be drawn prior to study start of plans for the study, its risks and expected benefits
  - Public disclosure after the study ends, to apprise members of the community of the demographic characteristics of the participants and the results of the study
  - A commitment to contact a non-LAR family member and ask if there are any objections to the participant's participation, if the therapeutic window of using/applying the Investigational Product allows.
    - Documentation of the contacts is to be submitted to the IRB at continuing review of the study.



## Emergency Situations Exception from Informed Consent

26

- Research studies under 21 CFR 50.24 must be performed under a separate IND or IDE that identifies the protocol as one that may include participants who are unable to consent. (Separate even if another IND or IDE for that investigational product already exists.) 21 CFR 50.24 (d).



## Updates of the Study Informed Consent Form: When To Re-Consent

27

- The initial version of the ICF approved by the IRB at study start may not last throughout the entire research study.
- Protocol Amendments can be (but are not always) accompanied by corresponding changes in the ICF.
- New information that becomes available during a study that may impact the participants' willingness to remain on the study is to be communicated (e.g. new information from a corporate sponsor, corporate collaborator or the medical literature).
  - Here the ICF may be revised when there is no change contemplated to the study protocol.



## Updates of the Study Informed Consent Form: When To Re-Consent

28

- A study runs most smoothly when the IRB guides the PI as to when all current participants should review and sign each new updated ICF to continue in the study, and when a revised ICF is to be used only in 'here forward' fashion, only for the enrollment of new participants.
  - The IRB should communicate their assessment in the approval letter for the revised ICF.
- Two versions of the new ICF are approved by the IRB when re-consent is to occur:
  - A plain one, to be used with new participants only as enrollment continues.
  - An additional one with all changes in **bold text**. This is the form version to be used to re-consent all participants still active in the study (treatment phase and in follow-up).



## Required Elements of the Informed Consent Form

*UC Research Policy II.01  
"Obtaining Informed Consent  
in Human participants  
Research", 21 CFR 50.25 and  
45 CFR 46.116*

- A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the participant's participation, a description of the procedures to be followed, and identification of any procedures that are experimental.
- A description of any foreseeable risks or discomforts to the participant.
- A description of any benefits to the participant or to others that may reasonably be expected from the research.



## More Required Elements of the Informed Consent Form

- A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the participant.
- A statement regarding the extent, if any, to which confidentiality of records that identify the participant will be maintained. In FDA-regulated research, the consent process must disclose a statement noting the possibility that the FDA may inspect the records.
- The consent form will include all individuals and organization(s) that have access to the participant's records, including the study sponsor, funding entities, agents of the University of Cincinnati and any applicable federal agencies.



## More Required Elements of the Informed Consent Form

- For research involving more than minimal risk, an explanation as to whether any compensation or medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained.
- An explanation of whom to contact for answers to pertinent questions about the research and research participant's rights, and whom to contact in the event of a research-related injury to the participant.
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and that the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.



## New FDA Requirement for the ICF

- The FDA has amended 21 CFR Part 50 to require that ICFs and processes for applicable drug, device and biologic trials include a specific statement: that study information will be entered into a databank that is maintained by the National Institutes of Health/National Library of Medicine.
  - Compliance is expected now.
  - Enforcement start, for this new requirement: March 2012.
  - UC IRBs has made the needed addition to their ICF templates. Please be sure you have an updated copy.
  - ICFs for new studies should be on the new template.
  - Current studies do not have to put in an ICF modification in 2011, but consider whether your study will extend beyond March 2012.
- “A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.”



## Additional Elements of an Informed Consent Form

<sup>33</sup>  
*UC Research Policy II.01 "Obtaining  
Informed Consent in Human  
Participants research", 21 CFR 50.25  
and 45 CFR 46.116*

- When appropriate, one or more of the following informational elements will also be provided to each participant:
  - A statement that the particular treatment or procedure may involve risks to the participant (or to the embryo or fetus if the participant is or may become pregnant) that are currently unforeseeable.
  - Circumstances under which participation may be terminated by the Investigator.
  - Additional costs to the participant that may result from participation in the research.
  - The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the participant.
  - A statement that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant.
  - The approximate number of participants in the study.
  - Additional information that the IRB has determined adds meaningfully to the protection of the rights, safety and/or well-being of the participants.



## Informed Consent Form Template

<sup>34</sup>

### Institutional Review Board

Quick Links: [IRB Contacts](#) [Reporting Concerns](#) [Investigator Responsibilities](#)

[IRB Consulting Services: 09 - 10 Academic Year](#)

[IRB Home](#)

[Human Research Protection](#)  
[Key Personnel](#)  
[Post Approval Activities](#)  
[IRB Contacts](#)  
[E-mail the IRB](#)

[Contact Us](#)  
[Compliance Home](#)  
[Research Home](#)

### Forms for New Submission Protocols

### Forms for New Submission Protocols

- [Determining Human Research Activities](#)
- [Medical Submission Packet](#)
- [Social/Behavioral Submission Packet](#)
- [External Submissions](#)
- [New Protocol Submission Flowchart](#)
- [Recruitment Guidance for Investigators](#)

Select  
by type  
of study.



• [http://researchcompliance.uc.edu/irb/Forms\\_For\\_New\\_Submissions\\_Protocols.html](http://researchcompliance.uc.edu/irb/Forms_For_New_Submissions_Protocols.html)

## Medical Protocol Submission Packet

- Guidelines for Submitting New Medical Studies
- Research Review Submission Form
- Conflict of Interest Form Word / PDF
- Conflict of Interest Instructions
- Checklist for Research Involving Children
- Checklist for Research Involving Participants Who are Cognitively Impaired
- Checklist for Research Involving Women/Fetuses (Unborn Baby) / Neonates (Newborn Baby)
- Checklist for Research Involving Prisoners
- Protocol Format
- Guidelines for Writing Informed Consent
- Informed Consent Template
- Waiver of Consent Signature
- Waiver of Consent Process
- Information Sheet Template
- Humanitarian Use Device
- Genetics Consent Template
- Assent Format
- Waiver of Indemnification
- Sponsor's Indemnification Statement
- Explanation of Indemnification
- Guide for Submitting New Protocols
- Instructions to add TUH as a site



## HIPAA Authorization Alongside of IC

- HIPAA Authorization from the participant (or LAR) for access to a participant's personal health information is crucial.
- A separate HIPAA Authorization form that is approved by the IRB is the acceptable method. The participant (or LAR) are administered two forms, both of which must be appropriately signed and dated.
  - If signed by an LAR, the capacity that person has to be the participant's LAR is also to be indicated.
  - Foster parents are not suitable LARs for research, they are neither parent nor legal guardian of the child.
- If a UC Investigator is receiving oversight from a different IRB (the IRB of Record is not the UC IRB), the HIPAA language can be incorporated into the ICF and the combined ICF and HIPAA form signed by the participant and other appropriate parties as approved by that other IRB (example, the CCHMC IRB).
  - The ICF alone is allowed to cover HIPAA needs if all required HIPAA text has been incorporated.



## Assent of Participants When Consent Comes From Someone Else

37

- Children and adults of sufficiently diminished capacity are not able to consent for research themselves. Informed consent is obtained from the legally authorized representative(s) that each such person has.
- In accordance with UC Research SOP CL 007, an adult potential participant's incapacity to consent for him/herself will be documented, either by examination by a qualified person, or by using a standardized screening tool.
- Assent is the agreement of a participant who cannot give informed consent, to participate in research. **When obtained, assent is in addition to and never instead of, the informed consent of the LAR.**



## Assent of Participants When Consent Comes From Someone Else

38

- Whether or not a study includes assent is a study-specific decision that is made by the IRB, if not made by the PI and approved by the IRB.
  - Example, in a study with participants aged 5 through adult, the PI may decide to obtain the assent of 10 year olds through 17 year old participants, and not to secure the documented assent of children aged 9 years and under.
  - The PI may suggest if assent is needed or not and of what sub-group(s), but if the IRB differs for a given study, it is the IRB's opinion that governs.



## Assent of Participants When Consent Comes From Someone Else

- Assent is documented by an IRB-approved method:
  - Signature on a separate assent form that was written in language understandable to the participant.
  - Signature on the same consent form signed by the participant's LAR(s).
    - Just one, or both parents of potential child subjects may be required, depending on the study. The IRB will guide the Investigator.
  - Check-box that verbal assent was obtained, usually used when the assented participant cannot read primary education level text.
- Like informed consent, assent is obtained in advance of participation, usually contiguous with the informed consent of the LAR. The IRB may require the presence of an independent third party or an advocate.
  - Contact the IRB if assent is not obtained (e.g., the individual refuses), but the parent(s)/LAR(s) want the person enrolled into the study nonetheless.



## Assent of Participants When Consent Comes From Someone Else

- Assented persons can withdraw their assent, and if so, interventions stop and the individual's study participation is to cease as quickly as possible in a safety-maintaining manner.
  - In contrast, if a non-assented participant (who became a participant *via* the informed consent of an LAR) grows uncooperative, the participant remains in the study unless their LAR withdraws his or her consent.



## Assent of Participants When Consent Comes From Someone Else

- If a child participant (assented or not) reaches the age of majority during the study, the informed consent of the LAR which admitted the participant to the study becomes ineffective informed consent, and any previous assent obtained from the child becomes insufficient.
  - For the new adult participant to continue in the study, the current adult informed consent form must be administered to him/her promptly. Differing paths to an IC process with the new adult may be used depending on study and participant circumstances:
    - IC at the participant's next scheduled study visit, if within a reasonably short time after the participant's birthday into majority, and before any additional study procedures occur.
    - IC at an unscheduled study visit, when the participant is asked to return to the site in order to be re-consented as an adult (next scheduled visit is too far in the future).
    - IC using participant not physically present procedures, if the birthday into majority is too far from a study visit and it is not convenient for the new adult to return to the site for an unscheduled study visit.



## The Special Case of Emancipated Minors

- For some studies emancipated minors may consent for research themselves though they are not adults by age.
- Laws for when a minor is considered emancipated vary by State.
- **Contact the IRB before allowing an emancipated minor to consent for themselves in any study with UC IRB oversight.**



## AAHRPP Accreditation



- Association for the Accreditation of Human Research Protection Programs
  - UC holds full accreditation (there are other types)
  - UC values the accreditation that the University holds.
- AAHRPP divides its standards into three areas
  - Researcher and Research Staff
  - The Organization
  - Institutional Review Board or Ethics Committee

*Informed Consent is found  
in the first and third of these areas.*



## AAHRPP on Informed Consent: Researchers



Element III.1.F. Researchers employ consent processes and methods of documentation appropriate to the type of research and the study population, emphasizing the importance of comprehension and voluntary participation to foster informed decision-making by participants.

Researchers and research staff should understand:

- The concept of respect for persons and the obligation to obtain the consent of participants or their legally authorized representatives.
- That consent is a continual process, and conduct the consent process in a way that meets the criteria for legally effective consent.
- The difference between the consent process, itself, and documentation of the consent process.

Researchers and research staff should know how to document the consent of a participant or a legally authorized representative.



## Common Problems with Informed Consent

- Issues with IC seen by Monitors and Auditors tend to be preventable. Examples:
  - Inadequate process.
  - Inadequate documentation of the process used.
  - Form not dated by participants in all places where indicated, or dated by someone else for the participant/LAR.
  - Incorrect version of the ICF provided to the participants/LARs.
  - Missing and/or delay in obtaining signatures.
  - Missing elements in the form itself.
  - Inconsistencies between the form and the study protocol.



## Getting You Credit

**We appreciate your review of this module.**

To achieve credit for having done so, please complete the corresponding quiz provided in the CPD system.

You will receive a certificate of completion when your quiz is satisfactorily passed (score >80%).



# How to Avoid Protocol Deviations and Violations in Clinical Research Conduct

**For the University of Cincinnati**

IND/IDE Assistance Program  
May 2011



## Agenda

2

- Protocol Defines the Study
- Definitions
- To Avoid
- When a Deviation is Required
- Elements of Avoidance
- Study Protocol Should
- Examples from Clinical Investigator Site Audits
- Case Report Form
- Protocol Variance from Standard Practice, Example
- Visit Windows
- Protocol Change Without Amendment, Examples
- Suggestions for Protocol Authors
- Equip the Research Team
- Practical Limit on Avoidance: the Subjects
- Documenting and Reporting
- Parting Thoughts



## The Protocol Defines the Research Study

3

- The goals, objectives and aims of the research.
- Criteria for eligible subjects: Inclusion and exclusion criteria.
- Treatments/interventions/observations to be given/made.
  - What and when, study schedule and timeline.
  - How, e.g. dose or procedure modification if toxicity is noted.
- What data will be generated/gathered.
  - Data Management procedures, especially if needed from/at the site.
- Human Subject protections.
- How subject safety will be assured.
  - Includes management and reporting of adverse events and unanticipated problems
- As applicable, includes stopping rules and whether withdrawn subjects may be replaced.
- Usually also includes background and rationale for the trial; depending on local requirements.
- There can also be separate documents that are incorporated into the protocol by reference.



## Protocol Deviations and Violations

4

- These terms are not explicitly defined in GCPs from the U.S. FDA or in the ICH E6 GCPs.
- Some IRBs define deviations and violations.
- NIH does also.



## The NIH Offers Definitions

5

- **Protocol Deviation-** A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB.

Changes or alterations in the conduct of the trial which do **not** have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data are considered minor protocol deviations.

- **Protocol Violation-** A protocol violation is a deviation from the IRB approved protocol that may affect the subject's rights, safety, or well being and/or the completeness, accuracy and reliability of the study data.



## UC IRB-specified Definitions from Policy II.02

6

- **VIOLATION:** an accidental or unintentional change to the IRB approved protocol that placed one or more participants at increased risk or has the potential to occur again.
- **SIGNIFICANT DEVIATION:** Any unapproved deviation from the protocol that significantly affects the safety of the subject, the scientific quality of the study, or the safety of researchers. **Examples:** deviations from eligibility criteria that are intended to exclude those for whom the study poses unreasonable risks, failure to perform safety assessments intended to detect drug toxicity at the right times.
- **SUBJECT NON-COMPLIANCE:** Occurs when, despite the best efforts of the research staff, the subject fails to follow the protocol. **Could become a Significant Deviation if it occurs in a significant number of subjects.**
  - Some types could be also considered a safety violation, e.g. the subject took medication that per protocol was contraindicated for the study.
- **UNANTICIPATED PROBLEMS:** Any problems which were not contemplated when the research was approved and which present risk of serious harm to participants or to others, including the research team, the university community, or the broader community.



## Different IRBs Go with Different Terms

7

- Significant Deviations, Subject Non-Compliance and Unanticipated Problems (UC IRB)
- Deviations, Non-Compliance with Protocol, Non-Compliance with Board Requirements, Non-Compliance with Regulations, and Unanticipated Problems (Schulman IRB)
- Deviations and Unanticipated Problems (Copernicus Group IRB)
- Deviations, Serious Non-Compliance, Continuing Non-Compliance and Unanticipated Problems (Goodwyn IRB)

When you are working with multiple IRBs on different studies, it's best to speak to each IRB in its own language.



## To Avoid Deviations and Violations

8

**JUST DON'T DO IT  
(OR DON'T FAIL TO DO IT)**

When the deviation is:

- The commission of an aspect/event outside of the protocol provisions [don't],
- or,
- An omission of a protocol requirement [don't fail to fulfill requirements].



## When a Deviation is Required

9

- There is a situation in clinical research that requires protocol deviation: when a subject becomes at imminent risk of harm.
  - The Investigator makes a commitment, when he/she is conducting human subjects research, that he/she will make changes in a protocol only after notifying the sponsor and after prior review and approval by the IRB, *except when necessary to protect the safety, the rights, or welfare of subjects.*
- Deviations should be rare events. If not rare as the conduct of the study progresses, then:
  - Was the protocol not written appropriately for the disease/condition being studied?
  - Were the study team members not trained properly on their roles and tasks?



## Elements of Deviation/Violation Avoidance

10

- Start with a well-written and IRB-approved study protocol.
  - Have IRB-approved amendments in place, as needed, before modifications are made in study conduct.
- Have a trained and qualified research staff:
  - Trained in GCP requirements.
  - Trained on prevailing Institutional policies.
  - Trained on protocol specifics, per role.
  - Who are delegated tasks that are consistent with staff's education training and experience, and licensure if needed.
- Have and be knowledgeable of coherent SOPs for the conduct of research.
  - Could be a combination of Institutional, Departmental and/or study-specific SOPs.
- Maintain an attitude of wanting to be compliant.
  - *This is the most important element.*



## A Clinical Study Protocol Should

11

- Be internally consistent.
- Clearly identify requirements and recommendations.
- Be consistent with medical practice.
  - Unless new practice is the point or a key part of the study.
- Have changes made only by IRB-approved amendment.
  - Approved BEFORE the changes are put into practice on the study.

When protocols don't have these characteristics, and not all of them do, likelihood for deviations is high.

Examples of such situations follow on the next group of slides.



## Example 1: Protocol Violation due to Lack of If-Then Specified Testing

12

- A protocol stated that if any subject had condition Z during the trial, then the site was to:
  - Exclude two named infective agents being causal **and**
  - Give treatment for the agent(s) found, if necessary.
- There were enrolled subjects at the site who reported condition Z and this was well documented.
- ☒ No testing for the named agents was done on those subjects.
- ☒ The site said their monitor told them the protocol-required testing for the named infective agents was discretionary.



## Lack of If-Then Specified Testing

13

- It is the protocol which indicates whether a provision is discretionary or a requirement. This is signaled with protocol text such as:
  - For example.
  - It is suggested.
  - At the discretion of the Investigator.
  - If necessary.
- In this example, the testing provision was a requirement for those subjects who incurred the stated condition Z.
- Because of site inaction the sponsor did not get to find out whether either of the infective agents of concern was or was not present in that site's subjects.



## Example 2: Who Dosed the Subjects

14

- Who would administer the study drug to subjects was specified in a multi-site study protocol.
  - In one section, protocol said the anesthesiologist in the operating room will administer the study drug.
  - In the very next section, only the Investigator and Sub-investigators listed on the FDA Form 1572 would administer the drug.
- Anesthesiologists and Gynecologists were eligible to be PIs for this multi-site study.



## Who Dosed the Subjects

- At one site, the PI was an Anesthesiologist.
  - ⊗ This PI delegated dosing of many Subjects to other anesthesiologists **who were not sub-Investigators on his Form FDA 1572.**
- At another site, the PI was a Gynecologist.
  - ⊗ This PI dosed several of his Subjects himself. And had his nurse dose other Subjects.



## Example 3: Protocol Violation, Lack of Repeat Labs<sup>16</sup>

- A protocol stated the site would **repeat or explain** routine clinical laboratory results that were out of the normal range.
  - ⊗ At the time of the audit, some of the out of range results on file for study subjects were 2x to 10x outside of the closest limit of the normal range (Lows and Highs).
  - ⊗ But no assessment of the out of range values was documented whether they were clinically significant or not. No explanations were documented in the study records.
  - ⊗ No repeat testing was done on any such subject.
- ⊗ A note to file was present: "Laboratory determinations are considered not clinically significant unless they are acted upon."



## Lack of Repeat Labs

17

- The note to file did not explain the out of range results.
- The site did not follow the protocol and re-test, in the absence of explanation: the up to 10x too high and too-low values had no documented follow-up.
- 'If we didn't do anything, there must have been no significance' is an approach that does not belong in research.
- Charting by exception is insufficient for research.



## Example 4: Subject Enrolled Without All Admission Criteria Evaluated

18

- A protocol required *Legionella* status determinations of all subjects prior to entry.
- ☒ Subject XYZ999 was admitted to the trial without any determination of it.
- Prior to the audit, the lack of specimen for the *Legionella* test from Subject XYZ999 had been documented by the study monitor. Study records indicated the monitor asked the site to inform their IRB of this subject's admission without the testing.
  - However the site had not informed the IRB of this subject safety-related issue before the audit (which was months after the monitor's visit).



## Example 5: Not On the CRF Was Reason Given for Protocol Violation

19

- A protocol required periodic examination of urine for red blood cells, to serve as an indication of possible hemorrhagic cystitis.
- ☒ On audit, it was noted that no urine examinations for RBCs were done.
- ☒ In the audit discussions, the site pointed out that there were no spaces on the CRF (case report form) pages, for reporting out urine red blood cell examination results.



## The Case Report Form (CRF)

20

- A Case **Report** Form is a data transfer document that is used to move needed study data from the source records at a site to the sponsor's database for the study analyses. CRFs can be in hard copy or electronic.
- Study data not needed in the database are usually not on the CRF.  
**But:** all protocol-specified parameters for study conduct are to be documented in the source records.
  - Sometimes CRFs are incomplete at the start of a study, and correspondence such as a newsletter goes out to sites mid-study about how to accomplish the addition of missing data that are indeed wanted in the database. Simple to accomplish, for those sites that did collect the data missing from the CRF design.
- The study testing not done in this example was for subject safety and was not discretionary.
- **Lesson Learned: Not on the CRF does not mean optional to be performed, if it's in the study protocol.**



## Protocols at Variance with Standard Practice

21

- When it is central to the purpose of the study to incorporate variances from the care standard, then those variances are necessary.
  - But make the research and related care teams aware, in-patient studies in particular. The care team might apply the care standard to the subject who should not have it, but rather have something else done.
- When the variance was not a core part of the research being done and the protocol departs from the care standard, it's less likely that the protocol will be followed.
  - Especially when the research team perceives the variance to constitute subject risk, as in the next example.



## Example 6: How Soon to Walk After Spinal Surgery

22

- Encouragement to walk within 24 hours of spinal surgery was required by a study protocol that used a spinal fusion device.
  - ✘ No encouragement to walk or actual walking could be located in the Subjects' research charts or their hospital charts.



## How Soon to Walk

23

- Per the study team, no encouragement to walk was made **to preserve Subject safety**.
- The site's standard of care was log rolling in bed at 24 hours post surgery with encouragement to walk coming later.



## Example 7: Dosing at a Time Relative to a Surgical Event

24

- A protocol for an organ transplantation-related trial specified that the first dose of Drug Q was to be given to all subjects within 24 hours **of reperfusion**.
- ⊗ However, time of organ reperfusion/declamping was not routinely noted in the operative record by the transplant surgeons at that institution, and thus was not documented for the Subjects at the site.
- The study team had start of surgery and end of surgery times documented in the source records.



## Dosing at a Time Relative to a Surgical Event

25

- The team dosed so close to 24 hours from end of surgery, they could not demonstrate they were also within 24 hours of reperfusion when Drug Q was given.
- If the drug had been given within 24 hours of surgery start, not having the declamping time would not have mattered. The available data concerning the surgery would have been sufficient to show that the protocol was followed.
- However, at this site the Drug Q doses were in general so close to the time limit that the missing declamping time became crucial to demonstrating compliance.



