UC Irvine's Clinical Research Coordinator Certification Preparation Series

PI Roles and Responsibilities

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SESSION 4

Data Collection and Source Documentation

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Data Collected Preparatory to Research

ICH Guidance: E6 GCP 1.51, 1.52, 6.4.9, 8.3.13, 21 CFR 312.62 21, CFR 812.140, 21 CFR 11, FDA guidance: computerized systems used in clinical trials

- Preparatory to research activities are defined as:
  - the development of research questions;
  - the determination of study feasibility (in terms of the available number and eligibility of potential study participants);
  - the development of eligibility (inclusion and exclusion) criteria; and
  - the determination of eligibility for study participation of individual potential subjects
- No data can been collected other than described above without approval by the IRB

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Data Collection and Management

- Methods are appropriate for type of research
- Data recorded such that it can be validated
- Appropriate authorization: human subjects; animal subjects; hazardous material & biological agent use; proprietary data; copyrighted or patented materials
- Research records attained according to protocol
- The investigator needs to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

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Data Collection and Documentation

- Data derived from source documents should be consistent with those documents or any discrepancies should be explained.
- Any correction to a CRF should be initialed, dated, and explained and should not obscure the original entry.
- The Investigator is responsible to maintain all study documentation as required by the contract and by all applicable regulations.

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Data Collection and Documentation

A = Accurate (information must be correct)

L = Legible (must be easy to read)

C = Contemporaneous(must be completed at the time of event)

O = Original (it must not be a duplicate copy)

A = Attributable (must be signed and dated)

IF IT'S NOT DOCUMENTED, IT DIDN'T HAPPEN, SO DOCUMENT EVERYTHING!

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Source Documentation

Definition of Source Document/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.

Original documents or certified copies can include the following:

- Hospital records
- Clinic and office chart records
- Laboratory notes
- Patient diaries
- Pharmacy dispensing records
- Photographic negatives
- X-rays

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Documentation

- Original signed informed consent and the research HIPPA Authorization. If applicable, you must add the assent and documentation of surrogate consent
- Source Documentation
- Case Report Forms
- Documentation of the research consenting process
- Subject inclusion/exclusion assessment checklist completed and signed by the investigator
- Copies of the research test and procedure results
- Drug Administration

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Data Protection

- Proper storage to avoid accidental damage, loss or theft
- Confidentiality & privacy agreements honored
- Data retention according to contract &/or institutional practice

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Documenting Adverse event

ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards or Expedited Reporting, Oct 1994

- An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

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Documenting Serious Adverse Event

ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards or Expedited Reporting, Oct 1994

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event.

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Serious Adverse Event

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

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Serious Adverse Event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias, or development of drug dependency or drug abuse.

Note:

- A procedure is not an AE or SAE, but the reason for the procedure may be an AE.
- Pre-planned surgeries or hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

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Adverse Event Assessment

It is the responsibility of ***Investigators***, based on their knowledge and experience, to determine those circumstances or abnormal lab findings that should be considered AEs.

Assessments:

- Severity
- Causality/ Relatedness
- Action Taken Regarding the Study Products
- Adverse Event Outcome
- Other Action Taken for Event

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Adverse Event Severity

NCI CTCAE, version 4.0 (see Section 17.2; publish date 01 Oct 2009); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 for links to the NCI CTCAE, version 4.0

All AEs will be graded 1 to 5

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death related to AE

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Adverse Event Severity vs. Seriousness:

- ***Severity*** is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache).
- This is not the same as ***"seriousness"*** which is based on subject/event outcome at the time of the event. For example, the NCI CTCAE Grade 4 (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness.
- An AE assessed as Grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

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Adverse Event RELATEDNESS to the study drug

The relationship between an AE and the drug will be determined by the Investigator on the basis or his/her clinical judgment and the following definitions:

1 = Not Related

- The AE does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

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Adverse Event RELATEDNESS to the study drug

2 = Related

- The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concomitant diseases, and concomitant medications).
- The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology

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Adverse Event RELATEDNESS to the study drug