## Control of Visit Windows

26

- Visit windows not being adhered to are a common source of protocol deviations.
  - ⊗ Deviations are incurred when an out-patient study protocol is written with no windows at all, and study visits do not occur on the exact days that become required (e.g., Sundays, holidays).
  - ⊗ Also when the plus or minus number of study days is exceeded at one visit, then made worse when the site re-sets the target dates of subsequent visits to the out of range visit date [to keep the between-visit spacing correct per protocol. But that puts the subject's data on a different scale than everyone else in the study].
  - ⊗ And when a site takes the number of days plus or minus as meaning work days instead of calendar days: Plus 2 days from a Friday does not actually include the Tuesday or Wednesday following, even when the Monday following is a holiday.



## Considerations in Setting Visit Windows

27

- How much of a window is reasonable is inherent in study design and depends on the spacing between visits and total length of the study.
- The spacing of visits is most often relative to first dose of study drug (or first use of a study device). When a visit falls out of range the established projections for the subsequent study visits should not be re-adjusted relative to that one visit.
  - Rather, the subject should be eased back onto the intended overall study schedule (in one step if possible, multiple steps if necessary).
- Allowed windows should not result in calendar overlap or different visits' allowed date ranges meeting each other. In these instances the intent to have a number of calendar days elapse between visits could go unfulfilled and yet be compliant with the protocol.
- Sometimes careful scheduling of when to start particular subjects will spare the site and the subjects difficulty with later study visits.
  - Time of year, National holidays and day of week restrictions on when sensitive specimens can be shipped to a central lab are all factors to be considered.



## Protocol Changes without Amendment

28

- Changes to a research protocol are to be made by formal amendment, with IRB approval of the amendment that pre-dates the revisions going into force at the site.
- The PI and staff are usually aware of what the revisions are, but if they put them into place ahead of IRB approval, compliance is not maintained.
- The PI is authorized to conduct the study that the IRB approved. Until the IRB approves changes, the current version of the protocol remains the official description of what the study is, and is to be followed.

When less formal means are used to make changes in the study, deviations and violations from the approved protocol are incurred. Some of the ways this has happened are illustrated on the following group of slides.



## Change Example 1: Unsigned Sponsor Memorandum

29

- Revision of Inclusion and Exclusion Criteria
  - Sponsor told the site, in writing, that the changes were FDA approved under the five-day notification procedure.
  - Sponsor told the site, in writing, that the changes were by FDA request.
  - ⊗ The sponsor memo went on to say that prior approval by their local IRB would not be needed, the changes were to be implemented immediately.
  - ⊗ Sponsor did say in the memo that the site should notify their IRB as soon as possible.



## Change by Unsigned Sponsor Memorandum

30

- ➔ Though the Sponsor did not give a compliant instruction, it was well documented and the site followed that instruction.
- ➔ If the memo to the PI had been signed, it would not have made the compliance situation any better for the site. Protocol inclusion and exclusion criteria do not change at a compliant site until the site's IRB for that study has approved the revision(s).



## Change Example 2: CRO Correspondence

31

- The protocol stated that the sponsor would supply commercially available Drug X for this study.
- ⊗ A site had two subjects who failed screening with a documented reason for failure: No Drug X was available at the site.
  - ⊗ The subjects had not actually failed screening, they did fully qualify for the study.
  - ⊗ The subjects could not be dosed with study drug since the site had none.
- ⊗ Correspondence was on file from the CRO engaged by the sponsor.
  - ⊗ Instructions to the site to obtain Drug X from its manufacturer.
  - ⊗ Another later correspondence asking whether the site had been successful in acquiring its own supply of Drug X.



## Change by CRO Correspondence

32

- The sponsor did not follow their own protocol and supply the study drug to the site.
- The site declared eligible subjects to be screen failures, when those persons qualified for the study and the issue was they could not be given study drug soon enough. (The protocol included a time limit for start of screening and first dose of study drug.)
- The protocol amendment about drug sourcing was not yet drafted, at the time of the audit.



## Change Example 3: Monitor Verbal Permission

33

- A study protocol specified that specimens destined for microbiological assay at a central lab were to be maintained at  $-70^{\circ}\text{C}$  until shipment on dry ice to the lab.
- ⊗ The freezer used by the site audited was  $-20^{\circ}\text{C}$ .
- ⊗ The site had no access to a  $-70^{\circ}\text{C}$  freezer.
- ⊗ On audit, the site reported they had received verbal approval from their monitor, for use of a higher freezer temperature.
- ★ There was documentation on file that  $-70^{\circ}\text{C}$  and not  $-20^{\circ}\text{C}$  pre-shipment storage at the site was critical to the accuracy of the microbiological assay results.



## Change by Monitor Verbal Permission

34

- Immediate dry ice freezing and same day shipment from this site not equipped to hold the specimens could have dealt with the lack of  $-70^{\circ}\text{C}$  freezer and preserved the integrity of the eventual study data.
- Instead, to save costs, doubts about the study data were introduced due to the deviations in sample handling prior to analysis.



## Suggestions for Protocol Authors

35

- Set meaningful inclusion/exclusion criteria.
  - Wider limits will result in a greater number of people qualifying (good for recruitment), but brings in “noise” reflected in the data at analysis.
- Account for the standard of care.
- Set reasonable windows for study visits, as tolerated by the study design.
- Over-specifying paints the research team into a corner that could be difficult to stay in and still get the work done.
  - But staying within the multidimensional corner that the protocol author has defined and the IRB approved of, is required for compliance maintenance.
- Sometimes it’s better for a site to decline a study, if the protocol is written in a compliance-unsustainable way and the Sponsor is not amenable to revision.



## Fundamental to Deviation Avoidance: Equip the Research Team

36

- Foster an expectation of maintenance of compliance.
- Assure training of all staff members on the protocol and any amendments.
  - Assure that documentation of the training that was given exists and can be readily retrieved on request of a reviewer.
- Avoid over-delegation of duties, meaning assigning a task to someone not sufficiently educated and trained or not properly licensed to perform it.
- Assure completeness of record-keeping.



## A Practical Limit on Deviation Avoidance: A Site Cannot Control their Subjects

- Avoidance of all deviations is a goal at times not met **because of subject behaviors**, such as when they:
  - Don't keep their appointments that were within the allowed time windows, but come too much earlier or later instead.
  - Stop coming back to the site and cease responding to attempts made by the site to reach them.
  - Don't return the unused drug they promised to bring back for accountability, but instead say they discarded it.
  - Don't bring the samples they were asked to provide, e.g. first-morning urine.
  - Don't keep the diaries they were asked to record well, or at all.
  - Don't take the study drug faithfully.
  - Take concomitant medications that are forbidden for the study.



## A Practical Limit on Deviation Avoidance: A Site Cannot Control their Subjects

- A site should deal with non-compliant subjects, with documentation of the site's due diligence:
  - Reminders offered.
  - Counsel given.
  - Telephone contacts attempted and made.
- PIs should consider withdrawing a subject from the study once subject-led deviations become too numerous or too severe or extensive for the Subject's safety or validity of the data being gathered.
  - When missing site visits/contact calls induces lack of medical oversight.
  - When not dosing with a study drug (or using a study device) faithfully, renders the data from that subject meaning too little.



## Documentation and Reporting of Deviations and Violations

39

- Not reporting the deviations and violations that occur is an issue in and of itself, in addition to their existence being an issue.
- Reports of deviations and violations go to:
  - The Sponsor.
  - The IRB, using the forms provided (UC IRB example on next slide).
  - A Regulatory Agency (when applicable and required, usually from a Sponsor).
- Reporting is to be sufficiently timely.
  - The IRB, Institutional policies and Institutional SOPs will be of as much guidance on this as are the GCPs themselves.
  - How quickly to report after the event has occurred depends on what the event is, how severe it is and whether one or multiple subjects was/were put at risk because of it.
- Reporting should include not only what occurred and what was done in response (corrective action), but also how that deviation or violation will be avoided in the future (preventive action).



## Forms for Reporting Deviations to the UC IRB

40

[http://researchcompliance.uc.edu/irb/Miscellaneous\\_Reporting\\_Information.html](http://researchcompliance.uc.edu/irb/Miscellaneous_Reporting_Information.html)

UC Home UC News Visiting UC Admission to UC Give to UC Search UC Directories Home

### Institutional Review Board

UNIVERSITY OF Cincinnati

Quick Links: [IRB Contacts](#) [Reporting Concerns](#) [Investigator Responsibilities](#) [CITI](#)  
[IRB Consulting Services: 09 - 10 Academic Year](#)

#### Miscellaneous Reporting/Information

Miscellaneous Reporting/Information

- Event Reporting Form - [Word](#)
- [Deviation Report](#) - for minor events
- Investigator Brochure Information Sheet [Word](#)
- [Conflict of Interest Form & Instructions](#)
- [HIPAA](#)
- [CITI Training Instructions](#)

Which form to use depends on the significance of the deviation being reported.

Electronic submissions are coming. UC IRB and CCHMC IRB are collaborating to establish a shared CLIC Commerce/ePAS electronic environment.



## Parting Thoughts

41

- Study data that come from a protocol-adherent clinical research site have a high level of compliance, thus of acceptability and utility.
  - Data of high reliability come from the science of the study as much as the compliance. A Sponsor is best off by far with both present.
- A well-written protocol enhances smooth operations at the site, and the achievement of a high level of compliance.
- A reputation for adhering to protocol and few deviations/violations makes for a site that receives future participation invitations from Sponsors.



## Getting You Credit

**We appreciate your review of this module.**

To achieve credit for having done so, please complete the corresponding quiz provided in the CPD system.

You will receive a certificate of completion when your quiz is satisfactorily passed (score >80%).



## References

- Definitions on slide 5 are from NIH IRB Professional Administrators Committee Version 5.1 Regulatory Process Workgroup 1 11/18/2005
- Violations, Significant Deviation, Subject Non-Compliance and Unanticipated Problems on slide 6 from the UC IRB in Policy II.02 “Reporting to the IRB: Unanticipated Problems Involving Risks to Participants or Others, Adverse Events, and Other Problems”.
- Slide 7 from Schulman IRB, Cincinnati, OH, at <http://www.sairb.com/SitePages/Investigators/ResearchEvents/noncompliance.aspx>
- Slide 7 from Copernicus Group IRB, at <http://www.cgirb.com/forms.php>
- Slide 7 from Goodwyn IRB, at <http://www.goodwynirb.com/ProtocolDeviations.htm> and <http://www.goodwynirb.com/UnanticipatedProblems.htm>



# Case Report Forms: From Source Records to Data(base) Entry

**For the University of Cincinnati**

IND/IDE Assistance Program  
May 2011



## Agenda

2

- Case Histories, Case Record Form and Case Report Form
- Case Report Form (CRF)
- Source Records: Definition, Examples, UC Policy and SOPs, and Regulatory Requirements
- Source Records: Original and Transcribed
- Source Record Authorship
- Source Record Additions, Corrections, and CRF Discrepancies
- Source Record Worksheets from CRF Copy
- CRFs Used as the Source Records
- CRFs Not Required for All Human Research Studies
- CRF Completion, Review and Correction
- Database Entry and Confirmation of Database Accuracy
- Pen-and-Paper *versus* Electronic Case Report Forms
- Compliance with FDA's Electronic Records, Electronic Signature Rule, 21CFR Part 11
- Storage and Retention of Case Histories: Source Documents and CRFs



## Case History, Case Record and Case Report

3

*Cf. 21 CFR 312.64(b),  
812.140 (a), 45 CFR 46.*

- Case histories and case records are synonymous. Neither is the same as case report forms (CRFs), however both case report form and case record form are abbreviated as CRF.

*It is unfortunate that in clinical research the abbreviation "CRF" means two such different things.*
- Investigator site personnel make and keep case histories on and about all study participants. Case histories are the sum of the CRFs and the source documents. FDA GCPs call source documents supporting documentation or supporting data.
  - In speaking and writing about them, source documents and source records are often referred to as simply 'source', or 'the source' (of the study data and results).
- Case Report Forms are not study source documents unless the protocol has said so, and even then usually only individual pages of the CRF become source.



## Case Report Form

4

*Cf. ICH E6 1.11, 4.9.1, 4.9.2*

- Case report forms are most often used when the study database and/or the performance of database entry is at another location, separate from the Investigator's site.
- The CRF is the means that enable those data the study Sponsor needs in the study database to be transcribed out of the source records and delivered to the people who will populate the study database.
  - The CRF, *most of the time*, is an information transfer document created by transcription from study source records.
    - **Well-defined exceptions, where the CRF is the source record, are possible (addressed further below in this module).**
- The CRF should contain all of the study data needed to present the study results and perform protocol-specified data analysis/es.
  - Efficacy data
  - Safety data
  - Demographic data as specified in the protocol; however assure **no** participant names appear on the CRFs or in the study database.



## Case Report Form

- CRFs don't have to contain every bit of data that a protocol specifies be collected for a study.
  - The results of the other protocol-defined study observations, information or tests that are not on the CRF will reside in the source records at the site.
    - As long as the protocol is followed and the CRF was made correctly this is not a compliance issue.
    - It is permissible to have protocol-specified information in the source documents that is not on the case report form.
    - However the reverse is not true. Protocol-specified information to be gathered that is not present in the source records only because it is not needed on the CRF would be a compliance issue.



## Case Report Form

- CRFs can be a few pages to a few hundred pages or more long, depending on the study.
- If the study uses a CRF it is the responsibility of the Principal Investigator to assure that each completed CRF is an accurate reflection of the source data, for all of the information the Sponsor wanted shown on the CRF.
  - CRFs are usually equipped with a signature page at the end to document this assessment and PI assurance of complete reporting of study data to the Sponsor.
- The lines, spaces and boxes on a CRF are blank until they are filled in with information and data from the study source records.
  - A CRF that is completed in advance, before the source data exist, presents a compliance issue.



## Source Records: Definition

*ICH E6 1.51 and 1.52*

7

- Source Records and Source Documents are synonymous.
  - Source Documents: Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, the laboratories, and at medico-technical departments involved in the clinical trial).
  - Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)



## UC Policy: Requirements for Source Records

8

- UC Policy IV.01 “Rights and Responsibilities of Principal Investigators in Human Participants Research” includes as a PI responsibility, “Maintaining adequate and accurate records.”
- UC SOP 1-1, “Responsibilities of the Research Team” includes “Maintaining adequate and accurate records...” as a PI and Co-PI responsibility, and “Accurate and timely data entry” as a Research Nurse/Research Coordinator/Research Assistant/Data Manager/Research Lab Personnel responsibility, which a PI without a staff retains.

Also “Maintain confidentiality of all clinical trial related information (including patient records...” as a responsibility of all research team members.



## UC SOPs: Requirements for Source Records

9

- **UC SOP 1-4 “Source Documentation”** includes “Case Report Forms and source data are maintained separately, but source documents should accompany the case report form for sponsor verification.”
- **UC SOP 1-7, “Confidentiality of Research Participants”**, includes “All study related documents (including regulatory and participant records) will be stored “in a secure location with access limited to appropriate study personnel.”



## Examples of Source Record Types

10

- Examinations and tests.
- Operative records.
- Anthropomorphic measurements.
- Progress notes: Physicians', Nurses', OT/PT, Nutrition.
- Dipstick or test kit results such as pregnancy testing.
- Local and central lab reports, please with recorded Investigator assessment for clinical significance of any out of normal range results.
- Participant responses to stimuli.
- Specialists' reports concerning for example X-ray films.
- ECG tracings or scan data.
- Completed study questionnaires.
- Telephone contacts.
- Joint counts.
- Study-related interviews, such as with participants.
- Concomitant medications or treatments.
- Adverse events that occurred
- How the participant left the study: (completed; early withdrawal, participant-led; withdrawn, Investigator-led; lost to follow-up).
- Investigational product (IP) procurement, control, and storage records, for studies that use them.
- Dose making and/or dispensing records for applicable drug studies.
- Unused IP supplies' return and/or destruction at study end.



## UC SOP on Source Documentation

- Source Documents are used to record all original data from participants that support and verify information recorded on the Case Report Form. Information subject to source documentation includes information from screening visits, telephone conversations, screening and study procedures, diagnostic and study related data and study visits.
- The IRB approved protocol describes the information to be obtained from each participant during screening and study visits.
- Original documentation, containing the participant's health information and medical test results, must be retained in the participant's medical/study record.
- When possible, source documents should not identify participants by name but rather by identifiers such as the study participant number or initials. Such identifiers facilitate the cross-indexing of a participant's data while protecting the participant's privacy.
- The Principal Investigator will assure the adequacy of the source documentation by review of documentation with the designated person.



## Regulatory Requirements for Source Records

*Cf. 21 CFR 312.62, 21  
CFR 812.140,  
ICH E6 4.9.4, 8.3.13.*

- Source records should show 'Who Did (or Said) What, When' in study conduct.
- There's a useful mnemonic for records requirements: ALCOA.
  - A -- Attributable (who did it?)
  - L -- Legible (can a reviewer read it?)
  - C -- Contemporaneous (when did they do it?)
  - O -- Original (has it changed?)
  - A -- Accurate (is it right?)
- **Source records are to be stored in a confidential manner with limited access.**



## Source Records

21 CFR 312.60, 312.62, 21 CFR 812  
100, 140; ICH E6 4.3, 4.5, 4.6, 4.8,  
8.3.13

- Original source records are the first place and manner in which study-related information is recorded. These include:
  - Records that show the participants were real people and not made up.
  - Records of the informed consent process and the procurement of the participants' documented willingness to participate in the study (prior to study participation), and continued willingness when reconsenting is needed.
  - Records that provide participants' demographic information, medical history, medical treatments received and medications taken.
  - Records that demonstrate fulfillment of the study eligibility criteria.
  - Study conduct records that show the protocol was followed and identify who did (or said) what, when, in the course of the study.
  - Event records that document the unanticipated problems and adverse events that occurred, and the actions taken as a result of their occurrence.
  - Drug dose making if this is done at the site, such as for IV drugs.
  - Investigational Product (drug or device) records including procurement, control, storage, and unused supplies' return and/or destruction at study end.



## Original and Copied or Transcribed Source Records

14  
*Cf. FDA "Guidance for Industry:  
Computerized Systems Used in  
Clinical Investigations" May 2007*

- Original source records are the first place and manner in which study-related information is recorded, be it electronic, on film, or on paper.
- Certified copy of an original record such as an electronic medical chart can be used by the study team in the place of the (electronic) original, as the source document.
- There are times when study team convenience or organizational requirement results in transcribing information from original source to documentation used by the study team for CRF completion or data entry, in the place of the original. Examples:
  - A summary page of adverse events, when each event was originally fully captured in a study visit-specific source document (worksheet or progress note).
  - A summary page of concomitant medications, for example transcribed from in-patient hospital charts.
    - However, a study information summary page populated directly from interviews of the participant as the study progresses, would be original source.



## Source Record Authorship

- Source records should indicate who made the records and when.
- First-person record-keeping is needed; second-person records (staffer 'A' recorded what the Investigator observed or said) do not fulfill the expectations of research record-keeping.
- When participants author any CRF pages, such as with questionnaires, sites will have an issue to deal with if the participant puts his/her name on the CRF.
  - For instance, a participant decides to sign a CRF-based questionnaire after he/she fills it in, or, initials or signs on a correction he/she decided to make.
    - This is occasionally observed on audit, especially with adult participants.



## Source Record Authorship

- When participants write on CRF pages, sites will have an issue to deal with if the participant's name is put on the CRF by the participant.
  - This phenomenon is avoided by studies that use stand-alone questionnaires: an original questionnaire written on by the participant that is held in the source records at the site, with corresponding fields on the CRF filled in at the site. The original CRF then can go to the Sponsor and the site does not lose its original source data. However, the site personnel must transcribe each participant's answers onto CRFs.
    - More transcription effort for the site, but avoids having participant initials or name on the CRF and often results in more legible CRFs, thus easier database entry of questionnaire write-ins.



## Source Records: Additions and Corrections

- Real people make occasional mistakes (errors of commission) and occasionally accidentally leave things out (errors of omission). How the errors are corrected matters in research, and depends on whether the record containing the error is hard copy or electronic.
- Errors of commission are best corrected by the original record author. On hard copy:
  - A single line is made through the incorrect entry.
  - The correct information is written nearby (or foot-noted to another portion of the same page that has more available space). The correct entry may be circled if needed for clarity.
  - The person making the correction initials (or signs) it and dates, to indicate when the correction was made.
  - When the change is not self-evident, the reason why the change is needed is recorded along with the correction.
  - When the change is on a page that the Investigator has previously reviewed and signed, the Investigator should be asked to review the change and re-sign and date that page.



## Source Records: Additions and Corrections

- Errors of commission in electronic source:
  - Certified copies of electronic originals are not to be written on to make corrections. Making a change on a certified copy negates the certification that the printed copy matches the electronic original.
  - The mechanisms provided for correction in the e-system used should be followed.
    - Often this will involve an additional record that acts as an amendment to the previous one (that contains the error being corrected).
  - Print and certify a copy of the additional or corrective electronic record, then store that certified copy with the original record's certified copy (that contains the error).
    - By the two copy certification dates (also times if important for understanding), one can tell which version superseded which other version.



## Source Records: Additions and Corrections

19

- Errors of omission are corrected by an appropriate study staff member using a late entry (or addendum) to add the missing information. 'Late' means on a date and/or at a time later than the original writing on the page. On hard copy:
  - The author should date on, make the needed additional entry, and initial or sign it.
  - If the late entry was by a study staff member on a page with review signature of an Investigator already signed/dated, the Investigator should review the page again after the late entry, re-sign and date.
- On electronic source:
  - The mechanisms provided for additions to the e-system used should be followed.
    - If the system does not provide an electronic means to link the new record to the incomplete, previous one, text within the added record that describes the connection with the previous record is helpful to provide a documented link.
  - Print and certify the copy of the additional record, then store it with the original record's certified copy (that contained the omission).



## Source Records: Additions and Corrections by Whom

20

- It is important who is making the additions and corrections.
- An addition is best made by the study staff member with first-hand knowledge of the missing information.
- A records error is best corrected by the individual who made it.
  - If this is not possible, make a thoughtful choice of who on the study team will author the corrections.
    - Example: source records written by the PI and corrected by a study coordinator do not give the appearance of good practice. One the PI has said, the PI and not anyone else should decide that something else was actually meant.



## Source Records: Additions and Corrections by Whom

- Monitors are not appropriate source record authors.
  - He or she can flag suspected omissions or errors for discussion with and action by a study team member, but only delegated team members should be authoring the study source records.
- Auditors are not appropriate source record authors.
  - Suspected errors or omissions brought up in an audit should be noted by site personnel and resolved with their (study conduct compliance) Monitor without mention of the audit or the auditor in any written correspondence between site and Monitor.



## Source Record-CRF Discrepancies

- UC Research SOP ADM 014 includes: “The principal Investigator will ensure the adequacy of the clinical site’s source documentation by review of documentation with the designated person. Any discrepancies between the medical record and CRF will be corrected and documented by a note to file signed by the investigator and designated person.”
- In this context, note also ICH GCPs 4.9.2: Data which are reported on the CRF, which are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.



## Source Data Worksheets from CRF Copy

- It is not a best practice to copy a paper CRF (or print an electronic CRF), then use the copy or print-out as the site's master copy set of source document worksheets.
  - The study team may lose the ability to have source record worksheets reflect the protocol-specified order of individual study visit events.
    - Many CRFs are formatted for ease of database entry, and do not align with the flow of each study visit.
  - CRFs formatted for ease of database input may not have enough physical space on individual CRF pages to put in signature and date boxes or other lines that are needed to have a complete source record.
  - Should CRF preparation fall out of synchronization with protocol preparation, the CRF may be missing needed fields.
    - When this is recognized during the study, **if** the site has the needed data in source records, the missing CRF data can be added (example, onto a free text Comments page or area).
      - A site that leans solely on the CRF may not have the missing data in their source records.



## Source Data Worksheets from CRF Copy

- Sponsors may provide sets of source data worksheet pages for a particular study. This is not a requirement, and the Investigator is free to have his/her team use their own study-specific worksheets in addition to **or instead of** the Sponsor's.
  - Some Sponsors deliberately do not supply source document worksheets to sites to encourage a thorough study of the protocol, which occurs as the source document worksheets are being made.



## CRF Used as the Source Record

*ICH E6 6.4.9*

- There are instances where CRF pages are and may be used as source documents, **but**: unless such use is defined in the protocol (and therefore up front), the research site is not compliant with ICH GCPs if any of the CRF is used to capture original source data.
- Once the protocol has said so, then the originals of the indicated CRF pages are the site's original source.
  - A site using the CRF as the source, for example with a participant-completed questionnaire, has to decide if the original source record (the original CRF pages) will stay at the site (as original source data should). Sponsors used to taking the original of a CRF may try to remove them. For the site to keep their original source, the Sponsor would take a copy of those CRF pages for data entry.



## CRF Used as the Source Record

*ICH E6 6.4.9*

- One common example of protocol-specified use of CRF as source is when a study uses a CRF-based study questionnaire. Instead of having it in the usual standard published booklet form, the Sponsor puts the questionnaire on CRF pages.
  - The CRF pages are given to the participant to fill in, and the participant is the author of that source record.
- Another common example is joint counts, where the Sponsor elects to avoid massive transcription of study data from source document worksheets.
  - The CRF pages for joint counts include indicated spaces for identification and signature/date of both persons involved: the assessor who examined the joints and called the results and the scribe who was present during the joint exam and filled in the CRF page.



## CRFs Are Not Required for All Human Research Studies

- When study site personnel have database entry responsibility, database entry access plus training on how to do the data entry, the study data can go direct to database from the study source records. Such a study may have no CRF document existing. This also provides for one fewer set of transcriptions of the study data.
  - When under these conditions the study Investigator is also the study Sponsor, case report forms to report the site's study data to the Sponsor can be superfluous.
- When there is no case report form, some source data are in a medical chart and the rest are on study-specific worksheets, a study team may elect to print an e-chart (medical chart) or do some transcription from the medical chart (the original source), to provide a convenience copy in the research record from which to do data entry.
  - The recorded transcriptions or copies become part of the participant's case history, and document source data but are not themselves the original source data.
    - Certified copies may be used in the place of original source data.



## CRFs Are Not Required for All Human Research Studies

- A study structured to not need a CRF can always have one if the Sponsor so wishes or if the institution requires that a case report form be used.
- For best study outcome and shortest overall developmental timeline for studies with CRFs, have CRF design include the input of the study biostatistician if the study team includes one.



## CRF Completion, Review and Correction

29

- CRFs are completed by the study team at the clinical site. No one should be writing on a CRF unless the PI has delegated CRF completion to him or her.
  - The documented delegation assures selection of persons who have been trained and are qualified to perform the task.
  - Training should include how to make corrections once any transcription errors become discovered, e.g. by the site or the site's compliance Monitor (Clinical Research Associate).
- Internal quality control, review of CRFs by the study team for accuracy, is important. Any omissions or errors made are most easily and best resolved or corrected when discovery is contemporaneous.
- When the study Monitor visits, a supporting level of review occurs before the original (paper) CRF page leaves the site. At this stage any needed additions or corrections may still be made directly on the original CRF pages. **By the site personnel and not by the Monitor.**



## CRF Completion, Review and Correction

30

- Once an original page is collected or transmitted to data management, then making additions or corrections involves queries.
  - Query forms, also termed DCFs (data correction forms), clarify or correct the CRF after the original CRF page has left the Investigator site.
  - Queries are most often generated by Data Management as a result of incomplete, illegible or internally conflicting CRF entries.
  - Query forms are not source records, but are important study correspondence documents often conveniently retained with the site's copy of the related CRFs.
- If the original CRF has been delivered for data entry and then the site itself discovers an omission or error, the site may generate a query.
  - These discoveries may have been made by site personnel, their Monitor or be brought to attention during an audit.
  - The site completes a query form, sends it to Data Management (who is not expecting it) and files a copy of the query with the affected CRF.
  - Data Management personnel will process the site-generated query results into the database in the course of data entry.



## Database Entry and Database Accuracy Confirmation

31

- Entry of study data and information into a database is an act of transcription that is done by real people who can at times make inadvertent errors.
- Confirmation of database accuracy should be a part of the overall study quality control program.
  - Determining the accuracy of the database involves the study team. It is not a requirement for the study Monitor or an Auditor to do this for a PI and team.
    - However a Monitoring Plan or Audit Plan for the study can include verification from source records to database. In these instances suitable database access will be needed.
- Double data entry systems have 2 different persons transcribing from the CRFs into a database buffer. Entries move from the buffer into the actual database when both individual entries for each data field match. Queries are generated for any mismatches that the data entry team cannot resolve themselves.



## Database Entry and Database Accuracy Confirmation

32

- Reasonableness checks are built into some database entry processes, to flag data that are out of pre-programmed expected ranges for confirmation by site personnel.
- Queries are also made prior to data entry for illegible CRF entries.



## Pen-and-Paper versus Electronic CRFs

- Hard copy CRFs come in differing physical forms.
  - Multipart forms (typically 3- or 4-part, color coded carbonless forms)
    - Transmission of the CRF to data management is by the Sponsor's Monitor collecting and removing the original pages from the site. Usually the site retains the bottom one or 2 copies.
  - Single original paper forms, with transmission of completed pages *via* Fax from the site to the Sponsor or their data management designee.
  - Training on using the CRF can be individual, on-line or covered during a site initiation visit. Who the trainer was will be documented if in person.
- Electronic CRFs are accessed in varying ways.
  - A secure web portal that the site accesses using site-owned computers.
  - Transmission from a laptop that belongs to the Sponsor, laptop on loan to the site for the study and returned at the site closure visit.
    - Data transmitted over the site's Internet connection.
    - Data transmitted *via* modem over a site telephone line.
  - Training on using the e-CRF can be individual, on-line or covered during a site initiation visit. If in person who the trainer was must be documented.



## UC SOP on Use of e-CRFs

- When a UC PI has a Sponsor who wants e-systems used in study conduct, the PI is to obtain the following from that Sponsor:
  - The hardware and software necessary to fulfill the protocol (if not already available at the site).
  - Names and contact information of support services associated with the e-system.
  - A usage manual or operational instructions.
  - Certificates of training of the PI and pertinent site staff on the e-system.
  - If applicable, the source data worksheets and a copy of any CRF to be used.
  - Data entry personnel/requirements.
  - Security procedures to be used.
  - Data storage requirements.



## Compliance with FDA's 21CFR Part 11, the Electronic Records, Electronic Signature Rule

21 CFR 11 1 (a), (b), (e)

- FDA regulations 21 CFR Part 11 express "...the criteria under which [the FDA] considers electronic records, electronic signatures and handwritten signatures executed to electronic records to be **trustworthy, reliable, and generally equivalent** to paper records and handwritten records on paper."
- "This part applies to **records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted**, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetics Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations."
- "Computer systems (including **hardware and software**), **controls, and attendant documentation maintained under this part shall be readily available for, and participant to, FDA inspection.**"



## Electronic Signatures

21 CFR 11 50, 70, 100

- Electronic signatures are to be the legally binding equivalent of the individual's handwritten signature.
- Before a person receives an e-signature designation, the institution must verify his/her identity.
- Signed electronic records will include the printed name of the signer, time and date signed, and the meaning of the signature (such as review, approval, responsibility, or authorship). These items shall be included in any human-readable form of the electronic record.
- Electronic signature shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.



## ICH GCPs on Electronic Systems

37  
ICH E6 5.5.3, 5.5.4

- Sponsor responsibilities which Sponsor-Investigators have, in regard to using electronic trial data handling and/or remote electronic trial data systems, include:
  - Ensure and document that the e-systems confirm to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (*i.e.*, validation).
  - Maintain SOPs for using the e-systems.
  - Ensure system design includes maintenance of audit/data/edit trails with no deletion or overwriting of entered data, when data changes are made.
  - Maintain a security system that prevents unauthorized access to the study data.
  - Maintain a list of those individuals who are authorized to make data changes.
  - Maintain adequate back-up of the data.
  - Safeguard the blinding, if any, during data entry and processing.
  - If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.



## Storage and Retention of Case Histories: Source Records and CRFs

38

- The Sponsor is responsible for retention of the CRF originals that the Sponsor takes from the site.
- The Sponsor is responsible for retaining any copies of source records that were taken from the site (*e.g.*, in support of SAE reports).
- The PI is responsible for retaining the original source records, transcribed source made in the course of study conduct, and the PI's copy of the CRFs.
  - Under site control, with limited access during the storage period.
  - Safe from loss or accidental destruction (*e.g.*, water, mold, fire).
  - Well-organized and readily retrievable on request. This includes appropriately cross-referenced to other storage locations, if all pertinent study records are not together in one place. Rule of thumb for "readily retrievable":
    - Within 20 minutes from an on-site archive.
    - Within 24 hours from an off-site archive.



## Storage and Retention of Case Histories: Source Records and CRFs

39

- The PI is responsible for retaining the original source records, (continued).
  - For a sufficient length of time. This will vary by study type and sponsor.
    - Minimum 2 years after study end or until no longer needed for a Regulatory submission (anywhere in the world), or in support of another study, whichever is latest.
    - Can be 2 to 15 to 25 years (or more), it depends on the study, any follow-on studies that draw from that study, stage of drug development and needs/actions of the Sponsor.
    - If the PI leaves the institution where the site was located, the study records remain at the institution.



## Getting You Credit

**We appreciate your review of this module.**

To achieve credit for having done so, please complete the corresponding quiz provided in the CPD system.

You will receive a certificate of completion for this module when your quiz is satisfactorily passed (score >80%).



# Device Accountability in Human Research Studies

**For the University of Cincinnati**

**IND/IDE Assistance Program  
May 2011**



## Agenda

2

- Investigational Medical Devices
- Individually Accounted For
- ICH GCPs on Accountability
- UC Policy on Investigational Device Accountability
- FDA Expectations for Accountability: From the BIMO Manuals
  - Investigator
  - Sponsor
- Labeling Requirements
- The Joint Commission on Investigational Devices
- Use of Trade Devices in Research
- AAHRPP on Device Accountability
- Logs and Records
- Errors Made by Others: Words of Warning from the FDA



## Investigational Medical Devices

- Differing terms are used for a medical device under test.  
Examples:
  - Investigational Device
  - Investigational Product (IP)
    - A more general term applied to the devices being tested in a drug research study, also applicable to investigational drugs in drug studies.
      - **IP is the preferred term used in ICH GCPs.**
  - Test Article (TA)
    - A standard term possibly familiar from nonclinical research (animal, GLP, preclinical studies), also however observed applied to devices for humans such as in FDA Bioresearch Monitoring program manuals.
  - Comparator [Device]
    - A device used as a positive control. This is most often an approved device from the trade therefore already approved for the application under test, to which the investigational device is being compared.



## Individually Accounted For

- Investigational new devices are not trade materials for the indication being studied.
  - New device, not yet approved for sale.
  - However, a medical device in the trade being tested for a new indication becomes investigational due to the desired new indication.
- The Sponsor may ship investigational devices in inter-state commerce only for controlled, investigational use.
  - However for an Investigator site to be shipped any study devices, the Sponsor must have documentation that the IRB providing study oversight has approved of the study and the PI.
  - The PIs must then restrict the investigational device(s) only to properly consented study participants, and prescribe/dispense to them only according to the study protocol.
- It is crucial that no investigational devices go unaccounted for and that no lot or batch of an investigational device is used beyond its expiration date (expiry), if the device has one.



## Within Expiration and Individually Accounted For

- The expiration date is often not visible on IP packaging, as the Sponsor may be determining the shelf life of the IP in parallel with a given human research study.
- Sometimes the current, known date is provided by the Sponsor on the shipping records and then revisions of the date for a given lot occurs and is communicated during a study.
  - When the site does not have access to the expiration date, it is the Sponsor's responsibility to notify the site when known expiry is near, and supply fresh devices to the site in a timely manner.
- Expired devices, if a device has an expiration date, are labeled as such and are not used.
  - Study devices that have expiry dates should not expire while in the hands of the participants.
  - A batch of devices that will expire during interval between the current study visit and the next visit should be considered too close to expiry to be dispensed.



## Within Expiration and Individually Accounted For

- In some instances there may be device supply that the participants are given but do not use. If so, this supply is returned to the site and accounted for.
- Devices may break and be returned to the site by participants who receive replacements. Depending on the device, repairs may be possible and be made at the site. The source records must indicate the return and repair activity.
- Devices delivered to the site that are not dispensed to any participant are fully accounted for and removed from the site at the end of the study.
  - Removal is accomplished by documented return to Sponsor or documented destruction.
  - Which removal method is to be used depends on site capability and procedures, as assessed by the Sponsor, then by Sponsor direction.



## ICH GCPs on Device Accountability: Investigator

7

- Responsibility for device accountability at the trial site rests with the investigator/institution. **ICH E6 4.6**
- Where allowed/required, the investigator should assign some to all of the IP accountability duties to a suitable pharmacist. **Not at TUH**
- Records to be maintained for each device involved with a study are:
  - Device delivery to the site
  - Device inventory at the site
  - Use of the device(s) by each participant, including repairs if any.
  - Return to the sponsor or alternative disposition, of unused devices.
- Device accountability records are to include:
  - Dates
  - Quantities
  - Batch/serial numbers
  - Expiry dates (if applicable)
  - Any unique serial or code numbers assigned to the investigational product, and to the participants
  - Adequate records to demonstrate that the participants were provided the devices in kind and number as required by the study protocol.
  - Adequate records to reconcile all IP received from the sponsor.



## ICH GCPs on Device Accountability: Investigator

8

- The devices should be stored as specified by the sponsor and in accordance with applicable regulatory requirements. **ICH E6 4.6**
  - There will be records to demonstrate this, from date of first device arrival at the site through the date the last study devices leave the site.
  - The investigator should ensure that study devices are used only in accordance with the approved protocol.
  - The investigator, or a person designated by the investigator/institution, should explain the correct use of the devices to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly.



## ICH GCPs on Device Accountability: Investigator

9

*ICH 8.2.14, 8.2.15,  
8.3.8, 8.3.23*

- Before the first participant enrolls, the Investigator's study files will include:
  - Instructions for handling of IP(s) and trial-related materials, if the instructions are not included in the protocol or information provided to the Investigator that describes the device.
  - Shipping records for IP(s) and trial-related materials, which will include dates, batch/lot and serial numbers, and the method of shipment that was used.
- During enrollment the Investigator's study files will include:
  - Documentation of subsequent shipments of IP, as was documented for the pre-enrollment initial shipment(s)
  - Ongoing accountability records, to document the IP(s) have been used according to the study protocol.



## ICH GCPs on Device Accountability: Investigator

10

*ICH 8.4.1, 8.4.2*

- After the last participant has completed study participation at the site, the Investigator's files will include:
  - Records of full accountability of IP(s) at the site, to document that all IP was used according to the protocol.
  - Records of the final accounting of IPs received at the site, dispensed to participants, returned by the participants and returned to sponsor.
  - And, if destroyed at the site, documentation of destruction of unused IPs.



## ICH GCPs on Device Accountability: Sponsor

11

*ICH E6 5.12, 5.13*

- Information on IPs
  - When planning a human research study a Sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or previous clinical trials are available to support human exposure by the route, for the duration and in the human population to be studied.
  - The sponsor should update the information provided to study Investigators as significant new information becomes available.



## ICH GCPs on Device Accountability: Sponsor

12

*ICH E6 5.12, 5.13*

- Manufacturing, Packaging, Labeling, and Coding IPs:
  - The sponsor should:
    - Ensure that the IPs including as applicable active comparators are:
      - Characterized as appropriate to the development of the products.
      - Manufactured in accordance with any applicable GMP.
      - Labeled in a manner that complies with applicable regulatory requirements.
      - Coded and labeled in a manner that protects the blinding, if applicable.
    - Determine, for each IP, acceptable storage temperature and conditions (e.g. protect from moisture) storage times, procedures.
    - Inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.



## ICH GCPs on Device Accountability: Sponsor

13

ICH E6 5.14

- Supplying and Handling the IPs. The Sponsor
  - Is responsible for supplying the investigator/institution with the IPs.
  - Should not supply an investigator/institution with investigational devices until the sponsor obtains all required documentation, including approval/favorable opinion from IRB/IEC and regulatory authorities (as required).
  - Should ensure that there are written procedures that include instructions for the investigator/institution to follow for the handling and storage of the IP(s), and for documentation thereof. The procedures should address adequate and safe:
    - Receipt
    - Handling
    - Storage
    - Dispensing
    - Retrieval of unused device(s) from participants
    - Retrieval and/or repair of broken devices, if applicable.
    - Return of unused device(s) to the sponsor or alternative disposition if authorized by the Sponsor and consistent with site regulatory requirements.



## ICH GCPs on Device Accountability: Sponsor

14

ICH E6 5.14

- The Sponsor should:
  - Ensure timely delivery of IP(s) to Investigator(s)
  - Maintain records that document shipment, receipt, disposition, return, and destruction of the IP(s)
  - Maintain a system for retrieving IPs and documenting the retrieval.
    - *E.g.*, for deficient product recall, reclaim after trial completion, expired product reclaim
  - Take steps to ensure that the IP(s) are stable over the period of use.
  - Maintain sufficient quantities of the IP(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analysis and characteristics.
    - To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents longer retention.



## ICH GCPs on Device Accountability: Sponsor

15

- The Sponsor's Monitors' responsibilities include: *ICH E6 5.18.4 (c, k, p), 8.2.14, 8.2.15, 8.2.16, 8.3.8, 8.3.9, 8.3.23, 8.4.1, 8.4.2*
  - Verifying for the IPs at each Investigator site, that:
    - Storage times conditions are acceptable.
    - Supplies are sufficient.
    - The IPs were supplied only to participants eligible to receive them and at in the protocol-or study plan-specified manner.
    - participants were provided with necessary instruction on properly using, handling, storing, and returning the IP(s).
    - The receipt, use, and return of the IP(s) at the site are controlled and documented adequately.
    - The disposition of unused IP(s) at the site complies with applicable regulatory requirement and is in accordance with the Sponsor's authorized procedures.
  - Verifying that trial records are accurate, complete, kept up-to-date, and maintained.
  - Determining whether the investigator is maintaining the essential documents.



## ICH GCPs on Device Accountability: Sponsor

16

- The Sponsor will name and describe the IP(s) in the study protocol. The protocol is to include: *ICH E6 6.2.1, 6.4.4*
  - The usage and usage regimen.
  - Description of the device(s).
  - Description of packaging and labeling of the IP(s).



## Pharmacy

- A PI is permitted to delegate many of the IP functions such as receipt and storage, to an available and qualified Pharmacist who has suitable facilities for the storage and control of the IP.
  - If the Pharmacy accepts devices that are not in combination with an investigational drug.
- PI sites without Pharmacy access for medical devices must provide suitable controlled storage, controlled dispensing, handling and documentation of IPs themselves.



## UC Policy on Investigational Device Accountability

*Cf. UC Research Policy VI.02 "Supplying and Handling Investigational Products in Human Participants Research"*

### Policy

- IPs may be administered to study participants during the course of a study so long as:
  - Prior to the start of the study the PI has reviewed:
    - This Policy.
    - The research unit's SOPs for receipt, distribution, storage, and inventory of IPs, and use of the Investigational Drug Service.
  - The study Sponsor has provided assurance to the PI that the manufacture and formulation of the IP comply with federal regulations.
  - The IPs are administered in accordance with an IRB approved protocol
  - The IPs are identified, stored, administered, and disposed of in accordance with applicable FDA and OHRP regulations and University policy.
  - The researchers are appropriately licensed under state and federal law to administer the IP.



## UC Policy on Investigational Device Accountability

19

*Cf. UC Research Policy VI.02 "Supplying and Handling Investigational Products in Human Participants Research"*

### Responsibilities

- The PI is responsible for the inventory, storage, management, administration, and disposition of IPs in accordance with the approved protocol or study plan, the sponsor's instruction, with FDA and the policy of the institution where the research is conducted.
- The PI will assure that appropriate records are kept of receipt, inventory, distribution, storage and disposition of IPs.
- Researchers will maintain current licenses required by federal, state and local law and by University policy for managing, storing, or supplying IPs.
- When the IP is an implantable device, the PI must include in the study records the specific device used with a specific research participant.
- Each research unit involved with an IP will follow the unit's SOPs for receipt, distributing, storing, inventory, and distribution of the IP and for preventing unauthorized use of the IP.
- Researchers storing, handling, or disposing of hazardous IPs will follow guidance provided by the University's Biosafety committee.
- Researchers' compliance with IP policies and procedures is participant to audit by the FDA, OHRP, the IRB and UC's ORCRA. Researchers will cooperate with the auditors.