A crucial assessment made by a study physician whether or not the event is:

- ***Definitely related*** - direct association with study agent
- ***Probably related*** - more likely explained by study agent
- ***Possibly related*** - study agent and other cause explained equally well
- ***Probably not related*** - more likely explained by other cause
- ***Not related*** - clearly explained by other cause

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Adverse Event Outcome

- 1 = ***Recovered/Resolved*** -the subject fully recovered from the AE with no residual effect observed.
- 2 = ***Recovered/Resolved with Sequelae*** - the residual effects of the AE are still present and observable.
- 3 = ***Not Recovered/Not Resolved*** - the AE itself is still present and observable.
- 4 = ***Fatal***
- 5 = ***Unknown***

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Action Taken Regarding the Study Products

- 1 = ***None*** - No change in study drug dosage was made.
- 2 = ***Discontinued Permanently*** - The study product was permanently stopped.
- 3 = ***Reduced*** -The dosage of study product was reduced.
- 4 = ***Interrupted*** -The study product was temporarily stopped.
- 5 = ***Increased*** -The dosage of study product was increased.

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Other Action Taken for Event

- 1 = ***None*** - No treatment was required.
- 2 = ***Medication required*** - prescription and/or over-the-counter medication were required to treat the AE.
- 3 = ***Hospitalization or prolongation of hospitalization required*** -hospitalization was required or prolonged due to the AE, whether or not medication was required.
- 4 = ***Other***

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Adverse Event and SAE Reporting

- Adverse Events (AEs) – already known potential risks of participating in the research study
  - Usually reported on case report forms
  - Study subject should have baseline assessment before intervention
- Serious Adverse Events (SAEs)
  - Serious, unexpected and related to the study intervention
  - Need to be reported immediately to the IRB within 5 working days of becoming aware of the event
  - Report to Clinical Research Billing
  - Sample SAE form
  - See IRB Policy on Reporting SAEs in your binder
- IND Safety Reports
- Data Safety Monitoring Board

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Adverse Event and SAE Reporting

Serious Adverse Event Reporting-Procedure for Investigators

Within 24 hours of an Investigational Site's receipt of an SAE report.

Follow-up Reports

This is NEW information received on a previously reported SAE.

Within 24 hours of the receipt of new information for a reported SAE.

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Protocol Deviations

- Accidental or unintentional changes to, or non-compliance with the research protocol that does not increase risk or decrease benefit or; does not have a significant effect on the subject's rights, safety or welfare; and/or on the integrity of the data. Deviations may result from the action of the subject, researcher, or research staff.
- Examples of deviations include: a rescheduled visit; an incomplete study visit; and failure to collect ancillary study measures (e.g., questionnaire, baseline BP).

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Protocol Violations

- Accidental or unintentional changes to, or non-compliance with the IRB approved protocol without prior sponsor and IRB approval. Violations generally increase risk or decrease benefit, affects the subject's rights, safety, or welfare, and/or the integrity of the data.
- Examples of incidents that may be considered violations include: enrolling a participant who does not meet the inclusion criteria; obtaining verbal consent before the initiation of study procedures when the IRB requires signed, written informed consent; and failure to collect screening labs before initiation of study procedures.

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Paper and Electronic Records

- Keep all CRF and study material stored in a safe secured area.
- FDA policy requires that all electronic systems must meet validation and functionality testing.
- UC Irvine HAIS is working to assure our electronic systems meet federal security and encryption criteria, including flash drives, laptops, etc.
- Industry sponsors relying on computerized system to create, modify, maintain, archive, retrieve, or transmit data will be required to submit certification (validation and functionality testing) criteria that meets FDA guidelines identified at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072322.pdf

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Safeguards

- Protect against reasonably anticipated threats or hazards to security of PHI created, used or maintained for research

- Researcher Responsibilities
  - *Establish Administrative Safeguards*
    - ✓ Make sure all research staff are trained on privacy obligations (check with the Privacy Office if you're not sure)
  - *Establish Physical Safeguards*
    - ✓ Retain sensitive information in locked buildings/offices/file cabinets
    - ✓ Secure any non-encrypted computers or devices under lock and key
    - ✓ Shred any documents with sensitive information when no longer needed

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Safeguards (cont.)