## FDA Expectations for Accountability: BIMO Manual, Investigator

20

- For Accountability [812.40 (a)(2)] the inspector is to:
  - **Determine** who is authorized to administer or dispense the test article.
  - **Determine** whether the test article was supplied to a person not authorized to receive it.
  - **Compare** the amount of test article shipped, received, used, and returned or destroyed. **Verify** the following:
    - Receipt date(s), quantity received, and the condition upon receipt;
    - Date(s), participant number, and quantity dispensed; and
    - Date(s) and quantity returned to sponsor. If not returned to sponsor, **describe** the disposition of the test article.
  - **Determine** where the test article is stored, whether it was stored under appropriate conditions as specified in the study protocol, and who had access to it.
  - If the test article is a controlled substance:
    - **Determine** how it is secured; and
    - **Determine** who had access.
- The inspector is also to **inspect** unused supplies and **verify** that the test article was appropriately labeled.



## FDA Expectations Specific to Devices: BIMO Manual, Investigator

21

- **Determine** whether the clinical investigation poses a significant risk (IDE), non-significant risk (abbreviated requirements at 21 CFR 812.2(b)), or is IDE exempt (21 CFR 812.2(c)).
- **Determine** whether the clinical investigator has used the test article under the emergency use or expanded access provisions.
- **Determine** if the clinical investigator is involved in any nonsignificant risk (NSR) studies and, if so, obtain a list of these studies from the clinical investigator and ascertain if they are being conducted in compliance with the regulations (Note: Unless FDA made an NSR determination for the study, the inspector will look for an NSR determination by an IRB. IRB approval is also required for NSR studies; see 812.2(2)(b)(1)(ii).)
- **Determine** if the clinical investigator has been involved in any use of a custom device. If so, the inspector is to first make sure the device meets the definition of a custom device (21 CFR 812.3(b)) [The Inspector is to contact the Center for further guidance. ]
- **Determine** if the clinical investigator has utilized a Humanitarian Use Device (HUD) as provided by 21 CFR Part 814, Subpart H. If so, **obtain** the following:
  - Name of the device;
  - Documentation of IRB approval (see 21 CFR 814.124);
  - Number of patients treated and the indications for which the HUD was used; and **document** any emergency use.



## FDA Expectations: BIMO Manual, Sponsor

22

*FDA CPGM 7348.810  
"Sponsors, Contract Research  
Organizations and Monitors"*

- Requests for inspections from CDRH normally involve Significant Risk (SR) devices that require full compliance with the Investigational Device Exemption (IDE) requirements.
- In addition to covering the identified SR device, the investigator should **determine** whether the sponsor/monitor is involved in clinical investigations of Nonsignificant Risk (NSR) devices, which require compliance with abbreviated IDE requirements.  
[21 CFR 812.5, 812.7, 812.46, 812.140(b)(4) and (5), 812.150(b)(1) through (3) and (5) through (10)]
- When appropriate, the investigator should choose at least one (1), but no more than three (3), NSR device investigations to **determine** the level of compliance with the abbreviated requirements. [Your inspector will be reviewing records of multiple studies during the visit.]



## FDA Expectations: BIMO Manual, Sponsor

23

*FDA CPGM 7348.810  
"Sponsors, Contract Research  
Organizations and Monitors"*

The FDA inspector is to:

- **Determine** whether the sponsor/monitor is involved in any clinical studies involving the humanitarian use of a device described in 21 CFR Part 814 Subpart H.
- **Determine** whether the sponsor has submitted any Humanitarian Device Applications Exemptions.
  - **Review** distribution records for humanitarian use devices at the sponsor site to ensure compliance with:
    - Exemption criterion (<4000 patients/year).
    - Proper accountability.
    - Confirmation of institutional review board (IRB) approval prior to distribution.
    - Prompt notification to CDRH's Office of Device Evaluation of the withdrawal of approval by an IRB.



## FDA Expectations: BIMO Manual, Sponsor

24

*FDA CPGM 7348.810  
"Sponsors, Contract Research  
Organizations and Monitors"*

The FDA inspector will look for appropriate records of:

- Test Article integrity from manufacturing to receipt by the clinical Investigator(s).
  - Review the certificate of analysis and determine of the lots used met release specifications.
  - Determine where the TA was stored, were the conditions appropriate.
  - Determine how the sponsor assured TA integrity during shipment to the Investigator.
  - Determine if the TA was properly labeled.
  - Determine if any TA was recalled, withdrawn or returned.



## FDA Expectations Concerning IPs: BIMO Manual, Sponsor

25

*FDA CPGM 7348.810  
"Sponsors, Contract Research  
Organizations and Monitors"*

The FDA inspector will look for appropriate records of Test Article Accountability:

- Does the Sponsor have records of:
  - Names and addresses of all Investigators receiving IP.
  - Shipment dates, quantity, batch or code mark, or other identification of which lot was shipped.
  - Final disposition of the test articles.
- Are the Sponsor records sufficient to reconcile TA usage (compare amount shipped to Investigators with amount returned and disposed of)
- Were all unused or reusable supplies of TA returned to the Sponsor when the Investigator either discontinued or completed the study at his/her site, or when the study was terminated.



## FDA Expectations Concerning IPs: BIMO Manual, Sponsor

26

*FDA CPGM 7348.810  
"Sponsors, Contract  
Research  
Organizations and Monitors"*

The FDA inspector will look for appropriate records of Test Article Accountability:

- If TA was not returned to the Sponsor, do the Sponsor records describe the method of disposition and are there adequate records thereof.
- To determine if the Sponsor charged for the test article, and if so is there adequate documentation of the fees charged.
- **To determine** how the sponsor controls and monitors the use of devices that are not single-use products, such as lithotripters or excimer lasers.



## The Joint Commission and Medical Devices

Cf. TJC Standards RI.01.03.05,  
EC 02.04.01, EC 02.04.03

- The Joint Commission Standards for Hospitals are explicit concerning medication and investigational medication, but JC Standards are not explicit concerning medical devices, either trade or investigational.
  - Patients' Rights Standards apply in Device trials, though these do not overlap Accountability of the medical devices.
  - The Joint Commission also has standards concerning medical equipment which may be pertinent, depending on the device under test.



## Labeling

- There is great variability in the devices in human research studies and their packaging. Examples include:
  - Boxes.
  - Pouches.
  - Blister packages.
- However packaged, for the IP to have been manufactured lawfully there will be a label, labels, or in general, labeling.
  - ICH GCPs state that applicable regulatory requirements are to be followed.
  - FDA regulations list Device IP labeling specifics in 21 CFR 812.5 (next slide)
- Devices manufactured for a particular study may have the protocol code in the labeling.



## FDA GCP Device Labeling Requirements

- Multiple labels are allowed; labeling is a term used to describe all of the labels and accompanying printed insert(s), taken together.
  - 812.5(a) *Contents*. An investigational device or its immediate package shall bear a label with the information: the name and place of business of the manufacturer, packer, or distributor (in accordance with 801.1), the quantity of contents, if appropriate, and the following statement: “CAUTION-Investigational device. Limited by Federal (or United States) law to investigational use.” The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and prohibitions.
  - 812.5(b) *Prohibitions*. The labeling of an investigational device shall not bear any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.

Included among the 21 CFR 812.5 (a) aspects that device labeling is to describe, are the storage conditions needed to preserve device quality and stability.



## FDA GCP Device Labeling Requirements

- Multiple labels are allowed; labeling is a term used to describe all of the labels and accompanying printed insert(s), taken together.
  - 812.5 (c) *Animal Research*. An investigational device shipped solely for research on or with laboratory animals shall bear on its label the following statement: “CAUTION-Device for Investigational use in laboratory animals or other tests that do not involve human participants.”
  - 812.5 (d) The appropriate Center Director may grant an exception or alternative to 812.5 (a) and (c)...for specified lots, batches or other units of a device ... that will be included in the Strategic National Stockpile.



## Additional Aspects of Device Studies

- Blinded studies and placebo-controlled studies are uncommon in medical device research. This is related in part to nature of the medical devices being tested.
  - Blinding of labeling makes no sense when anyone can look at two devices and see physical differences between them.
  - Placebos may not be ethical to employ with some devices, particularly implantable devices (such as stents, pacemakers, vertebral spacers and artificial disks).
- Device and drug combination products, on the other hand, can employ the same test device in all study arms, with active drug and matched placebo combined with devices produced for each arm of the study (example: inhalers).
- Devices may break and become repaired during a study. Why and how many units of the device have become repaired is to be captured in the Investigator's records of the study [see 21 CFR 812.140 (a)(2)(iii)].
- Devices may need routine maintenance to keep them functioning correctly, which in a research context would be captured and documented (example battery replacement).



## AAHRPP Accreditation

- Association for the Accreditation of Human Research Protection Programs
  - UC holds full accreditation (there are other types)
  - UC values the accreditation that the University holds.
- AAHRPP divides its standards into three areas
  - Researcher and Research Staff
  - The Organization
  - Institutional Review Board or Ethics Committee



*IP Accountability is found in the Organization area, and is implied in the Researcher and Research Staff area.*



## AAHRPP on IP Accountability: Organization



Element I.7.A: When research involves any investigational unlicensed test articles, the Organization confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.

Element I.7.B: The Organization has and follows written policies and procedures to ensure that the handling of investigational or unlicensed test articles conforms to legal and regulatory requirements.

- Investigational test articles are used only in approved research protocols and under the direction of approved Researchers.
- The Organization has a process to ensure the proper handling of investigational test articles.

Element I.7.C: The Organization has and follows written policies and procedures for compliance with legal and regulatory requirements governing emergency use of an investigational or unlicensed test article.



## AAHRPP on IP Accountability: Researchers



**IP Accountability is not explicitly mentioned in the Researcher Domain as it is in Organization, but is reflected in this Element:**

Element III.2.C: Researchers and Research Staff follow the requirements of the research protocol or plan and adhere to the policies and procedures of the Organization and to the requirements or determination of the IRB or IEC.

- Researchers and Research Staff are knowledgeable about and follow all legal and regulatory requirements and the Organization's policies and procedures that pertain to their research.
- Researchers and Research Staff follow the requirements of the research plan or protocol.



## When the Research Study Uses Trade Devices

- This often occurs with comparator-controlled, open-label studies.
- The comparator is obtained from the trade and is dispensed in the trade containers with any applicable (patient) informational inserts included (also keep a copy of each insert in the PI's regulatory binder).
- Batch/lot or serial numbers and expiration dates will be known to the PI's site from the labeling. There would be no communication from the Sponsor needed, to track when the supplies of devices from the trade might become too old to be dispensed.



## Logs and Records

- Device records for a study start with the first shipment receipt, include use of the devices at the site, and end with final disposition.
- Disposition records include:
  - 1) Device supplies returned to the site by participants at study visits. Devices that have been out in the hands of participants are not re-dispensed.
  - 2) Unused devices remaining at the site after the last participant's last dispensing visit.
- The flow and balance of devices to the site and devices from the site should be reconstructable at any time during the study as well as after, from the IP accountability records alone.
- Device records being up to date is crucial.
- Records should reflect prompt and vigorous actions taken by the site to secure additional supply when needed, such as
  - Instances of damage (of receipts or accidental damage in storage)
  - An unexpected dwindling of the available supply such as when enrollment is more rapid than expected.



## Logs and Records

- Device accountability logs are key to being able to determine:
  - That no devices were shipped to the site until after the IRB approved of the PI and the study.
  - That the site had a sufficient supply of devices throughout the time they had participants who were active in the study.
  - That all participants received the correct study device(s) as intended from the investigational plan.
  - That no devices that were expired was dispensed to, or for, participants.
  - That no study devices remained in the hands of the participants at the end of their study participation.
  - That no study devices remained at the site at the time of site closure.
- Device logs are often kept on different sets of worksheets, in two ongoing ways:
  - A participant-by-participant accounting of which devices (with lot/serial numbers identified) were dispensed by whom, when.
  - A running inventory total accounting of devices available at the site on any given date.



## Errors Made by Others: Words of Warning From FDA

- IP Accountability is commented upon in Warning Letters issued by the U.S. FDA.
  - The Warning Letter (WL) is the last pre-sanction level of FDA correspondence with a PI.
- Typically, a WL is preceded by a Clinical Investigator inspection by the FDA with a Form FDA 483 that the PI did not adequately respond to.
  - However, it has been known for a WL to generate without waiting for response to a Form FDA 483, in egregious instances.
- WLs are made public in redacted form on the FDA web-site.
- The letters represent an opportunity to learn from the mistakes of others rather than learning from making them one's own self.
- A few examples of Device Accountability issues from Warning Letters follow.



## WL 25Jun10 to a PI of a Device Study

Failure to maintain accurate, complete, and current records of receipt, use, or disposition of a device that relate to the type and quantity of the device and the dates of receipt. [21 CFR 812.140(a)(2)].

- The “Product Accountability Log” only listed the UltraShape system once and seven [REDACTED]. There are **no records of receipt, use, or disposal of any [REDACTED]** or the UltraShape system. A total of [REDACTED] participants were enrolled at your site; however, the **log does not provide information related to which participants were treated with which [REDACTED]**
- The product accountability log shows the receipt date for one investigational device and five [REDACTED] on June 30, 2008, and **lists receipt of two additional [REDACTED] but no receipt date.**
- There are **no records of the disposition** of the [REDACTED], including any shipping receipts.



## WL 20May09 to a Hospital-Based Device Sponsor-Investigator

A clinical investigator shall maintain the following accurate, complete, and current records relating to the Investigator’s participation in an investigation: records of receipt, use or disposition of a device that relate to the type and quantity of the device, the dates of its receipt, and the batch number or code mark. 21 C.F.R. 812.140(a) (2) (i)

You failed to adhere to the above stated regulation. Examples of this failure include, but are not limited to the following: Your device **receipt and disposition records were inadequately maintained.** You reported that you received enough from [REDACTED] not have any documentation of the exact quantity received. **You provided a spreadsheet** pertaining to device accountability at the close of the inspection; however **it did not state the quantity of device received not did it provide the date of its receipt.**



## WL 20May09 to a Hospital-Based Device Sponsor-Investigator

A clinical investigator shall maintain the following accurate, complete, and current records relating to the Investigator's participation in an investigation: records of receipt, use or disposition of a device that relate to the type and quantity of the device, the dates of its receipt, and the batch number or code mark. 21 C.F.R. 812.140(a) (2) (i)

Your response states that the nurse in the designated [REDACTED] kept a separate log relating to the quantity, date, and lot number of the device. This log was kept in the cabinet with the devices; however the log and the nurse were not available at the time of the FDA inspection. You stated that you subsequently provided the patient names, lot numbers and amount given. Your response is inadequate. The spreadsheet provided did not include the quantity of device received or the date on which they were received. Moreover, your response does not provide substantive corrective actions or any preventive actions to ensure appropriate device accountability and to avoid recurrence of these violations...



## WL 01Jun08 to a Device Sponsor

Failure to ship investigational devices only to qualified investigators participating in the investigation  
[21 CFR 812.43(b)]

A sponsor shall ship investigational devices only to qualified investigators participating in the investigation. You failed to adhere to this regulation in that you shipped replacement parts for your investigational device [REDACTED] to persons other than qualified clinical investigators, namely participants. Your device shipping log shows replacement parts such as stimulators, external wires, and batteries have been sent to participants' homes.

There's a participant confidentiality issue on the Investigator's part here also. This corporate Sponsor is not a Sponsor-Investigator thus should not have had the participants' names and home addresses.



## Getting You Credit

**We appreciate your completion of this module.**

To achieve credit for having done so, please complete the corresponding quiz that is in the CPD system.

You will receive a certificate of completion when your quiz is satisfactorily passed (score >80%).



# Drug Accountability in Human Research Studies

**For the University of Cincinnati**

**IND/IDE Assistance Program  
May 2011**



## Agenda

- Investigational Drugs
- Within Expiration and Fully Accounted For
- ICH GCPs
- The Joint Commission on Investigational Medications
- UC Policy on Investigational Drug Accountability
- FDA Expectations: From the BIMO Manuals
  - Investigator
  - Sponsor
- Pharmacy
- Labeling Requirements
- Use of Trade Drugs
- AAHRPP on Drug Accountability
- Logs and Records
- Errors Made by Others: Words of Warning from the U.S. FDA

2



## Terms for Investigational Drugs

3

- Differing terms are used for the drug being tested in human volunteers. Examples:
  - Study Drug
  - Investigational Drug
  - Investigational Product (IP)
    - A more general term applied to the drugs being tested in a drug research study that is also applicable to medical devices used in device studies.
    - IP is the preferred term used in ICH GCPs.
  - Test Article (TA)
    - A standard term possibly familiar from preclinical studies, nonclinical (animal, GLP) research: also however observed applied to drugs for humans in FDA Bioresearch Monitoring program manuals.
- Comparator is sometimes also seen. Comparator is a different active drug used as a positive control in a study.
  - The comparator is most often an approved drug from the trade, therefore already approved for the application under test.
  - Comparators that are repackaged or altered to visually match an IP become Investigational due to the processing and repackaging.



## Investigational Drugs

4

- Investigational Drugs are not trade drug materials for the indication being studied.
  - Could be a new chemical entity.
  - Could be a new formulation, not yet approved for sale, of an existing drug active.
  - Trade drug active in a different dose form. Dose forms used in human research studies earlier in the overall development process may or may not be the ones that are planned for the trade.
  - Some are produced in packaging that is blinded with the labeling coded, to not directly indicate whether the package contents are active-containing product or placebo.
  - And, a trade drug being tested for a **new indication** becomes investigational because of the indication.



## Investigational Drugs

- The Sponsor may ship investigational drugs (actives and placebos) in inter-state commerce only for controlled, investigational use.
  - However for an Investigator site to receive investigational drugs, the Sponsor must have documentation that the IRB providing study oversight has approved of the study and the PI.
  - The PIs must then restrict the investigational drug to only properly consented study participants, and prescribe/dispense to them only according to the study protocol.



## Within Expiration

- It is crucial that no lot of an investigational drug is used beyond its expiration date (expiry).
  - The expiration date is often not visible on IP packaging, as the Sponsor may be determining the shelf life of the IP in parallel with a given human research study.
  - Sometimes the current, known date is provided by the Sponsor on the shipping records and then revision of the date for given lots occur. The revisions are communicated during a study.
    - When the site does not have access to the expiration date it is the Sponsor's responsibility to notify the site when known expiry is near and supply fresh product to the site in a timely manner.
  - Supplies in expired drug lots at a site are labeled as expired and are not dispensed to participants.
    - Study drug should not expire while in the hands of the participants.
    - A lot of drug that will expire during interval between the current study visit and the next visit should be considered too close to expiry to be dispensed.



## Fully Accounted For

- It is crucial that no amount of investigational product goes unaccounted for.
  - Drug supply that the participants are given but do not take is returned to the site and accounted for.
  - Drug supply remaining at the site after the last participant's last visit is fully accounted for and removed from the site at the end of the study.
    - Unused drug, that was not dispensed to any participant.
    - Drug dispensed to then later returned to the site by, participants.
  - Removal from the site is accomplished by documented return to Sponsor (often done by the study Monitor) or by documented destruction.
    - Which method is used depends on site capability and procedures. The Sponsor is to assess the site and then provide the site with written directions.
    - In a multi-site study, different sites may use different methods as long as the methods are approved for each site by the Sponsor.



## ICH GCPs on Drug Accountability: Investigator

ICH E6 4.6

- Responsibility for drug accountability at the trial site rests with the investigator/institution.
- Where allowed/required, the investigator should assign some to all IP accountability duties to a suitable pharmacist. **Required at TUH.**
- Records to be maintained for each drug involved with a study are:
  - Drug delivery to the site.
  - Drug inventory at the site.
  - Use of the drug by each participant.
  - Return to the sponsor or alternative disposition, of unused product.
- Drug accountability records are to include:
  - Dates.
  - Quantities.
  - Batch/serial numbers.
  - Expiration dates (if applicable).
  - Any unique code numbers assigned to the investigational product, and to the participants.
  - Adequate records to demonstrate that the participants were provided the doses required by the study protocol.
  - Adequate records to reconcile all IP received from the sponsor.



## ICH GCPs on Drug Accountability: Investigator

9

*ICH E6 4.6*

- The drug should be stored as specified by the sponsor and in accordance with applicable regulatory requirements.
  - There will be records to demonstrate this, from date of first arrival at the site through the date the drug leaves the site.
  - The investigator should ensure that the IP(s) are used only in accordance with the approved protocol.
  - The investigator, or a person designated by the investigator/institution, should explain the correct use of the IP(s) to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly.



## ICH GCPs on Drug Accountability: Investigator

10

*ICH 8.2.14, 8.2.15,  
8.3.8, 8.3.23*

- Before the first participant enrolls, the Investigator's study files will include:
  - Instructions for handling of IP(s) and trial-related materials, if the instructions are not included in the protocol or Investigator's Brochure.
  - Shipping records for at least an initial receipt of IP(s) and trial-related materials, which will include date, batch number(s) and the method of shipment that was used.
- Throughout the time there are participants in the study at the site, the Investigator's study files will include:
  - Documentation of subsequent shipments of IP, as was documented for the pre-enrollment initial shipment(s)
  - Ongoing accountability records, to document the IP(s) have been used according to the study protocol.



## ICH GCPs on Drug Accountability: Investigator

11

*ICH 8.4.1, 8.4.2*

- After the last participant has completed their study participation at the site the Investigator's files will include:
  - Records of full accountability of IP(s) at the site, to document that all IP was used according to the protocol.
  - Records of the final accounting of IPs received at the site, dispensed to participants, returned by the participants and final disposition of the site's supplies.
  - Either return to Sponsor of all remaining IP at the site or documentation of destruction. Study records should demonstrate balance: total amount to that came to the site equals drug taken by subjects plus drug returned to the Sponsor plus (if any) drug destroyed at the site.



## ICH GCPs on Drug Accountability: Sponsor

12

*ICH E6 5.12, 5.13*

- Information on Study Drugs
  - When planning a human research study a Sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or previous clinical trials are available to support human exposure by the route, at the dosages, for the duration and in the trial population to be studied.
  - The sponsor should update the Investigator's Brochure as significant new information becomes available.



## ICH GCPs on Drug Accountability: Sponsor

13

ICH E6 5.12, 5.13

- Manufacturing, Packaging, Labeling, and Coding Investigational Drugs: The Sponsor should
  - Ensure that the drugs including as applicable active comparators and placebo(s) are:
    - **Characterized** as appropriate to the development of the products.
    - **Manufactured** in accordance with any applicable GMP.
    - **Coded** and labeled in a manner that protects the blinding, if applicable.
    - **Labeled** in a manner that complies with applicable regulatory requirements.
  - Determine, for each drug, acceptable storage temperature, conditions (e.g. protect from light) , storage times, reconstitution fluids and procedures, and devices needed for product infusion if any.
  - Inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.



## ICH GCPs on Drug Accountability: Sponsor

14

ICH E6 5.14

- Supplying and Handling the Drugs: The Sponsor
  - Is responsible for supplying the investigator institution with study drugs.
  - Should not supply an investigator/institution with investigational product until the sponsor obtains all required documentation, including approval/favorable opinion from IRB/IEC and regulatory authorities (as required).
  - Should ensure that there are written procedures that include instructions for the investigator/institution to follow for the handling and storage of the IP(s), and for documentation thereof. The procedures should address adequate and safe:
    - Receipt
    - Dispensing
    - Handling
    - Retrieval of unused product(s) from participants
    - Storage
    - Return of unused IP(s) to the sponsor or alternative disposition if authorized by the Sponsor and consistent with site regulatory requirements.



## ICH GCPs on Drug Accountability: Sponsor

15

ICH E6 5.14

- The Sponsor should:
  - Ensure timely delivery of drug(s) to Investigator(s).
  - Maintain records that document shipment, receipt, disposition, return, and destruction of the drug(s).
  - Maintain a system for retrieving investigational drugs and documenting the retrieval.
    - *E.g.*, for deficient product recall, reclaim after trial completion, expired product reclaim.
  - Take steps to ensure that the drug(s) are stable over the period of use.
  - Maintain sufficient quantities of the drug(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analysis and characteristics.
    - To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), which ever represents longer retention.



## ICH GCPs on Study Drug: Sponsor

16

ICH E6 6.2.1, 6.4.4

- The Sponsor will name and describe the drug(s) in the study protocol, which will include
  - The dosage and dosage regimen.
  - Description of the dosage form.
  - Description of packaging and labeling of the drug(s).



## ICH GCPs on Drug Accountability: Sponsor

17

- The Sponsor's Monitors' responsibilities include:

- Verifying for the IPs at each Investigator site, that:

- Storage times conditions are acceptable.
- Supplies are sufficient.
- The IPs were supplied only to participants eligible to receive them and at the protocol-specified dose(s).
- participants were provided with necessary instruction on properly using, handling, storing, and returning the IP(s).
- The receipt, use, and return of the IP(s) at the site are controlled and documented adequately.
- The disposition of unused IP(s) at the site complies with applicable regulatory requirement and is in accordance with the Sponsor's authorized procedures.

*ICH E6  
5.18.4 (c, k,  
p), 8.2.14,  
8.2.15,  
8.2.16, 8.3.8,  
8.3.9, 8.3.23,  
8.4.1, 8.4.2*

*It may be the Monitor him- or herself who performs disposition by return shipment to Sponsor, or the Monitor may check, confirm, then document that the site is OK to ship to Sponsor, or IP destruction may occur at the site.*

- Verifying that trial records are accurate, complete, kept up-to-date, and maintained.
- Determining whether the investigator is maintaining he study essential documents.



## From The Joint Commission Regarding Investigational Products

18

*Cf. TJC Standard  
MM.06.01.05*

- 1 The hospital has a written process addressing the use of investigational medications that includes review, approval, supervision, and monitoring.
- 2 The hospital's written process for the use of investigational medications specifies that the pharmacy controls the storage, dispensing, labeling, and distribution of investigational medications.
- 3 The written process for the use of investigational medications specifies that when a patient is involved in an investigational protocol that is independent of the hospital, the hospital evaluates and, if no contraindication exists, accommodates the patient's continued participation in the protocol.
- 4 The hospital implements its processes for the use of investigational medications.

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## UC Policy on Investigational Drug Accountability

19

*Cf. UC Research Policy VI.02 "Supplying and Handling Investigational Products in Human Participants Research"*

- IPs may be administered to study participants during the course of a study so long as:
  - Prior to the start of the study the PI has reviewed:
    - This Policy.
    - The research unit's SOPs for receipt, distribution, storage, and inventory of IPs and use of the Investigational Drug Service.
  - The study Sponsor has provided (documented) assurance to the PI that the manufacture and formulation of the IP comply with federal regulations.
  - The IPs are administered in accordance with an IRB approved protocol
  - The IPs are identified, stored, administered, and disposed of in accordance with applicable FDA and OHRP regulations and University policy.
  - The researchers are appropriately licensed under state and federal law to administer the IP.



## UC Policy on Investigational Drug Accountability

20

*Cf. UC Research Policy VI.02 "Supplying and Handling Investigational Products in Human participants Research"*

### Responsibilities

- The PI is responsible for the inventory, storage, management, administration, and disposition of IPs in accordance with the approved protocol, the sponsor's instruction, with FDA and the policy of the institution where the research is conducted.
- The PI will assure that appropriate records are kept of receipt, inventory, distribution, storage and disposition of IPs.
- Researchers **will maintain current licenses** required by federal, state and local law and by University policy for managing, storing, or supplying IPs.
- Each research unit involved with an IP will follow the unit's SOPs for receipt, distributing, storing, inventory, and distribution of the IP and for preventing unauthorized use of the IP.
- Researchers storing, handling, or disposing of hazardous IPs will follow guidance provided by the University's Biosafety committee.
- Researchers compliance with IP policies and procedures is subject to audit by the FDA, OHRP, the IRB and UC's ORCRA.  
**Researchers will cooperate with the auditors.**



## FDA Expectations for Accountability: BIMO Manual, Investigator

21

FDA CPGM 7348.811  
"Clinical Investigators"

- For Accountability the FDA inspector is to:  
[21 CFR 312.62(a), 511.1(b)(7)(ii)],
  - **Determine** who is authorized to administer or dispense the test article.
  - **Determine** whether the test article was supplied to a person not authorized to receive it.
  - **Compare** the amount of test article shipped, received, used, and returned or destroyed. **Verify** the following:
    - Receipt date(s), quantity received, and the condition upon receipt;
    - Date(s), participant number, and quantity dispensed; and
    - Date(s) and quantity returned to sponsor. If not returned to sponsor, **describe** the disposition of the test article.
  - **Determine** where the test article is stored, whether it was stored under appropriate conditions as specified in the study protocol, and who had access to it.



## FDA Expectations: BIMO Manual, Investigator

22

- For Accountability the FDA inspector is to:  
(continued):
  - If the test article is a controlled substance:
    - **Determine** how it is secured; and
    - **Determine** who had access.
- The inspector is also to **inspect** unused supplies and **verify** that the test article was appropriately labeled.



## FDA Expectations: BIMO Manual, Sponsor

23

*FDA CPGM 7348.810  
"Sponsors, Contract Research  
Organizations and Monitors"*

In a Sponsor inspection the FDA inspector will look for appropriate records of Test Article integrity from manufacturing to receipt by the clinical Investigator(s). The inspector is to:

- Review the certificate of analysis and determine if the lots used met release specifications.
- Determine where the TA was stored, were the conditions appropriate.
- Determine how the sponsor assured TA integrity during shipment to the Investigator.
- Determine if the TA was properly labeled.
- Determine if any TA was recalled, withdrawn or returned.



## FDA Expectations: BIMO Manual, Sponsor

24

*FDA CPGM 7348.810  
"Sponsors, Contract Research  
Organizations and Monitors"*

The FDA inspector will look for appropriate records of Test Article Accountability:

- Does the Sponsor have records of:
  - Names and addresses of all Investigators receiving IP.
  - Shipment dates, quantity, batch or code mark, or other identification of which lot was shipped.
  - Final disposition of the test articles.
- Are the Sponsor records sufficient to reconcile TA usage (compare amount shipped to Investigators with amount returned and disposed of).
- Were all unused or reusable supplies of TA returned to the Sponsor when the Investigator either discontinued or completed the study at his/her site, or when the study was terminated.



## FDA Expectations: BIMO Manual, Sponsor

25

*FDA CPGM 7348.810  
"Sponsors, Contract Research  
Organizations and Monitors"*

The FDA inspector will look for appropriate records of  
Test Article Accountability:

- If TA was not returned to the Sponsor, do the Sponsor records describe the method of disposition and are there adequate records thereof.
- To determine of the Sponsor charged for the test article, and if so is there adequate documentation of the fees charged.



## Pharmacy

26

- Hospital-based PIs are to use the hospital Pharmacy, for drug IPs. The PI delegates many of the drug-related functions such as receipt and storage, to an available and qualified Pharmacist who has suitable facilities for the storage and control of the drug(s).
- The drug(s) are stored in the Pharmacy, and dispensed from there.
  - Directly to qualified study staff members, to transport to out-patient participants who receive the drugs at study visits, to take home.
  - To a hospital floor or a surgical suite, for administration to in-patients.
- The Pharmacy may be preparing the doses, blinded ones or open-label ones (for example IV solutions or ready to inject syringes).



## Pharmacy

- It may be Pharmacy personnel who secure the randomization assignment of each participant.
- It may be Pharmacy personnel who destroy unused drugs (after final reconciliation by a Monitor).
- Pharmacy may archive study records separately from the PI's Investigator Site File (Regulatory Binder). The Investigator's files should identify where the drug-related records are, that reside elsewhere.
- Non-hospital PI sites without Pharmacy access must provide suitable controlled storage, controlled dispensing and handling of study drugs and associated record keeping themselves.



## Labeling Requirements

21 CFR 312

- There is great variability in IPs in human research studies and corresponding variability in the kinds of dose forms and packaging that is used. Packaging examples include
  - Bottles or boxes, often plain, opaque white.
  - Vials, single or multi-use.
  - Blister cards in a box or foil pouch.
- However packaged, for the IP to have been manufactured lawfully there will be a label, labels, or in general, labeling. ICH GCPs state that applicable regulatory requirements are to be followed. A few Drug IP labeling specifics are found in FDA GCP regulations in 21 CFR 312.6:
  - 312.6(a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement: **“Caution – New Drug – Limited by Federal (or United States) law to investigational use.”**
  - 312.6(b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.
  - 312.6 (c) The appropriate Center Director may grant an exception or alternative to 312.6 (a) ...for specified lots, batches or other units ... that will be included in the Strategic National Stockpile.



## Labeling Requirements

- General requirements for drug labeling are found in 21 CFR 201. Labeling will include:
  - A statement of identity, in terms of the established name for the drug active.
  - Strength of the active ingredient (e.g. mg per tablet or capsule, or per defined volume of a liquid).
  - A lot number or control code that identifies which batch or lot of product is in the container.
  - A declaration of the net quantity of contents in the container; this could be numerical count (such as of tablets or capsules) or amount (such as volume of a liquid or weight of a solid).
  - The storage conditions to be used (that maintain product quality and stability).
  - Some indication of who the manufacturer was (For IP this is typically study sponsor/corporate partner name, even if manufacture was sub-contracted).
- Drug manufactured for a particular study will also have the protocol code on the label.
- But: labeling must maintain any protocol-defined study blind. For blinded studies, the identity statement may be modified to identify the contents as “[Newdrug] or placebo”. *There must be a way to unequivocally determine which of the two is actually in each individual carton.* Coding methods are used.



## Labeling: Placebo Formulations

- Typically, placebo-controlled trials are either single blind (participant does not know which treatment, PI and team do) or double blind (neither participant nor investigator and team know which treatment).
- Each placebo has a formulation and is constructed to be a match for the drug in type, appearance and/or any other pertinent aspect.
  - Capsules and tablets are formulated to be of the same size, shape and color as used for the active-containing formula.
  - Oral liquids are typically color- flavor- and viscosity-matched.
- Injected and IV drugs are the most difficult to truly match a placebo to active, and at times one cannot. If the drug active gives a tint to the syringe or infusion bag contents when dissolved at dosing concentration, sites are challenged to mask the syringes or infusion sets and not have the color show to site personnel and participants.
  - Designated unblinded study personnel to receive the prepared doses and administer the injection or infusion would leave the PI and other staff who are performing the rest of the study procedures blinded. The unblinded personnel should do nothing else for a blinded study other than administer the doses of drug.
  - Prevention of participants seeing the infusion solution or injection syringe contents at the point of dosing, should be practiced.



## IP Labeling in Blinded Studies

- Double-blind studies may use fully identified drugs, as long as the Pharmacy is making and blinding the doses that are administered.
  - The IP collected by the study team member to give to the participant would not have the lot code identifier on it. Pharmacy personnel would know, and could break the blind in an emergency. Study team and participant remain blinded
- In double-blind studies, code, lot or batch numbers on IP labeling that study personnel see would not fully break the blind as long as the site did not know which lot number was active and which placebo. However, this method would tell the site which of their participants received like treatments.
  - This information in the hands of the PI and coordinators would constitute a partial blind break across the participants at that site.
  - Unless only Pharmacy sees the packaging with lot numbers, and the blinded staff receive the IP dispensed for each participant in Pharmacy containers that does not include the lot numbers.



## IP Labeling in Blinded Studies

- Some Sponsors have drug kits manufactured with participant study ID codes on the IP labels.
  - The site personnel must take care in dispensing, not to mix kits among different participants present in clinic on the same day.
  - In cases where a participant withdraws from the study, all unused kits coded for that participant become unusable for any other participant at that site.
- Many Sponsors elect to provide double-blind labeling as individual unit codes (on individual bottles, or kits of a measured number of IP does each) to mask whether the contents active or placebo. Lot numbers can be unknown to the site.
  - The site would be told which kits are to go to each participant by a central point of control that has both the code break information and a list of which kit codes that were shipped to each Investigator site. This is often done using an automated interactive voice response (IVRS) system.
  - With this labeling not even the Pharmacy knows which participant is in what study arm, and blind-break in emergency is done using the central control (or IVRS) system.



## When the Research Study Uses Trade Drugs

- Comparator-controlled studies are typically open-label studies, or with additional processing, blinded ones..
- IN open-label the comparator is obtained from the trade and is dispensed in the trade containers with the informational inserts included (also keep a copy of each insert in the regulatory binder).
  - If trade drug is obtained and then either repackaged or further processed for the study (e.g. over encapsulation for blinding purposes), the trade product has now become investigational in its repackaged or reprocessed and repackaged form.
- The quantity of trade drug obtained for the research study should be sequestered from the pharmacy's "ordinary" supply of that same drug for medicinal use, and kept in a separate Investigational pharmacy if there is one that serves the PI's site.
- Lot numbers and expiration dates will be known to the PI's site from the drug packaging, with no communication from the Sponsor needed to track when the supplies become too old to be dispensed.
  - Unless re-processing or re-packaging has occurred, in which case the Sponsor will have to assess if the processing has altered the stability profile of the drug and set a shorter expiration date. That new expiration date should be communicated to the sites using the reprocessed/repackaged drug.



## AAHRPP Accreditation

- Association for the Accreditation of Human Research Protection Programs
  - UC holds full accreditation (there are other types)
  - UC values the accreditation that the University holds.
- AAHRPP divides its standards into three areas
  - Researcher and Research Staff
  - The Organization
  - Institutional Review Board or Ethics Committee



*Drug Accountability is found in the Organization area, and is implied in the Researcher and Research Staff area.*



## AAHRPP on Drug Accountability: Organization



Element I.7.A: When research involves any investigational or unlicensed test articles, the Organization confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.

Element I.7.B: The Organization has and follows written policies and procedures to ensure that the handling of investigational or unlicensed test articles conforms to legal and regulatory requirements.

- Investigational test articles are used only in approved research protocols and under the direction of approved Researchers.
- The Organization has a process to ensure the proper handling of investigational test articles.

Element I.7.C: The Organization has and follows written policies and procedures for compliance with legal and regulatory requirements governing emergency use of an investigational or unlicensed test article.



## AAHRPP on IP Accountability: Researchers



IP Accountability is not explicitly mentioned in the Researcher Domain as it is in Organization, but is reflected in this Element:

Element III.2.C: Researchers and Research Staff follow the requirements of the research protocol or plan and adhere to the policies and procedures of the Organization and to the requirements or determination of the IRB or IEC.

- Researchers and Research Staff are knowledgeable about and follow all legal and regulatory requirements and the Organization's policies and procedures that pertain to their research.
- Researchers and Research Staff follow the requirements of the research plan or protocol



## Records and Logs

- For each human research study Investigator site drug records start with shipment receipts, include use of the drug at the site, and end with final disposition.
  - Disposition records include:
    - 1) Drug supplies that expire during the study.
    - 2) Drug supplies returned to the site by participants at study visits. Drug that has been out in the hands of participants is not re-dispensed, even if within expiry date.
    - 3) Unused drug remaining at the site after the last participant's last dispensing visit.
  - Disposition can occur as the study goes along (especially removal of expired supplies) or at the end of the study.
- The flow and balance of drug to the site and drug from the site should be reconstructable at any time during the study as well as after, from the IP accountability records alone.
- It is important for drug records to be kept up to date throughout.



## Records and Logs

- IP records should reflect prompt and vigorous actions taken by the site or site Pharmacy to secure additional supply when needed, such as
  - Instances of damage (damage on receipt or excessive thermal excursions during shipment or storage at the site).
  - An unexpected dwindling of the available supply (faster than expected enrollment).



## Records and Logs

39

- Drug accountability logs are key to being able to determine that:
  - No drug was shipped to the site until after the IRB approved of the PI and the study.
  - The site had a sufficient supply of drug throughout the time they had participants who were active in the study.
  - All participants received the correct study drug at the intended dose level(s).
  - No drug that was expired was dispensed to or for, participants.
  - No study drug remained in the hands of the participants at the end of their study participation.
  - No study drug remained at the site at the time of site closure.
- Drug logs are kept in two ongoing ways on different sets of worksheets:
  - A participant-by-participant accounting of how much of which drug (with lot identified) was dispensed when.
  - A running inventory total accounting, of drug available at the site.



## Errors Made by Others: Words of Warning From FDA

40

- IP Accountability is commented upon in Warning Letters issued by the U.S. FDA.
  - The Warning Letter (WL) is the last pre-sanction level of FDA correspondence with a PI.
- Typically, a WL is preceded by a Clinical Investigator inspection by the FDA with a Form FDA 483 that the PI did not adequately respond to.
  - However, it has been known for a WL to generate without waiting for response to a Form FDA 483, in egregious instances.
- WLs are made public in redacted form on the FDA website.
  - The letters represent an opportunity to learn from the mistakes of others rather than learning from making them one's own self.
- A few examples of Drug Accountability issues from Warning Letters follow, emphases in color added.



## WL 09Nov09 to a PI

### For participant #0011 enrolled in Protocol

- i. **Visit 4:** The study medication section of the source document worksheet documents medication dispensed for visit 4 on 11/14/05, yet the study medication compliance check for visit 4 documents kit number 5097765 was dispensed on 11/15/05. The medication bottle label for kit number 5097765 also documents that it was dispensed on 11/15/05. There is no written documentation to explain this discrepancy.
- ii. **Visit 7:** The study medication case report form for visit 7 documents 200 tablets returned on 2/20/07, yet the study medication compliance check for visit 7 documents 38 tablets returned on 2/20/07.

### For participant #00002 enrolled in Protocol

**Visit 5** CRF Drug Labels Form documents that kit number 513548 was dispensed on 11/21/06, yet the Drug Accountability Log fails to document this kit.



## WL 09Nov09 to a PI

### For participant #00004 enrolled in Protocol

- Visit 8:** Medication Re-Supply Call Worksheet dated 3/5/07 documents kit numbers 515201, 519282, and 519101 as being dispensed but ClinPhone Re-Supply Confirmation form dated 3/18/07 does not list kit number 515201 as being dispensed. There is no written documentation to explain this discrepancy.
- Visit 8:** Drug Accountability Log documents kit numbers 519282 and 519101 as being dispensed 3/19/07 but the Drug Summary Log dated 4/29/08 documents kit number 519101 as not dispensed. Additionally, Drug Labels forms fail to document the label for kit number 519101 and the study participant number for kit number 519282.



## WL 20Sep10 to a University-Based PI

Protocol [REDACTED] specified that study drugs were to be prepared by the pharmacist or designee who was trained in the safe handling and administration of a cytotoxic agent.

The Infusion Preparation Log for participant 040-001 documents that study drugs were prepared on March 24, March 27, March 31, and April 3, 2009, by an individual identified only by the initials [REDACTED]. There was no documentation in the study records that [REDACTED] was the pharmacist or designee, or that [REDACTED] had been trained in the safe handling and/or administration of a cytotoxic agent.



## WL 10Aug09 to a Pharmaceutical Sponsor Firm

- Study Monitors failed to identify deficiencies in drug accountability: for Study [REDACTED] at Site #551, study documents contained conflicting information regarding accountability of the drug.
- When [REDACTED] and Drug Accountability Form source document worksheets were compared, it appears that on multiple occasions, the same kit vial was recorded as having been given to more than one participant, and/or on more than one occasion to the same participant, or the recorded kit vial information was incomplete.
- [Numerous specific examples followed, with dates.]



## Getting You Credit

**We appreciate your review of this module.**

To achieve credit for having done so, please complete the corresponding quiz provided in the CPD system.

You will receive a certificate of completion when your quiz is satisfactorily passed (score >80%).



# Sponsor Responsibilities and Obligations in Clinical Research Studies with Sponsor-Investigators

**For Investigator-initiated study researchers at the University of Cincinnati**

IND/IDE Assistance Program, UC  
May 2011



## Agenda

- Investigator-Initiated Research when the Investigator is also the (Regulatory) Sponsor
- Responsibilities of Study Sponsors
- Regulations and Guidelines Governing Human Research Studies
- UC Policies and Procedures for Human Subjects Research
- Sponsor-Investigator's Standard Operating Procedures
- Data and Safety Monitoring Board
- Sponsor Obligations
- Sponsor Obligations of IND or IDE Holders
- Developing a Case Report Form (If any)
- Investigator/Site Selection
- The Investigational Product: Information and Control
- Monitoring and Auditing

2



## Investigator - Initiated Research

- The leader of the research at a site is the Principal Investigator of the study.
    - PIs have defined responsibilities and obligations.
  - The PI of Investigator-initiated research also has the role of Sponsor, in the Regulatory sense of the term.
    - “Sponsor” is often confusingly used to designate the source of a study’s funding, both Governmental and Industry.
- UC has determined that the University will not be a study Sponsor. Of any human research study. However individual faculty members are the Sponsor, when they become Sponsor-Investigators.