- *Establish Technical Safeguards*
  - ✓ If you maintain servers, protect them with appropriate firewalls, patches, and other technical safeguards
  - ✓ Research projects involving large sensitive data stores typically will require skilled and experienced IT staff support
  - ✓ Encrypt all desktops, laptops, flash drives, mobile devices, and similar electronic storage units if and as possible
  - ✓ This is not a direct mandate but where encryption is not utilized, some other safeguard is needed (e.g., the computer is not encrypted but it is always locked in an office that is accessible only by authorized staff with key cards)
  - ✓ Carefully store or transfer data that cannot be encrypted (e.g., digital cameras) … don't leave unencrypted devices in the car!
  - ✓ Use strong passwords and never share passwords
  - ✓ Log off of your computer when not in use and at the end of each day

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Study Documentation

Thou Shalt NOT
- Use White Out or obliterate an original entry
- Use different colored inks
- Let the study monitor write on the CRF
- Sign the investigator's name or sign in an area reserved for the investigator's signature
- Correct other's work or make interpretations

Thou Shalt
- Make one line through the incorrect entry leaving the incorrect entry visible
- Write the correct entry beside it
- Initial and date the correction
- Review all entries carefully with the source document and/or visit/procedure logs twice for accuracy

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Audits and Study Monitoring

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Audits and Inspections

- The purpose of an audit or inspection is to ensure compliance with applicable regulations and contract obligations.
- The investigator is responsible to notify the IRB immediately upon learning of a site visit by an auditor or a representative of any federal or other regulatory agency.
- Upon request of the auditor, IRB, FDA, or any other regulatory entity, the investigator need to make available for direct access, all trial related records
  - "Permission to examine, analyze, verify, and reproduce all records and reports that are important to evaluation of a clinical trial." – FDA
  - Note: Any party with direct access should take all reasonable precautions to maintain the subjects' confidentiality and the sponsor's proprietary information.

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External Study Monitors & Audits

- Some studies sponsored by external companies or governmental agencies will visit to review the medical records to ensure the study is being conducted according to the protocol.
- They can be granted access to the medical records as long as:
  - ✓ The PI of the study or the study coordinator accompanies them to the medical records office or provides a signed letter identifying the external study monitors
  - ✓ The external monitor has valid picture identification to verify their identity
  - ✓ In most cases, the study coordinator will accompany the study monitor
  - ✓ The study coordinator should notify you in advance to have the charts pulled.

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External Study Monitors & Audits

- Study Monitoring Visits
  - ✓ Usually, the first visit will be scheduled after the first patient goes on a study. Thereafter, visits are scheduled as accrual progresses.
  - ✓ Visits will usually be 1-2 days.
  - ✓ All regulatory documents will be reviewed.
  - ✓ Each completed case report form is checked against the medical record to verify data accuracy and source documentation backup.
- Audits
  - ✓ May be conducted by various entities, both internal and external.
  - ✓ Information reviewed is very similar to that of a monitoring visit.
  - ✓ There is normally a summary meeting at the end, followed by a formal, written report of the audit findings and follow up actions.

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Preparation for an Audit

Create and maintain sectioned **STUDY AUDIT BINDERS** containing the following:

- ✓ All sponsor correspondence (if it's in an e-mail, print it out and file)
- ✓ Master Protocol and Investigator Brochure
- ✓ Investigator meeting agenda and training documentation for all investigator and research study personnel
- ✓ Sponsor/CRO monitor reports
- ✓ All sponsor protocols revisions, amendments, and addendums
- ✓ FDA Form 1572
- ✓ FDA letter of authorization to reference and IND/IDE
- ✓ FDA Correspondence
- ✓ All investigator's CV's (updated and current every two years)
- ✓ Laboratory Certifications
- ✓ List of Laboratory reference ranges
- ✓ Randomization code reference (if applicable)