## Sponsor-Investigator

- An individual who both initiates and conducts an investigation, under whose immediate direction the investigational drug or investigational device are administered or dispensed.
- If the study is occurring at multiple sites, the Sponsor-Investigator may simultaneously be the PI of his/her own site, and the Sponsor of the PI(s) at the other site(s).
- If the study is occurring at one or multiple sites including the Sponsor-Investigator’s institution but not under his/her supervision there, then the individual is the study Sponsor **but is not also a Sponsor-Investigator.**



## Three Roles is One Too Many: Manufacturer, Sponsor and Principal Investigator

- With one person in all three roles: manufacturer of the Investigational Product (drug or device) for a research study, Sponsor of the study *AND* Principal Investigator of that same study, the avoidance of bias becomes too difficult and conflicts of interest become too great.
  - If a researcher is the Manufacturer and Sponsor, someone else should be the PI.
  - If a researcher is a Sponsor-Investigator, someone else should have manufactured the product.
  - **In no case should the same individual be the manufacturer and also the PI of a UC human research study involving the product that he/she produced.**



## Aspects of a Clinical Research Study that Belong to the Sponsor

- Study Design.
- Protocol Authorship.
- Investigator and Site Selection (Selection of one's own self at one's own site included).
- Provision and control of the Investigational Product(s), if any.
- Overall management of study conduct.
- The study Quality Assurance (QA) and Quality Control (QC) programs.
- Notifications of regulatory authorities.
- Confirming that IRB notifications and reviews occur as needed.
- Study data ownership.
- For applicable studies, IND or IDE holder.





## Requirements for Drug Sponsors: US FDA 21 CFR 312

Device studies in 21 CFR 812

### 312.20 Requirement for an IND

- Sponsor shall submit an IND to FDA if the planned study involves an IP that is subject to section 505 of the Federal Food, Drug and Cosmetics Act or to the licensing provisions of the Public Health Services Act.
- Sponsor will not begin the study until the IND is in effect.
- Sponsor will submit a separate IND for any study that is to run under the rules for exception from obtaining informed consent of the participants under the conditions of emergency research.

7



## Requirements for Drug Sponsors: US FDA 21 CFR 312

### 312.32 Review of Safety Information

- Sponsor will receive safety reports from the study Principal Investigator(s).
  - Adverse Events (AEs), Suspected Adverse Reactions (SARs).
  - Adverse Reactions (ARs).
  - Unexpected AEs, Unexpected SARs.
  - Unexpected ARs.
- Sponsor may also receive safety information from other sources (foreign or domestic).

8



## Requirements for Drug Sponsors: US FDA 21 CFR 312

### 312.32 Review of Safety Information (and Safety Reports)

- Sponsor must promptly review all information relevant to the safety of the drug obtained or received.
- Sponsor must notify FDA and all participating Investigators, in an IND Safety report, of potential serious risks; notification on established timelines.
  - Sponsor will include in each IND safety report, identification of all previously submitted IND safety reports concerning a similar suspected adverse reaction must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

9



## Requirements for Drug Sponsors: US FDA 21 CFR 312

### 312.50 General Responsibilities

- Selecting qualified Investigators.
- Providing them with the information they need to conduct the trial properly.
- Assuring proper (compliance) monitoring.
- Ensuring that the study is conducted in accordance with the protocol/investigational plan contained in the IND.
- Maintaining an effective IND.
- Assuring that all Investigators and the U.S. FDA are informed about significant new adverse effects or risks with respect to the drug.

10



## Requirements for Drug Sponsors: US FDA 21 CFR 312

- 312.52 Transfer of obligations to a contract research organization.
- 312.53 Selecting Investigators and monitors.
- 312.54 Emergency research under 50.24 of this chapter [exception from informed consent]
- 312.55 Informing Investigators [Investigator Brochure that conforms to 312.23(a)(5), new safety information]

11



## Requirements for Drug Sponsors: US FDA 21 CFR 312

- 312.56 Review of ongoing investigations conducted under the Sponsor's IND. The Sponsor is to:
  - Monitor the progress of all clinical investigations.
  - On discovery of non-compliance by an Investigator: promptly secure compliance or cease drug shipments to the Investigator, end that Investigator's participation in the study, and require the remaining investigational product to be disposed of or returned. Sponsor must notify FDA.
  - Review and evaluate safety and efficacy data as the data are flowing to the Sponsor from the PI(s).

12



## Requirements for Drug Sponsors: US FDA 21 CFR 312

312.56 Review of ongoing investigations conducted under the Sponsor's IND. The Sponsor is to:

- Make at least annual progress reports to FDA, but importantly also safety reports as AEs qualifying for shorter notification timelines become incurred.
- Discontinue the study if so led by the data to conclude that an unreasonable and significant risk to participants is present with use of the investigational product,
  - Study discontinuation requires the Sponsor to: **notify** all IRBs involved, all PIs who at any time have participated in the study, the FDA, **assure** removal of the investigational product from all Investigator site(s) and **send a full report** of all actions taken that follow the notification of study discontinuation to FDA.

13



## Requirements for Drug Sponsors: US FDA 21 CFR 312

312.57 Recordkeeping and record retention.

Sponsor shall maintain:

- Adequate and accurate records of receipt, shipment and disposition. Include name of PI to whom shipped, date, quantity, and batch or code mark of each shipment.
- Complete and accurate financial interest records including payments to PIs and financial interests the PIs have.  
(See 21 CFR 54.4 (a)).

14



## Requirements for Drug Sponsors: US FDA 21 CFR 312

### 312.57 Recordkeeping and record retention.

Sponsor shall maintain:

- Records will be kept until 2 years after the drug is approved for marketing, or, if the marketing application is not approved, until 2 years after the shipment/delivery of the drug is discontinued and the FDA is so notified.
- Reserve samples of test articles and reference standards identified or used in any of the bioequivalence or bioavailability studies conducted. Sponsor shall release the reserve samples to FDA on request (see 21 CFR 320.38).

15



## Requirements for Drug Sponsors: US FDA 21 CFR 312

### 312.58 Inspection of Sponsor's records and reports

[Sponsor shall allow FDA to inspect, permit access to review, copy and verify and on request shall submit records or reports, or copies of them, to FDA. Additional requirements if the product is a controlled substance.]

### 312.59 Disposition of unused supply of investigational drug [Sponsor shall assure return of unused supply from each PI: alternatives that assure no exposure of humans to risks from the drug are allowed.]

16



## Requirements for **Device** Sponsors: US FDA 21 CFR 812

### 812.40 General Responsibilities

- Selecting qualified Investigators, providing them with the information they need to conduct the trial properly, assuring proper monitoring, ensure that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation [study].

812.42 IRB and FDA approval before beginning an investigation or [new, revised] part of one.

812.43 Selecting Investigators and monitors.

812.45 Informing Investigators: investigational plan and report of prior investigations of the device *[Drug IB counterpart]*.

17



## Requirements for **Device** Sponsors: US FDA 21 CFR 812

### 812.46 Monitoring Investigations

- A Sponsor who discovers an Investigator is not in compliance: Sponsor must promptly secure compliance or discontinue device shipment to that Investigator and terminate that Investigator's participation in the study.

Sponsor will require disposal or return of the devices unless doing so would jeopardize the rights, safety or welfare of a participant.

18



## Requirements for **Device** Sponsors: US FDA 21 CFR 812

### 812.46 Monitoring Investigations

- Sponsor shall immediately conduct an investigation of any unanticipated adverse device effect.
  - If the effect is determined to present an unreasonable risk to participants, the Sponsor shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur **no later than 5 working days** after the Sponsor makes this determination and **not later than 15 days** after the Sponsor receives first notice of the effect.
  - Once terminated a study or the part of a study cannot be resumed until IRB approval is granted. In some instances FDA approval is also needed, see 21 CFR 812.47(b and c).

19



## Requirements for **Device** Sponsors: US FDA 21 CFR 812

### 812.47 Emergency research under 21 CFR 50.24 [exception from informed consent]

812.140 (b) Sponsor Records A Sponsor shall maintain the following accurate, complete and current records relating to an investigation:

- All correspondence with another sponsor, a monitor, an investigator, an IRB or FDA, including required reports.

20



## Requirements for **Device** Sponsors: US FDA 21 CFR 812

812.47 Emergency research under 21 CFR 50.24  
[exception from informed consent]

812.140 (b) Sponsor Records A Sponsor shall maintain the following accurate, complete and current records relating to an investigation:

- Device shipment and disposition, which shall include name and address of the consignee, type and quantity of the device, shipment date, and batch number or code mark.
- Also shall describe the batch number or code marks of any devices returned to the sponsor, repaired or disposed of in other ways by the investigator or another person with the reasons for and method of disposal.

21



## Requirements for **Device** Sponsors: US FDA 21 CFR 812

812.140 (b) Sponsor Records A Sponsor shall maintain the following accurate, complete and current records relating to an investigation:

- Signed investigator agreements including financial disclosure information in accordance with 21 CFR 54.
- For devices studies without an IDE that are not significant risk devices, other specifics. Detailed in 21 CFR 812.140 (b) (4) (i-vi).
- Adverse device effects, both anticipated and unanticipated) and complaints.
- Any other records that FDA requires.

22



## Requirements for Device Sponsors: US FDA 21 CFR 812

### 812.145 Inspections

- Sponsor (or Investigator) will permit authorized FDA employees to enter and inspect any establishment where devices are held, including manufactured, processed, packed, installed, used, or implanted or where records from use of devices are kept. Inspection includes copying.

23



## Requirements for Device Sponsors: US FDA 21 CFR 812

### 812.150 Reports

- Sponsor shall prepare and submit complete, accurate and timely reports of:
  - Unanticipated adverse device effects;
  - Withdrawal of IRB approval [to FDA, all PIs and other approving IRBs];
  - Withdrawal of FDA approval [to all PIs and approving IRBs];
  - Current Investigator list;
  - Progress reports at regular intervals at least yearly;
  - Recall and device disposition;
  - Notification to FDA of study completion or termination within 30 working days;

24



## Requirements for Device Sponsors: US FDA 21 CFR 812

### 812.150 Reports

- Sponsor shall prepare and submit complete, accurate and timely reports of:
  - Final report;
  - Any use of device without informed consent [to FDA within 30 working days];
  - Determination by any approving IRB that a device the Sponsor thought was a non-significant risk device was a significant risk device.
- FDA and any reviewing IRB can request that the Sponsor for information about any aspect of the investigation and the Sponsor shall provide the requested information.

25



## Requirements for Sponsors from ICH E6 GCPs

(Drug and Device studies)

- 5.1 Quality Assurance (QA) and Quality Control (QC):
- 5.2 Contract Research Organization (CRO)  
[If used]
- 5.3 Medical Expertise
- 5.4 Trial Design
- 5.5 Trial Management, Data Handling, Recordkeeping,  
and if needed, Independent Data Monitoring  
Committee [a.k.a. DSMB]
- 5.6 Investigator Selection
- 5.7 Allocation of Duties and Functions
- 5.8 Compensation to Subjects and Investigators
- 5.9 Financing

26



## Requirements for Sponsors from ICH E6 GCPs

- 5.10 Notification/Submission to Regulatory Authority(ies)
- 5.11 Confirmation of Review by IRB/IEC
- 5.12 Information on Investigational Product(s)
- 5.13 Manufacturing, Packaging, Labeling and Coding Investigational Product(s)
- 5.14 Supplying and Handling Investigational Product(s)
- 5.15 Record Access
- 5.16 Safety Information
- 5.17 Adverse Drug Reaction Reporting
- 5.18 Monitoring [of the study conduct, is QC]

27



## Requirements for Sponsors: ICH E6 GCPs

- 5.19 Audit [QA]
- 5.20 Noncompliance [actions to be taken when the PI is not compliant]
- 5.21 Premature Termination or Suspension of a Trial
- 5.22 Clinical Trial/Study Reports [Interim if any and Final]
- 5.23 Multicenter Trials [as applicable]

28



## FDA Guidance Documents and Information Sheets of Interest to Sponsors

Examples of guidance information made available on the U.S. FDA web site. [www.fda.gov](http://www.fda.gov)

- Drug Study Designs
- The Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors
- Monitoring Clinical Investigations
- Submitting and Reviewing Complete Responses to Clinical Holds
- Collection of Race and Ethnicity Data in Clinical Trials
- Bioanalytical Method Validation
- Computerized Systems Used in Clinical Investigations
- Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions – Statement of Investigator (Form FDA 1572)

29



## UC Policies and Procedures

From UC Research Policy VI.01  
“Research Unit Standard Operating  
Procedures in Clinical Human  
Subjects Research”

### Definition of Sponsor-Investigator

1. Is an individual who both initiates and conducts an investigation, under whose immediate direction the investigational drug or investigational device are administered or dispensed. The term does not include any “person” other than the individual. The Sponsor/Investigator complies with all the obligations of both a Sponsor and an investigator under 21 CFR 312 Subpart D or 21 CFR 812 Subparts C and E **when there is no corporation, agency, academic institution, or other organization serving as the Sponsor.**

*The University of Cincinnati will not serve as Sponsor for any human subjects research, per Policy III.02 “Review by the Institutional Review Board of Human Subjects Research”.*

30



## UC Policies and Procedures

From UC Research Policy VI.01  
"Research Unit Standard  
Operating Procedures in Clinical  
Human Subjects Research"

2. Any UC researcher who acts as a Sponsor-Investigator in an IND/IDE context will adopt the IND/IDE Assistance Program template SOPs for all aspects of the clinical trial(s) (aspects indicated in 21 CFR 312 and 21 CFR 812.)

31



## UC Policies and Procedures

A Sponsor-Investigator will have SOPs which will:

- Be used in day-to-day functioning of the researchers and departments of UC to assure subject safety and protocol/regulatory compliance.
- Be utilized to help assure data integrity.
- Be the basis for educating new people on the conduct of human subjects research.
- Include the name of the clinical research unit, an adoption date, and bear the signature of a person within the organization, designated by the department and/or practice corporation, with responsibility for compliance in the area of human subjects research.

32

## UC Policies and Procedures

A Sponsor-Investigator will have SOPs which will:

- Be used to guide regulatory agency inspectors, sponsor company monitors and auditors, and UC oversight staff as they examine and evaluate the conduct of human subjects' research.
- Be reviewed annually in the Office of Research Compliance to assure they accurately reflect (current) research processes within UC.
- Have an official, record copy maintained at the Research Unit Administration office or designated area.

33

## UC Policies and Procedures

From UC Research Policy VI.01  
"Research Unit Standard Operating  
Procedures in Clinical Human  
Subjects Research"

- UC Research Policies are available on line. Follow the Human Research Protection link on the IRB page, at <http://researchcompliance.uc.edu/irb/default.html>

### Records of Training on the SOPs

- Each research unit shall maintain records demonstrating that all persons engaged in human subject research are appropriately trained in [the unit's] SOPs.

34

# Clinical Research SOPs

Academic Health Center > HRP\_Policies

## HRP\_Policies

Home

View All Site Content

### Documents

- Shared Documents
- HRP Policies
- IRB Procedures
- Good Clinical Practice SOP Templates
- Sponsor-Investigator SOPs**

### Pictures

Lists

### HRP Policies

Type	Name
Folder	VII - QUALITY ASSURANCE, LEGAL AND COMPLIANCE
Folder	VI - CLINICAL RESEARCH
Folder	IV - INVESTIGATOR RESPONSIBILITIES
Folder	III - IRB REVIEW
Folder	II - CONDUCT OF RESEARCH
Folder	I - AUTHORITY AND INSTITUTIONAL COMMITMENT
Folder	V - VULNERABLE POPULATION

**Link to the SOPs for Sponsor-Investigator**

35

# Clinical Research SOPs

## HRP\_Policies

Home



HRP\_Policies > Sponsor-Investigator SOPs

### Sponsor-Investigator SOPs

View All Site Content

### Documents

- Shared Documents
- HRP Policies
- IRB Procedures
- Good Clinical Practice SOP Templates
- Sponsor-Investigator SOPs**

### Pictures

Lists

Actions

Type	Name
Folder	Administration
Folder	FDA
Folder	FORMS FOR MONITORING
Folder	Monitoring
Folder	Regulatory

These folders contain template documents in the indicated areas



## Clinical Research SOPs

The SOPs provided include the following examples:

- ADM 002 Sponsor/Investigator Study File Management
- ADM 004 Unanticipated Adverse Drug/Device Effect Reporting (UADE)
- ADM 005 Protocol Deviation Reporting
- ADM 007 Preparing Source Documentation Worksheets for Sites
  
- MON 001 Selection and Training of Monitors
- MON 002 Pre-Qualification Monitoring Visit
- MON 003 Site Initiation Visit
- MON 004 Interim Monitoring Visit
- MON 005 Close-Out Monitoring Visit
  
- FDA 001 Inspection of the Clinical Site

37



## DSMB: Data and Safety Monitoring Board

- A DSMB is not required for all human research studies conducted by Sponsor-Investigators. Complex studies with higher levels of subject risk benefit from the independent oversight provided by such committees.
- A DSMB is independent of the study team and ongoing study conduct. The DSMB is part of the human safety program for the study.
  - The PI, Co-Is and sub-Is on a study cannot be members of the DSMB for their own study.

38

## DSMB: Data and Safety Monitoring Board

- It is the Sponsor who indicates in the protocol if the study will have a DSMB, and if so, what the DSMB composition is to be.
  - How many members, what expertise or background each member is to have.
- The IRB may require that a particular study have a DSMB when the Sponsor has not programmed one, if the IRB sees the need.
- DSMB members review study data, adverse events and other study events, according to the DSMB Charter that the Sponsor prepares and according to the IRB-approved study protocol requirements.
  - The DSMB makes recommendations whether the study should continue or be amended in ways the DSMB defines, to maintain an appropriate level of subject safety.
  - A DSMB can also recommend that a study stop.

39

## DSMB: Data and Safety Monitoring Board

- The frequency of DSMB meetings is expressed in the DSMB Charter and may also be found in general terms in the study protocol.
- Sometimes a DSMB is constituted before the protocol is in final form and the DSMB is asked to input to the protocol itself.
  - In such a study, the DSMB Charter will pre-date the IRB approved protocol that describes the DSMB.

40

## DSMB: Data and Safety Monitoring Board

- Sponsor files of the study should include:
  - The nomination of and acceptance by each member to serve on the DSMB.
  - Identification of the DSMB Chair and a description of how selected.
  - Minutes of the meetings and a report of each meeting.
  - Correspondence with the PI concerning the meeting and the results (if the PI and the Sponsor are not the same person).
  - If replacement of a member or the Chair becomes needed, when replacement occurred, and with whom (identification of the replacement and his/her credentials).

41

## Reports that UC Requires Sponsor-Investigators to Make

- Unanticipated Adverse Drug/Device Effects – to FDA, all reviewing IRBs and all [additional] PIs.
- Withdrawal of IRB Approval (of the whole study, or of any part of a study) – to FDA.
- Withdrawal of FDA Approval – to reviewing IRB(s).
- Current List of Investigators every 6 months – to FDA.
- Progress reports (annual reports, continuing review reports) – to all reviewing IRBs.
- Annual report - to FDA.
- Recalls and drug/device disposition – request made to any PI to return or repair or dispose of any unit of an investigational drug/device - to FDA and all reviewing IRBs. With 30 working days of the request and include why the request to the PIs was made.

42

## Reports that UC Requires Sponsor-Investigators to Make

- Study Completion and Final Report - to FDA and all reviewing IRBs: study completion notice within 30 working days of completion or termination of the investigation. Final report to FDA and all reviewing IRBs within 6 months after completion or termination.
- Use of Drug/Device Without Informed Consent – to FDA within 5 working days after receipt of notice of such use, to IRB within 10 days (within 5 days if study is at the VA).
- Significant Risk Device Determination by the IRB, when Sponsor-Investigator had proposed the drug/device as an insignificant risk device – to FDA within 5 working days after the Sponsor-Investigator learns of the IRB's determination.
- Other Reports – To FDA or an individual reviewing IRB, as requested by the FDA or IRB.

43

## Report of Study Data by the PI to the Sponsor: The Case Report Forms

- Case Report Forms (CRFs) are not mandatory, but for many studies are useful. A CRF is a set of documents employed when study data from the PI's source records must be transported to the Sponsor's data entry people for the population of a study database.
- If used, CRFs must include all of the study data needed to perform the protocol-required analyses.
- Development of the CRF for a study is a Sponsor responsibility. Biostatistical input to CRF design is strongly recommended.
  - Intelligent design of a CRF can make the difference between rapid database building with little time taken for queries, and a difficult, drawn-out process with much correspondence between the site and Data Management personnel being needed.

44

## Report of Study Data by the PI to the Sponsor: The Case Report Forms

- Data-entry friendly CRFs are often shorter in number of pages but more difficult for site personnel to complete correctly and inefficient to use.
- CRFs arranged in the temporal flow of the study are often longer in terms of number of pages, but are often more rapidly and correctly filled out at the Investigator site.

45

## Study Files Differ by Role

- There are files the Sponsor must have, and files the Investigator(s) on a study must have. These are not duplicates of each other. Examples:
  - Sponsors do not often communicate directly with IRBs. PIs and their delegated Team members do.
  - PIs on an FDA-regulated study do not often communicate directly with a Regulatory Authority (such as US FDA) – the Sponsor does.
- Study files kept by a PI are the Investigator's Site File (ISF).
- Study files kept by a Sponsor are the Trial Master File (TMF).

46

## Study Files Differ by Role

- Sponsor-Investigators like to combine the ISF and the TMF for avoidance of duplication. However this is not a best practice.
- At UC, separation of the TMF and ISF has been deemed desirable.
  - Different drawers of the same filing cabinet is sufficient as long as each file is distinct and complete.
- It seems more efficient to make one all-encompassing file. However upon inspection if it is the ISF that is asked for, giving access to the TMF documents as well can unnecessarily lengthen and complicate the inspection.

47

## A Sponsor-Investigator's Staff Members May Have Dual Roles

- Study Coordinators who work at Investigator sites have tasks that the PI delegates to them. Coordinators should be knowledgeable of regulatory requirements for Investigators and sites.
- Sponsors have project management staff who are assigned to a project by their managers. Sponsor study staff should be knowledgeable of regulatory requirements of Sponsors.
- Study Coordinators who work with Sponsor-Investigators often are asked to do both, site duties and project management staff duties.
  - The tasks and needs of Sponsor study management may be unfamiliar to persons whose experience is as research nurses or Investigator site study coordinators.
  - Training of Sponsor staff is a Sponsor responsibility.

48

## Quality Control (QC ) and Quality Assurance (QA) for a Research Study:

- QC: Study team internal Quality Control
  - Completeness of the research records.
  - Accuracy of any transcriptions into summaries and reports.
  - QC activities are to be documented in the study conduct records.
- QC: Study Conduct Monitoring
  - Defined and arranged for by the study Sponsor ( or by the Sponsor-Investigator, if that is who the study has in total charge).
  - Done by an individual who works for the Sponsor (not the PI's delegation of duties log).
  - Correspondence and a signed log of monitoring activity will be in the PI's regulatory binder; reports of monitoring visits will be in the Sponsor's Trial Master File.

49

## Quality Control (QC ) and Quality Assurance (QA) for a Research Study:

- QA: Internal Audit by and for UC
  - Done by an individual who is independent of the study team and study conduct.
- QA: Sponsor audit at their discretion
  - With Sponsor-Investigators, the Sponsor auditor can be internal or external to UC, depending on how the Sponsor chooses to source the audit function, and whether the UC SI has a Corporate partner.

50

## UC Policies on Human Subject Research

- UC has made the University's research policies available in the Human Research Protection area of the University web site, at

[http://ahc-sharepoint.uc.edu/hrp\\_policies/HRP%20Policies/Forms/AllItems.aspx](http://ahc-sharepoint.uc.edu/hrp_policies/HRP%20Policies/Forms/AllItems.aspx)

- To the left on the UC home page, choose Research. Then choose Research Compliance on the left under Research Offices. That will lead to the ORCRA page. Choose HRP, then choose Research Policies.
- The policies are grouped topically into seven electronic folders.
- A Policy of particular relevance for Sponsor-Investigators is: Required Elements of Contracts, Protocol and/or Consent Agreements for the Performance of Human Subject Research (VII.04)

51

## UC Policies on Human Subject Research

The screenshot shows a SharePoint site for 'HRP\_Policies'. The breadcrumb trail is 'HRP\_Policies > HRP Policies'. The main heading is 'HRP Policies'. On the left, there is a navigation pane with sections for 'Documents' (Shared Documents, HRP Policies, IRB Procedures, Good Clinical Practice SOP Templates, Sponsor-Investigator SOPs) and 'Pictures'. The main content area displays a list of folders:

Type	Name
Folder	I - AUTHORITY AND INSTITUTIONAL COMMITMENT
Folder	II - CONDUCT OF RESEARCH
Folder	III - IRB REVIEW
Folder	IV - INVESTIGATOR RESPONSIBILITIES
Folder	V - VULNERABLE POPULATION
Folder	VI - CLINICAL RESEARCH
Folder	VII - QUALITY ASSURANCE, LEGAL AND COMPLIANCE

## AAHRPP Accreditation Standards: More Applicable to Investigators than to Sponsors



- Association for the Accreditation of Human Research Protection Programs
  - UC holds full accreditation (there are other types).
- Emphasis is on Protection of Research Participants
  - Sponsor's role in human subject protection is indirect: the Sponsor has written a protocol that the IRB approves of, with appropriate definition of the intended subject population for the study.
- AAHRPP Domains
  - The Organization
  - Institutional Review Board or Ethics Committee
  - Researcher and Research Staff
  - No domain for Sponsor

53

## Sponsor-Investigators Involved with IND Research: the Investigational Product is a Drug or Biologic



- An Investigational New Drug Application (IND) is a request for Food and Drug Administration (FDA) authorization to administer an investigational drug to humans.
- Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved new drug application.
  - Request is made using Form FDA 1571.
- Upon receipt of the IND by FDA, an IND number will be assigned and the application forwarded to the appropriate reviewing division.

54



## Sponsor-Investigators Involved with IND Research: the Investigational Product is a Drug or Biologic

- The reviewing division will send a letter to the Sponsor-Investigator providing:
  - Notification of the IND number assigned.
  - Date of receipt of the original application.
  - Address where future submissions to the IND should be sent.
  - Name and telephone number of the FDA person to whom questions about the application should be directed.
- **Studies shall not be initiated until 30 days after the date of FDA receipt of the IND** unless earlier notification from FDA is received that studies may begin.

55



## Sponsor-Investigators Involved with IND Research: the Investigational Product is a Drug or Biologic

Form FDA 1571 is used for multiple purposes:

- Initial Submission
- Protocol Amendments
  - New Protocol
  - Change in Protocol
  - New Investigator
- Information Amendments
  - Chemistry/Microbiology
  - Pharmacology/Toxicology
  - Clinical
- IND Safety reports
  - Initial
  - Follow-up
- Response to Clinical Hold
- Response to FDA Request for Information
- Annual Report
- General Correspondence
- Request for Reinstatement of IND that is withdrawn, inactivated, terminated or discontinued
- Other as specified by the Sponsor

56



## Sponsor-Investigators Involved with IDE Research: the Investigational Product is a Medical Device

- An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to FDA.
  - Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(k)'s require clinical data to support the application.

57



## Sponsor-Investigators Involved with IDE Research: the Investigational Product is a Medical Device

- Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices.
- All clinical evaluations of investigational devices, unless exempt, must have an approved IDE **before** the study is initiated.

58



## Sponsor-Investigators Involved with IDE Research: the Investigational Product is a Medical Device

- An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (Act) that would apply to devices in commercial distribution.
- Sponsors need not submit a PMA or Premarket Notification 510(k), register their establishment, or list the device while the device is under investigation.
- Sponsors of IDEs are also exempt from the Quality System (QS) Regulation except for the requirements for design control.

59



## Sponsor-Investigators Involved with IDE Research: the Investigational Product is a Medical Device

- Clinical evaluation of devices that have not been cleared for marketing requires the following:
  - An IDE approved by an institutional review board (IRB).  
If the study involves a significant risk device, the IDE must also be approved by FDA.
  - Informed consent from all participants.
  - Labeling for investigational use only.
  - Monitoring of the study.
  - Required records and reports.
- Note Forms FDA 1571 and 1572 do not apply.

Extensive “Device Advice” is  
given at [www.FDA.gov](http://www.FDA.gov)

60

## Labeling, Coding and Investigational Product (IP) Information

- It is the Sponsor who provides Investigators with the investigational product that is packaged or re-packaged in a manner suitable for use in the study. Examples:
  - Product manufactured only for investigational (controlled study) use, not a trade product (yet).
  - Blinded product with matching placebo, e.g. over encapsulated trade product, with labeling as required by regulations and guidelines, no package inserts *per se*.
  - Marketed (Trade) drug or devices with the labeling and package inserts used in the trade may be provided as comparators in open label studies.

61

## Labeling, Coding and Investigational Product (IP) Information

- Assure that the established expiration dates are observed. The site should but is allowed not to receive the dates. It is the Sponsor who must be vigilant and replace supplies lot for lot when the established expiration date as the Sponsor knows it draws near.
  - The Sponsor is running stability studies on new products and formulations, and knows what the expiry date is.
  - It is better if the site receives the expiry date on the shipping documents, so they may be alert for when the need for replacement with fresh product is approaching, relative to dispensing for particular subjects and time to next site visit.

62



## Labeling, Coding and Investigational Product (IP) Information

- Packages of non-trade product
  - Will identify the drug by name unless the study is double-blind.
  - Will state that the material is for Investigational use only.
  - May or may not have an individual unit (box, bottle or carton) code on them.
- Double-blind trials with controlled dispensing of active vs. placebo will commonly use individual package codes labeled “*DrugName* or Placebo” or similar, with the site instructed at each dispensing occasion as to which individually-coded cartons or boxes to give to that participant.

63



## Labeling, Coding and Investigational Product (IP) Information

- For drugs and biologics, there is an Investigator’s Brochure (IB) prepared by the Sponsor or may be obtained from Corporate collaborators.
- For devices, there is an analogous document that provides Investigators with information on previous testing of the device. When the study is on an approved, marketed device, the package insert and device labeling are used.

64



## UC Policy on Investigational Products

From UC Research Policy VI.02  
"Supplying and Handling  
Investigational Products in  
Human Subjects Research"

- The Sponsor provides the PI(s) with assurance that the manufacture and formulation of the investigational product comply with federal regulations.
  - This includes labeling.

65



## Control of Investigational Products

- The Sponsor is responsible for control from release upon manufacture through arrival at the Investigator's site.
- At the site the PI is responsible for controlled, limited access storage of the investigational products.
  - A PI may enlist his/her site Investigational Pharmacy to provide their facilities and support for the study.
  - When the PI must hold and store the IP, the PI and team must be able to provide a suitable limited access storage location, a monitored and documented storage unit in the appropriate temperature range.

66

## Control of Investigational Products

- At the site, the PI is responsible for controlled, limited access storage of the investigational products.
  - Accountability runs from each receipt through pre-dispensing storage, dispensing to subjects/LARs, storage of returned products, unused products past expiry that cannot be dispensed, and eventual disposition of supplies at or before the end of the study.
  - The Sponsor should assure that no IP remains at a PI site when the study closes at that site.

67

## Study Registration at *ClinicalTrials.gov*

- ClinicalTrials.gov is a registry of federally and privately supported clinical trials conducted in the United States and around the world.
- The Food and Drug Administration Amendments Act of 2007 (FDAAA or US Public Law 110-85) was passed on September 27, 2007. The law requires mandatory registration and results reporting for certain clinical trials of drugs, biologics, and devices. *In order to publish the results of a study, that study must be registered on the ClinicalTrials.gov web-site before subject enrollment begins.*
  - Late registration equals the Sponsor doesn't get to publish.

68



## Study Registration at *ClinicalTrials.gov*

- A trial must be approved by a human subject review board and must conform to the regulations of the appropriate national health authorities, in order to be registered.
- It is a Sponsor responsibility to register the study.
- More information at <http://prsinfo.clinicaltrials.gov/fdaaa.html>

69



## Clinical Study Essential Documents

- Essential Documents is a term used in ICH-GCPs to mean the minimum collection of documentation needed to support the results of a human research study.
  - The list is broken into three categories of documents, those generated:
    - Before the first participant begins study participation.
    - During the in-clinic portion of the study (including updates of documents in the first category).
    - Before site closure but after the in-clinic portion of the study concludes.

70



## Clinical Study Essential Documents

- The document types in all three categories are marked to indicate which should be with the Investigator and/or with the Sponsor.
  - Some documents are to be in both sets of files, Investigator's ISF and Sponsor's TMF.

71



## Study Monitoring

- All PI sites in the study are monitored.
- Selection of who will monitor is up to the Sponsor. The person or team engaged must be trained and qualified to do such work.
- Scope and frequency of study conduct monitoring are decided by the Sponsor.

72

## Study Monitoring

- Scope and frequency of study conduct monitoring are decided by the Sponsor.
  - 100% of the Regulatory Binder and all CRFs is possible, but time-consuming.
  - Subject eligibility, informed consent, key efficacy and safety data at 100% and sampling of the rest of the CRF is often what's done.
    - The onus is on each PI and study team to spread their learnings from monitoring to the unmonitored portion of the study.
      - Check the unmonitored data for those omissions and issues that are discovered in the data that are monitored.
  - Records of screen failures should be included, at minimum the informed consents and documented reasons for not being enrolled.

73

## Study Monitoring

- A Monitoring Plan which defines what the Monitor is to do and approximately how often, is written and approved by the Sponsor.
- Qualification and initiation visits pre-date Subject enrollment.
- Timing of interim monitoring visits is best to be flexible, as derived from recruitment and enrollment activity.

74

## Study Monitoring

- The monitoring close-out visit marks cessation of study activity at that site.
  - Monitoring close-out typically precedes cessation of IRB oversight, but no further study conduct is expected after Monitoring close.
- The site may have monitoring close-out follow-up activity, then has closure with the IRB.
- Records of monitor selection, training on the protocol, and development of the Monitoring Plan are held in the Trial Master File (TMF).
- A log of the monitor's presence on site is held in the Investigator Site File (ISF), with copy migrating to the TMF when the site is closed.
  - Some Sponsors prefer to take the original log, but then must leave the PI with a copy.

75

## Study Monitoring

- A written report of each monitoring visit is made to the Sponsor in a follow-up letter. The actual report is filed in the TMF. The report includes:
  - Screening and enrolment status.
  - Informed consent form version used to obtain consent from screened and enrolled subjects.
  - Discrepancies found during source data verification of the Case Report Form.
  - Protocol, Manual of Procedures, and SOP deviations noted during review of study records.
  - Missing and/or outdated documents from/in the Investigator site file.
  - Missing source data or data review documentation.

76



## Study Monitoring

- Correspondence the Monitor has with the PI includes arranging each visit date, a notification letter, and a visit follow-up letter. Documentation is held in the ISF. The Sponsor is copied on both notification and follow-up letters, which reside in the TMF with the monitoring report of the visit. The report belongs to the Sponsor.
  - The follow-up letter focuses on study status and actions needed at the Investigator site.
  - The report includes any needed Sponsor actions or follow-up **and these are not in the follow-up letter to the PI.**

77



## Study Monitoring

- Note the Monitoring reports are not provided to the PI directly by the Monitor, and no Monitoring correspondence goes to other PIs in a multi-site study directly from the Monitor either.

78

## Auditing

- A sub-set of sites in a multi-site study is audited.
  - There is an expectation that the Sponsor will reapply learnings from the audited site to the sites that are not audited.
- Audits must be performed by a trained and qualified person who is not involved with study conduct.

## Auditing

- The best time to audit for maximum utility of the findings for the study is as follows:
  - No sooner than enrollment of the 3<sup>rd</sup> subject at the site.
  - During study enrollment, ideally at 25-50% of projected enrollment overall.
  - In a multi-site study with multiple sites to be audited if there are no events or trends of concern from any of the PIs, the first audit should occur early. Then time should be allowed for learnings from that audit to be assimilated, disseminated and incorporated at the other sites, in scheduling the subsequent audits.
    - This will allow the Sponsor to see if changes, revisions or updates from the first audit(s) have been put into effect at other sites of the study.

## Auditing

- When audit findings from one site are shared with other sites of a multisite study (such as in a study newsletter or Dear Investigator letter) do not identify that the news resulted from an audit and do not identify the audited site.
- Reports to an IRB as a result of an audit should not mention the audit or the auditor, either. “It was discovered, as a result we have done XYZ” kind of text is acceptable.
- The auditor does not sign a log for presence at the site as Monitors do.

81

## Auditing

- Audit correspondence in the ISF is a notification letter. If the Sponsor has opted, a ‘thank you’ letter is sent after the visit, which contains no findings but does document that an audit did actually occur.
- Sponsors have the option to share the audit reports with the audited PI. Audit reports should never be located in the ISF, however.
- Follow-up of audit findings from a PI site audit is the responsibility of the Sponsor and normally occurs through the assigned Monitor.
- Monitoring correspondence should never reflect the audit, or that any particular request to the site or matter for discussion between Monitor and site is occurring as a result of an audit.

82

## Auditing and Monitoring: Sponsor responsibilities supported by UC ORCRA programs

- Quality Assurance (Auditing) services are available to UC Sponsor-Investigators from the Post-Approval Marketing Program, Angela Braggs-Brown, Director.
  - A Sponsor-Investigator may have sufficient budget to hire an outside auditing consultant or firm to supply these services.
- Quality Control (Monitoring) services are not available from the IND/IDE Assistance Program at this time.
  - A **Sponsor-Investigator will need** to have sufficient budget available to hire an outside consultant or firm to supply these services.

## Getting You Credit

**We appreciate your review of this module.**

To achieve credit for having done so, please complete the corresponding quiz provided in the CPD system.

**You will receive a certificate of completion when your quiz is satisfactorily passed (score >80%).**

# Submissions and Reports per Federal Authority

**For Investigator-initiated  
Study Researchers the University of Cincinnati**

**IND/IDE Assistance Program, UC  
May 2011**



## Agenda

- Federal Authority
- Code of Federal Regulations
- Drugs and Biologics: the IND
- Exceptions: When an IND is Not Required
- IND Content and Format
- Form FDA 1571: Uses
- Medical Devices: the IDE
- Exceptions: When an IDE is Not Required
- IDE Content and Format
- The Treatment IDE
- FDA Reporting Requirements: Device Study Sponsors
- FDA-required Device Investigator Reports
- FDA Reporting Requirements: Drug Study Sponsors
- ICH E6 Reporting Requirements: Sponsors (Drug and Device)
- UC-Required Sponsor-Investigator Reports
- Financial Reports
- Study Registration at [clinicaltrials.gov](http://clinicaltrials.gov)

2

## Federal Authority

- In the United States, as with many other countries of the world, human subjects research is subject to laws. The laws in place give differing Federal agencies the authority to promulgate regulations by which research is properly conducted.
- Health and Human Services Office of Human Subject Protection
  - Through the Public Health Services Act
- Food and Drug Administration
  - Through the Federal Food, Drug & Cosmetics Act
- New drugs, biologic products and medical devices fall under the Food and Drug Administration (U.S. FDA).
  - Drugs in CDER: FDA Center for Drug Evaluation and Research
  - Biologics in CBER: FDA Center for Biologics Evaluation and Research
  - Devices in CDRH: FDA Center for Device and Radiologic Health

3

## Code of Federal Regulations

- The Code of Federal Regulations (CFR) is the codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the U.S. Federal government. CFR is divided into 50 titles that represent broad areas subject to Federal regulation. Each volume of the CFR is updated once each calendar year and is issued on a quarterly basis.
- The CFR is available over the Internet on [www.fda.gov](http://www.fda.gov) and [www.gpoaccess.gov](http://www.gpoaccess.gov)
- Individual titles or related groups of titles are often published in hard copy in pocket reference form, in individual books pertinent to a type of research or endeavor (preclinical, drug or device research, drug or device manufacturing).
- Department of Health and Human Services (DHHS) regulations are in Title 45 of the CFR.
- Food and Drug Administration regulations are in Title 21 of the CFR.

4



## Drugs and Biologics: the IND

21 CFR 312.20

- IND: Notice of Claimed Investigational Exemption for a New Drug
  - The exemption being from drug manufacturing laws and requirements, to allow an unapproved drug for human use in a controlled clinical trial be shipped in inter-State commerce.
- An IND is applicable for
  - New molecular entity – drug or biologic active not now approved and in the trade.
  - An approved drug or biologic product being studied for a new indication.
  - New dose form or strength version of an already approved drug or biologic.
- A Sponsor shall submit an IND to FDA if the Sponsor intends to conduct a clinical investigation with an investigational new product that is subject to section 505 of the Federal Food, Drug and Cosmetics Act or to the licensing portions of the Public Health Service Act.
- A sponsor shall submit an IND to FDA if the Sponsor intends to conduct a clinical investigation with an investigational new drug [that is not exempt per 312.2(b)].

5



## Requirement for an IND

21 CFR 312.20-22

- A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under 21 CFR 50.24. Such a clinical investigation is not permitted to proceed without the prior written authorization of the FDA.
  - FDA shall provide a written determination 30 days after FDA receives the IND or earlier.
- An IND may be submitted for one or more phases of an investigation...[Clinical development Phases 1, 2, 3].
- The amount of information on a particular drug that must be submitted in an IND to assure the accomplishment of the FDA's [stated objectives in 21 CFR 312.22(a)] depends on such factors as the novelty of the drug, the extent to which it has been studied previously, the known or suspected risks, and the developmental phase of the drug.

6

## Requirement for an IND

21 CFR 312.22

- The central focus of the initial IND submission should be on the general investigational plan and the protocols for specific human studies.
- Subsequent amendments to the IND that contain new or revised protocols should build logically on previous submissions and should be supported by additional information, including the results of animal toxicology studies or other human studies as appropriate.
- Annual reports to the IND should update the general investigational plan for the coming year.
- A sponsor shall not begin a clinical investigation subject to section 505 of the Federal Food, Drug and Cosmetics Act or to the licensing portions of the Public Health Service Act until the investigation is subject to an IND and the IND is in effect in accordance with 21 CFR 312.40.

7

## Requirement for an IND

21 CFR 312.22

- A sponsor-investigator who uses, as a research tool, an investigational new drug that is already subject to a manufacturer's IND or marketing application should follow the same general format.
  - Ordinarily may, if authorized by the manufacturer, refer to the manufacturer's IND or marketing application in providing the technical information supporting the proposed clinical investigation. **The package insert may be referenced.**
- Sponsor-investigators who use an investigational drug not subject to a manufacturer's IND or marketing application are ordinarily required to submit all technical information supporting the IND, unless such information may be referenced from the scientific literature.

**IND is drug and biologic: IND does not apply to devices. The corresponding filing for devices is an IDE (see Slide # 18ff).**

8

## Exceptions: when an IND is Not Required

- A clinical investigation of a marketed drug product does not require submission of an IND if **all six** of the following conditions are met concerning the study:
  1. Not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling of the drug.
  2. Not intended to support a significant change in the advertising for the product.
  3. Does not involve a route of administration or dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
  4. Conducted in compliance with the requirements for informed consent and IRB review (see 21 CFR parts 50 and 56, respectively).
  5. Conducted in compliance with the requirements concerning the promotion and sale of drugs.
  6. Does not intend to invoke a waiver of informed consent for emergency research.

9

## Exceptions: when an IND is Not Required

- A clinical study involving a placebo is exempt from needing an IND if the study meets all of the six criteria on the previous slide.
- In vivo bioavailability studies in humans invoke an additional regulation, 21 CFR 320.
- Unlabeled indications, or “off-label use” of an approved marketed product FDA has determined to be a matter of medical judgment in the practice of medicine. IND does not apply to medical care.

### If Uncertainty Reigns

- On request, FDA will advise on the applicability of 21CFR 312, Investigational New Drug Application, to a planned clinical investigation.

10

## When an IND is Not Required

- UC has provided a checklist to support decisions on whether or not an IND is required for a particular project.
- The completed form is recommended as part of the initial submission to the IRB, and should be retained in the study file.
- The checklist is available from:
  - Angela B. Braggs-Brown, RAC
  - Director, IDE /IDE Assistance Program
  - Post-Approval Monitoring Program
  - Office of Research Compliance
  - University of Cincinnati
  - 51 Goodman Drive
  - 238 University Hall, ML 0629
  - Cincinnati, OH 45221-0629
  - Tel: (513) 558-3005
  - Fax: (513) 558-3539
  - Email: [broag@ucmail.uc.edu](mailto:broag@ucmail.uc.edu)

11

## IND Content and Format

21 CFR 312.23

**An IND must contain, *in the following order*:**

- Cover Sheet, which is Form FDA-1571
  - Available at [www.fda.gov](http://www.fda.gov) and described in detail in 312.23 (a)(1)
- A table of contents
- Introductory statement and general investigational plan
  - Five defined sections, see 312.23 (a)(3).
- Investigator's brochure
  - The information it is to contain is listed in 312.23 (a)(5).
- Protocols – one for each planned study.
  - Seven specific elements to be included in each protocol are listed in 312.23(a)(6)(iii).
  - Protocols not submitted initially in the IND should be submitted as IND amendments, see 312.30(a).