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- ✓ Investigator reporting of serious adverse events to IRB and sponsor
- ✓ Sponsor notification letters of serious adverse events
- ✓ Study protocol/protocol narrative
- ✓ IRB approval/s (including protocol modifications, changes in investigator/research staff status, and advertising)
- ✓ IRB approved consent form/s
- ✓ All IRB Correspondence
- ✓ Required ancillary approvals
- ✓ Delegation of Authority form
- ✓ Conflict of Interest Form and COIOC approval
- ✓ Research staff study responsibility and signature log
- ✓ Patient/Subject Enrollment log
- ✓ Inclusion/Exclusion criteria check list
- ✓ Signed consent/Assent and research HIPAA forms
- ✓ Notifications to the IRB of any/all changes, modifications, revisions, and amendments to the protocol and informed consent
- ✓ Notification to the IRB that the study has closed/terminated

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Common Contributors to Compliance Problems

- Inadequate resources
- Lack of understanding of roles and responsibilities of institutional staff
- Inadequate staff training and education
- Outdated or nonexistent policies and procedures
- Inadequate management systems (e.g., effort reporting, financial management)
- Perception that internal control systems are not necessary

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Study Closure and Record Retention

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Study Closeout

- All final reports, data submitted
- All outstanding data queries resolved
- Analysis and publication completed
- Make sure all billing is complete (if you have a question call our research biller)
- Review document storage obligations
- Closeout of acct/fund (though the study may remain open with the IRB for some longer period of time during data analysis and publication)
- Closeout Visit

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Study Completion

- Notify IRB when enrollment is closed and then again when the study is retired
- Data audit summary to sponsor and IRB (close of study form) signed by investigator
- Final drug accountability, drug returned to sponsor (pharmacy to provide documentation)

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Study Completion

- Lab supplies, sponsor CRFs, other study supplies returned to sponsor or destroyed. (This does not include source documents, enrollment logs, signed consent forms, IRB approvals, collected study data, or the protocol. These study documents must be maintained for the period of time required by the institution and/or specified by the sponsor's contract with the institution

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Record Retention

- All research records are University property. Accordingly, researchers are required by University policy to keep their research records on site at all times for access by authorized agents of the Federal and State government, the sponsor, and the University.
- Essential subject data must be maintained at the site until 2 years past FDA marketing approval for the drug/device or upon determination not to approve.

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Record Retention

- All protocol records must be kept in the Department a minimum of 3 years past the close of the site's protocol.
- Keep/Store study records for a minimum of 6 years .
- IRB must retain study records for 3 years past close of protocol.
- The contract between the institution and the sponsor may require longer retention.

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References

- OHRP (Office of Human Research Protection) http://www.hhs.gov/ohrp/index.html
- HHS (Department of Health and Human Services) http://www.hhs.gov/
- CDPH (California Department of Public Health) https://www.cdph.ca.gov/Pages/DEFAULT.aspx
- FDA (U.S. Food and Drug Administration) http://www.fda.gov/default.htm
- NCCN (National Comprehensive Cancer Network) http://www.nccn.org/default.aspx
- NCI (National Cancer Institute) http://www.cancer.gov/ https://clinicaltrials.gov/

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References

CMS' Clinical Trials Policy (310.1)

Medicare Coverage Database - Database of Medicare policies

Medicare Benefit Manual - Includes information about services that are a benefit of Medicare

Managed Care Benefit Manual - Includes information about Medicare Advantage Patients

IDE Approval Forms - Noridian IDE Policy

Privacy Rule for Researchers

Office of Research Integrity

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http://www.cancer.gov/
http://www.research.uci.edu/compliance/human-research-protections/hrp-policy-library/hrppPolicies.htm
https://intranet2.ha.uci.edu/Compliance/research/GuidancePolicies/research-GuidancePolicies.htm
David Handelsman. "Electronic Data Capture: When Will It Replace Paper?". *SAS Institute Inc.* Retrieved 2010-09-03.
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https://intranet2.ha.uci.edu/Compliance/research/Default.htm

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Have a nice day!

"Compliance means doing the right thing when no one is looking."

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