12

## IND Content and Format

21 CFR 312.23

### Continued:

- Chemistry, manufacturing and control information, to describe the composition, manufacture and control of the drug substance and the drug product.
  - Include sufficient information to assure the identification, quality, purity, and strength of the investigational drug. How much information is sufficient depends on the phase, scope and length of the study, the dosage form and the amount of information otherwise available.
  - Include stability data for the drug substance and drug product.
  - Amend this section as manufacturing scale-up is under development.
  - Include a description of the chemistry, manufacture and control of any placebo to be used in the study(ies).
  - Include labeling, a copy of all labels and labeling to be provided to each clinical investigator.
  - For additional perspective see 312.23(a)(7)(i-iv).

13

## IND Content and Format

21 CFR 312.23

### Continued:

- Pharmacology and toxicology information; adequate information from *in vitro* studies and/or studies in animals which are the basis for the sponsor's belief that the drug may now be tested in humans. Details in 312.23(a)(8).
- Previous human experience with the investigational drug, if any is known to the applicant, such as from another country. The IND is to include detailed information about such experience that is relevant to the safety of the proposed study(ies) or to the rationale behind it/them. Details in 312.(a)(9).

14

## IND Content and Format

21 CFR 312.23

### Continued:

- Additional information in certain applications:
  - Drug dependence and abuse potential.
  - Radioactive drugs
  - Pediatric studies
  - Other information in general that would aid evaluation of the proposed clinical study(ies) with respect to safety, design, and potential as controlled trials to support marketing of the drug.
- FDA may request that other relevant information wanted for review of the application be included, such as information previously submitted, rather than being incorporated by reference, or English translation of material in a foreign language.

15

## IND Content and Format

21 CFR 312.23

### Continued:

- An original and two copies are to be submitted for all IND filings, the original submission all amendments and any reports.
- Each submission relating to an IND is to be numbered serially **using a single 3 digit serial number chronologically in sequence. The initial submission is required to be numbered 000.**
- Identification of exception from informed consent if applicable. If the clinical study(ies) involve(s) exception from informed consent of the participants per 21 CFR 50.24, the cover sheet of the IND will prominently say so.

16

## Form FDA 1571

Form FDA 1571, the IND Cover Sheet, is used for multiple purposes:

- Initial Submission for a new drug
- Protocol Amendments
  - New Protocol
  - Change in Protocol
  - New Investigator
- Information Amendments
  - Chemistry/Microbiology
  - Pharmacology/Toxicology
  - Clinical
- IND Safety Reports
  - Initial
  - Follow-up
- Response to Clinical Hold
- Response to FDA Request for Information
- Annual Report
- General Correspondence
- Request for Reinstatement of IND (that is withdrawn, inactivated, terminated or discontinued)
- Other as specified by the Sponsor.

17

## Medical Devices: the IDE

21 CFR 812

- Medical Devices are classified based on their design complexity, their use characteristics, and risk: their potential for harm if misused.
  - Class I devices are not intended for use in supporting or sustaining life or to be of substantial importance in preventing impairment to human health, and they may not present a potential unreasonable risk of illness or injury
  - Class III devices are usually those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.
  - Class II falls between: devices that do not classify as Class III, but cannot be classified as Class I.

18

## Medical Devices: the IDE

21 CFR 812

- An investigational device exemption (IDE) allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application (Class III devices that are not pre-amendment devices) or a Premarket Notification [510(k)] submission to FDA (non-exempt Class I and II devices and preamendment Class III devices).
- Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(k)'s require clinical data to support the application. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. ***All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.***

19

## Medical Devices: the IDE

21 CFR 812

- An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (Act) that would apply to devices in commercial distribution.
  - Sponsors of IDEs are also exempt from the Quality System (QS) Regulation except for the requirements for design control.
  - Clinical evaluation of devices that have not been cleared for marketing requires:
    - An IDE approved by an institutional review board (IRB).  
If the study involves a significant risk device, the IDE must also be approved by FDA;
    - Informed consent from all subjects;
    - Labeling for investigational use only
    - Monitoring of the study and;
    - Required records and reports.
- Extensive "Device Advice" is given at [www.FDA.gov](http://www.FDA.gov)**
- **Forms FDA 1571 and 1572 do not apply.**

20

## Medical Devices: the IDE

21 CFR 812

- Investigational Device Exemptions. Permits a device that otherwise would be required to comply with a performance standard or to have pre-market approval to be shipped lawfully for the purpose of conducting investigations with that device. [Investigations here means human research studies]
- An approved IDE or an IDE that is “considered approved” exempts the device from regulatory requirements in the Act and regulations issued thereunder, concerning:
  - Misbranding (section 502)
  - Registration, listing and premarket notification (section 510)
  - Performance Standards (section 514)
  - Premarket Approval (section 515)
  - Banned device regulation (section 516)
  - Records and Reports (section 519)
  - Restricted device requirements (section 520e)
  - Good Manufacturing Practice requirements [however exceptions to this exception are listed in 21 CFR 812.1(a)]

21

## Exceptions: When an IDE is Not Required

21 CFR 812

- IDE regulations apply to all clinical investigations of devices to determine safety and effectiveness except:
  - A device in commercial distribution on a particular historical date in or after 1976, separate dates for Class I, II and III devices.
  - A diagnostic device of the sponsor complies with 21 CFR 809.10(c) and if the testing is noninvasive, does not require invasive sampling that presents significant risk, does not by design or intention introduce energy into the subject, and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
  - A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put the subjects at risk.

22

## Exceptions: When an IDE is Not Required

21 CFR 812

- IDE regulations apply to all clinical investigations of devices to determine safety and effectiveness except:
  - A device solely for veterinary use.
  - A device shipped solely for research on or with laboratory animals and labeled in accordance.
  - A custom device unless the device is being used to determine safety or effectiveness for commercial distribution. Definition of custom device is in 21 CFR 812.3(b), includes a device intended for use by only one individual patient.
- However, transitional devices of the above kinds are not excepted. Transitional device is a term that means a device that existed before 28May1976 that the FDA considered up until that time, to be a new drug or an antibiotic drug.
- Note that 812.119, disqualification of a clinical investigator, applies to all of the above, even to those studies excepted from the rest of the IDE regulations.

23

## Medical Devices: the IDE

21 CFR 812

- A Sponsor shall submit an IDE application to the FDA if:
  - The sponsor intends to use a significant risk device in an investigation
  - The Sponsor intends to conduct an investigation that involves an exception from informed consent under 21 CFR 50.24
  - If the FDA notifies the sponsor that an application is required for the investigation.
- A sponsor shall not begin an investigation for which FDA's approval is required until FDA has approved the application.
- A sponsor shall submit 3 copies of a signed "Application for an Investigational Device Exemption" (IDE application) together with accompanying materials **by registered mail or by hand** to the address specified in 21 CFR 812.19. Subsequent correspondence concerning an application or a supplemental application shall be submitted **by registered mail or by hand**.

24

## Medical Devices: the IDE

- UC has provided a checklist to support decisions on whether or not an IND is required for a particular project.
- The completed form is recommended as part of the initial submission to the IRB, and should be retained in the study file.
- The checklist is available from:

Angela B. Braggs-Brown, RAC  
 Director, IDE /IDE Assistance Program  
 Post-Approval Monitoring Program  
 Office of Research Compliance  
 University of Cincinnati  
 51 Goodman Drive  
 238 University Hall, ML 0629  
 Cincinnati, OH 45221-0629  
 Tel: (513) 558-3005  
 Fax: (513) 558-3539  
 Email: [broag@ucmail.uc.edu](mailto:broag@ucmail.uc.edu)

25

## IDE Content and Format

21 CFR 812

**An IDE must contain, *in the following order*:**

- The name and address of the sponsor.
- A complete report of prior investigations of the device and an accurate summary of defined sections of the investigational plan, or in lieu of a complete summary, the complete plan.
- The sponsor shall submit to FDA the complete investigational plan and complete report of prior investigations if no IRB has reviewed them, if FDA found an IRB's review inadequate, or if FDA requests them. [See 812.25 and 812.27 for details of what is to be included in an investigational plan and report of prior investigations, respectively.]
- A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and where appropriate, installation of the device, in sufficient detail so that a person generally familiar with good manufacturing practices can make a knowledgeable judgment about the quality control used in the manufacture of the device.

26

## IDE Content and Format

21 CFR 812

Continued:

- An example of the agreements to be entered into by all clinical investigators to comply with investigator obligations and a list of the names and addresses of all investigators who have signed the agreement.
- Certification that the clinical investigators who will participate have all signed the agreement provided, and that no new Investigators will be added until they also sign the agreement.
- A list of name, address, and chair of each IRB that is to be involved. And a certification of the action taken by each participating IRB.
- The name and address of any institution at which part of the investigation may be conducted that is not co-located with any of the listed IRBs.
- If the device is to be sold, the amount to be charged and an explanation why such sale does not constitute commercialization of the device.

27

## IDE Content and Format

21 CFR 812

Continued:

- A claim for categorical exclusion or an environmental assessment under stated regulations [see 21 CFR 812.20(a)(9)]
- Copies of all device labeling.
- Copies of all forms and informational materials to be provided to subjects to obtain informed consent.
- Any other relevant information that FDA requests for review of the application.
- FDA may request additional information concerning an investigation or revision in the investigational plan. The sponsor may treat such a request as a disapproval of the application for purposes of requesting a hearing under part 16.

28

## IDE Content and Format

21 CFR 812

Continued:

- Information previously submitted to CDRH, CBER or CDER as applicable ordinarily need not be resubmitted, but may be incorporated by reference.
- A sponsor shall submit a separate IDE for any clinical investigation involving an exception from informed consent for emergency research (studies under 21 CFR 50.24). The sponsor shall prominently identify on the cover sheet that the investigation is subject to §50.24. Such clinical investigation is not permitted to proceed without the prior written authorization of the FDA.

29

## The Treatment IDE

21 CFR 812.36

- Treatment use of an investigational device under an IDE and a humanitarian use device used with a Humanitarian Use Device Exemption (HDE) differ in significant ways. The humanitarian use device is FDA approved and marketed, but only for humanitarian use. Humanitarian use devices are not investigational devices. Sponsors may advertise them but must clearly state the humanitarian use aspect of their availability.
- Treatment use under 21 CFR812.36 involves an unapproved device not yet on the market. The device must be applicable in a serious or immediately life-threatening condition or disease in patients for whom no comparable or satisfactory alternative device or other therapy is available. FDA approval is required for treatment use.

30

## The Treatment IDE:

21 CFR 812.36

- In order to file a treatment IDE, at the time of filing a Sponsor must have:
  - Already begun clinical trials for immediately life-threatening conditions.
  - Have completed all needed clinical trial in the case of serious disease.
  - The Sponsor must also be in the process of applying for a marketing permit.
- The idea is to facilitate the availability of promising new devices to desperately ill patients as early in the device development process as possible, before general marketing becomes allowed.
- A treatment IDE which differs in content from the standard investigational device IDE as described above is submitted to the FDA. Requirements for the content and format of a Treatment IDE can be found in 21 CFR 812.36(c).

31

## The Treatment IDE:

21 CFR 812.36

- Treatment use may not begin until 30 days after FDA receives the Treatment IDE application. FDA will communicate within that time, if/that treatment use may not begin.

*UC Sponsors and Sponsor-Investigators should contact the Director of the UC IND/IDE Assistance Program whenever a treatment IDE is being contemplated.*

32

## Requirements for **Device** Study Sponsors: 21 CFR 812

- Among the Sponsor's General Responsibilities in 21 CFR 812.40
  - Submit an IDE application to FDA.
  - Ensure that any reviewing IRB and FDA are promptly informed of significant new information about an investigation [study].
- Among the Sponsor's Monitoring Responsibilities in 21 CFR 812.46:
  - Should Sponsor find the Investigator is not in compliance, Sponsor must secure compliance or discontinue device shipment to that Investigator and terminate that Investigator's participation in the study.

Study termination qualifies as significant new information about the study (see above on this slide).

33

## Requirements for **Device** Study Sponsors: 21 CFR 812

- Sponsor's Reporting Responsibilities in 21 CFR 812.150: Sponsor shall prepare and submit complete, accurate and timely reports of:
  - Unanticipated adverse device effects (UADEs). Reporting is to FDA, all participating IRBs and PIs as soon as possible but no later than 10 working days after the Sponsor received notice of the UADE.
    - After the initial report FDA may ask for additional reports which the Sponsor shall submit.
  - Withdrawal of IRB approval (in whole or in part) to FDA, all PIs and other approving IRBs within 5 working days after receipt of notice from the IRB which withdrew approval.
  - Withdrawal of FDA approval to all involved PIs and approving IRBs, within 5 working days after being notified by FDA.
  - Names and addresses of all Investigators involved to FDA at 6 month intervals. First such report is due 6 months after FDA approval date.

34

## Requirements for **Device** Study Sponsors: 21 CFR 812

- Sponsor's Reporting Responsibilities in 21 CFR 812.150:  
Sponsor shall prepare and submit complete, accurate and timely reports of:
  - Progress reports to all reviewing IRBs at regular intervals but at least yearly. With significant risk devices, also send progress reports to the FDA. Under a treatment IDE, semi-annual progress reports to all reviewing IRBs and the FDA.
  - Sponsor shall report any request that an investigator return, repair or otherwise dispose of any units of a device to FDA and all reviewing IRBs. Such notice shall be within 30 working days of the request and include the reason the request was made.
  - Sponsor shall notify FDA of study completion or termination within 30 working days.
  - Investigator shall report to the Sponsor and the IRB any use of device without informed consent within 5 working days. Sponsor must report same to the FDA within 5 working days of the Sponsor being informed.

35

## Requirements for **Device** Study Sponsors: 21 CFR 812

- Sponsor's Reporting Responsibilities in 21 CFR 812.150:
  - Sponsor shall notify FDA concerning completion of a study **using a significant risk device** within 30 working days after study completion or termination.
    - Sponsor shall make a final report of the research study to the FDA and all reviewing IRBs within 6 months of study completion or termination.
  - Non-Significant Risk Device: Final report to all IRBs within 6 months of study termination or completion.
  - Sponsor shall report to FDA whenever a device the Sponsor thought was a non-significant risk device was determined by an IRB to be a significant risk device.
    - This report must be made within 5 working days of the Sponsor finding out about the IRB's determination.
  - FDA and any reviewing IRB can request information about any aspect of the investigation and the Sponsor shall provide accurate, current and complete information.

36



## FDA-Required **Device** Investigator Reports

21 CFR 812.150(a)

The PI of a device study is required to prepare and submit certain reports:

- Unanticipated adverse device effects: report to the sponsor and reviewing IRB. Report to be made as soon as possible and not later than 10 working days after the Investigator learns of the event.
- Withdrawal of IRB approval: report to the sponsor within 5 working days.
- Progress reports: to the sponsor, the monitor, and the reviewing IRB at regular intervals, in no event less than yearly.
- Deviations from the investigational plan: to the sponsor and reviewing IRB of any deviation made to protect the life or physical well-being of a subject in an emergency. Notice to be given as soon as possible, no later than 5 working days after the emergency occurred.
  - Except in an emergency, prior approval by the sponsor is required for changes in the investigational plan.
  - If **planned** changes impact the scientific soundness of the plan or the rights, safety or welfare of subjects, prior approval of FDA and the reviewing IRB also is required.

37



## FDA-Required **Device** Investigator Reports

21 CFR 812.150(a)

The PI of a device study is required to prepare and submit certain reports:

- Use of a device without informed consent [when the study involved IC by design]: report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
- Final report: Investigator shall within 3 months after termination or completion of the investigation (or the investigator's part of the investigation), submit a final report to the sponsor and the reviewing IRB.
- Other: an investigator shall, upon request by the reviewing IRB or the FDA, provide accurate, complete, and current information about any aspect of the investigation.

38

## US FDA Reporting Requirements for Drug Study Sponsors: 21 CFR 312

- Among the Sponsor's General Responsibilities in 21 CFR 312.50:
  - Maintain an effective IND.
  - Assure that all Investigators and FDA are informed on significant new adverse effects or risks with respect to the drug.
- Among the Sponsor's Responsibilities in 21 CFR 312.56:
  - On discovery of non-compliance by an Investigator, the Sponsor shall monitor and secure compliance or cease drug shipments to the Investigator and end that Investigator's participation in the study and so notify the FDA.
  - Make [routine] annual reports to FDA (progress reports).
  - If so led by the data the Sponsor shall discontinue the study and notify the FDA.

39

## US FDA Reporting Requirements for Drug Study Sponsors: 21 CFR 312

- The Sponsor studying an unmarketed drug has specific reports to submit (IND safety reports) that are described in 21 CFR 312.32:
  - No later than 15 calendar days after the Sponsor learned of the event, notify FDA and all participating PIs of:
    - SUSARs.
    - Findings from other human studies.
    - Findings from animal or in vitro testing.
    - Increased rate of occurrence of serious suspected adverse reactions.
  - No later than 7 calendar days after Sponsor's initial receipt of the information: notify FDA of unexpected fatal or life-threatening suspected adverse reactions.

## US FDA Reporting Requirements for Drug Study Sponsors: 21 CFR 312

- Sponsors studying unmarketed drugs:
  - Study endpoints would ordinarily be reported to FDA as described in the protocol but if a serious and unexpected AE occurs and there is evidence of a causal relationship between the drug and the event, the event is to be reported to FDA in an IND safety report as a serious and unexpected suspected adverse reaction.
  - Follow-up safety reports must be submitted as soon as the information is available and must be identified as a follow-up.
- For IND studies of marketed drugs, IND safety reports of SARs at domestic or foreign study sites are to be submitted to FDA, on time lines established in post-marketing reporting requirements (21 CFR 310.305, 21 CFR 314.80 and 21 CFR 600.80).

## ICH E6 GCPs Reporting Requirements: Sponsors

### 5.10 Notification/Submission to Regulatory Authority(ies)

If required by the applicable regulatory requirement(s), the Sponsor (or Sponsor and Investigator, if required ) should submit any required application to the applicable authority for review, acceptance and/or permission to begin the trial(s).

Any notification should be dated and contain sufficient information to identify the protocol.

5.17.3 The Sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirements.

5.20 Noncompliance: When a Sponsor learns through monitoring and/or auditing that a PI incurs serious and/or continuing noncompliance on the part of the investigator/institution, the Sponsor should terminate the investigator/institution's participation in the trial.

And the Sponsor must promptly notify the regulatory authority(ies) of such action.

## ICH E6 GCPs Reporting Requirements: Sponsors

- 5.21 Premature Termination or Suspension of a Trial: The Sponsor is to promptly notify all investigators/institutions, and the regulatory authority(ies) and provide the reason for the action. Either the Sponsor or the Investigators may inform the IRB, as specified by the applicable regulatory requirement(s)
- 5.22 Clinical Trial/Study Reports [Interim if any and Final]: Sponsor should assure that reports are prepared and provide to the regulatory agencies as required by the applicable regulatory authority(ies). The reports in marketing applications should meet the standards in the ICH Guidance for the Structure and Content of Clinical Study reports.

43

## UC-Required Sponsor-Investigator Reports

- The UC IRB web-site provides SOPs for Sponsor-Investigators. The following examples relate to reporting:
  - REG 001 Sponsor/Investigator Required Reports
  - ADM 003 Adverse Event Reporting
  - ADM 004 Unanticipated Adverse Drug/Device Effect Reporting (UADE)
  - ADM 005 Protocol Deviation Reporting

44

## UC-Required Sponsor-Investigator Reports

- Unanticipated Adverse Drug/Device Effects – to FDA, all reviewing IRBs and all [additional] PIs
- Withdrawal of IRB Approval (of the study, in whole or in any part) – to FDA
- Withdrawal of FDA Approval – to reviewing IRB(s)
- Current List of Investigators every 6 months – to FDA
- Progress reports (annual reports, continuing review reports) – to all reviewing IRBs.
- Annual report to FDA.
- Recalls and drug/device disposition – request made to any PI to return or repair or dispose of any unit of an investigational drug/device - to FDA and all reviewing IRBs. With 30 working days of the request and include why the request to the PIs was made.

45

## UC-Required Sponsor-Investigator Reports

- Study Completion and Final Report - to FDA and all reviewing IRBs: study completion notice within 30 working days of completion or termination of the investigation. Final report to FDA and all reviewing IRBs within 6 months after completion or termination.
- Use of Drug/Device Without Informed Consent – to FDA within 5 working days after receipt of notice of such use.
- Significant Risk Device Determination by the IRB, when Sponsor-Investigator had proposed the drug/device as an insignificant risk device – to FDA within 5 working days after the Sponsor-Investigator learns of the IRB's determination.
- Other Reports – To FDA or an individual reviewing IRB, as requested by the FDA or IRB.

Reports that go to the FDA are to be identified as IND or IDE Supplements and are submitted in triplicate.

46



## Financial Reports: Investigator

21 CFR 54

21 CFR Part 54, Financial Disclosure by Clinical Investigators, includes:

- FDA may consider clinical studies inadequate and the data inadequate if, among other things, appropriate steps have not been taken...to minimize bias.
- One potential source of bias in clinical studies is a financial interest of the clinical investigator in the outcome of the study because:
  - Of the way payment is arranged.
  - The Investigator may have a proprietary interest in the product.
  - The Investigator may have an equity interest in the Sponsor of a covered study.
- The clinical Investigator provides the Sponsor with financial information sufficient to meet the sponsor's reporting requirements when a marketing permit is filed.

47



## Financial Reports: Investigator

21 CFR 54

21 CFR Part 54, Financial Disclosure by Clinical Investigators, includes:

- The Investigator is to promptly update the financial information if relevant changes occur during a study and one year following study completion.
- The permit applicant (Sponsor) will retain the financial information which is subject to audit, and make it available for audit.

48

## Study Registration at *ClinicalTrials.gov*

- ClinicalTrials.gov is a registry of federally and privately supported clinical trials conducted in the United States and around the world.
- The Food and Drug Administration Amendments Act of 2007 (FDAAA or US Public Law 110-85) was passed on September 27, 2007. The law requires mandatory registration and results reporting for certain clinical trials of drugs, biologics, and devices. *In order to publish the results of a study, that study must be registered on the ClinicalTrials.gov web-site before subject enrollment begins.*
  - Late registration equals the Sponsor does NOT get to publish in a large group of journals.
- In order to be registered, a trial must be approved by a human subject review board and must conform to the regulations of the appropriate national health authorities.
- It is a Sponsor responsibility to register the study.
- And include in ICF templates, the needed statement concerning study registration.
- More information at <http://prsinfo.clinicaltrials.gov/fdaaa.html>

49

## Getting You Credit

**We appreciate your review of this module.**

To achieve credit for having done so, please complete the corresponding quiz provided in the CPD system.

**You will receive a certificate of completion when your quiz is satisfactorily passed (score >80%).**