UC Irvine's Clinical Research Coordinator Certification Preparation Series

PI Roles and Responsibilities

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SESSION 3 & 4: Investigator's Roles and Responsibilities

- Roles, responsibilities and obligations of the investigator
- Study conduct in accordance with investigational plan, investigator agreement and applicable regulations
- Protocol(s) and protocol related document(s) (i.e., informed consent documents, recruitment materials, safety reports, continuing reviews) development, review, and submission for reviewing authorities

- Recruitment, screening, enrollment, and retention of subjects
- Investigational site Investigational product accountability including training of subjects
- Study visits and follow up care

- Investigational site source documentation
- Documentation/Reporting discontinuation of study subjects
- Investigational site study related reports (i.e. progress reports, protocol changes, protocol deviations, final reports source documentation/case report forms

- Maintenance of essential study related documents (paper/electronic)
- Abstracting/verification of information from medical records
- Record retention requirements for clinical sites
- Quality control, quality assurance and corrective and preventive action plans (CAPA) at investigational site

Terminology

Code of Federal Regulations CFR Title 21 Part 50: PROTECTION OF HUMAN SUBJECTS

Investigator means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

Terminology

Sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

Terminology

Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

Principal Investigator (PI) Responsibilities

- Conduct study according to IRB approved protocol
- Provide documented training to all research personnel regarding the study requirements
- Maintain an investigator and research staff signature and responsibility log of all appropriately trained and qualified research personnel to whom the investigator has delegated study-related studies

Principal Investigator (PI) Responsibilities

- Assume responsibility for initial and ongoing IRB review
- Report any/all protocol and/or subject enrollment changes to the IRB
- Report unanticipated risks (AE/SAE) to IRB & protocol sponsor
- Assess and document subject eligibility criteria

Principal Investigator (PI) Responsibilities

- Inform subjects of investigational status of test article, including risks and benefits
- Ensure that research staff accurately follow up all procedures and timelines specified in the protocol
- Obtain and document the subject's informed consent to participate as a research subject and the subject's authorization to access protected health information
- Maintain adequate audit-ready research records

21 CFR Sec. 312.60 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in 50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

21 CFR Sec. 312.61 Control of the investigational drug.

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

21 CFR Sec. 312.62 Investigator recordkeeping and record retention.

(a) *Disposition of drug*. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under 312.59.

(b) *Case histories*. An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

(c) *Record retention*. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

21 CFR Sec. 312.64 Investigator reports.

(a) *Progress reports*. The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under 312.33 to submit annual reports to FDA on the progress of the clinical investigations..

(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 investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor. The investigator must record non-serious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.

(c) *Final report*. An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.

(d) *Financial disclosure reports*. The clinical investigator shall provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter. The clinical investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study

21 CFR Sec. 312.66 Assurance of IRB review.

An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

21 CFR Sec. 312.68 Inspection of investigator's records and reports.

An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

21 CFR Sec. 312.69 Handling of controlled substances.

If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

Protocol and Regulatory Review

What is a protocol?

Protocol: A written protocol describing the methodology to be used and an analysis of the protocol demonstrating that the investigation is scientifically sound. *CFR Sec. 812.25*

- A study plan on which all clinical trials are based.
- Carefully designed to protect the health of participants.
- Describes what types of people may participate in the trial (inclusion and exclusion criteria).
- Gives detailed schedule of tests, procedures, medications, dosages, and length of the study.
- Principal Investigator is responsible for assuring that the protocol is strictly followed for each participant.

Review of Protocol/Necessary Elements

- Summary
- Inclusion/Exclusion
- Randomization
- Visits/Procedures
- Clinical events/endpoints
- Adverse Events and Stopping Rules
- Amendments
- Version Control

Institutional Review Board (IRB)

- A group of scientists, doctors, clergy, and consumers
- All clinical trials must be reviewed and approved by your local Institutional Review Board (IRB). The IRB reviews the protocol and patient consent to make sure the study is conducted fairly and participants are not likely to be harmed.
- The IRB also decides how often to review the trial once it has begun. They also decide whether the trial should continue as initially planned and what changes should be made.
- An IRB can stop a clinical trial if there are safety concerns, inappropriate trial oversight, or if evidence becomes available that a new intervention is effective, in order to make it widely available.

Other Ethics Committee Approvals

- Cancer Center Protocols (PRMC)
- Data Safety And Monitoring Committee (DSMB)
- Research Revenue Integrity (RRI)
- Conflict of Interest Oversight Committee (COIOC)
- Scientific Review Committee
- Institutional Biosafety Committee (IBC)
- Radioactive Drug Research Committee (RDRC)
- Radiation Safety Committee (RSC)
- Environmental Health and Safety (EH&S)
- Human Stem Cell Research Oversight (hSCRO)
- Laser Safety Committee (LSC)
- Epidemiology and Infection Prevention (EIP)

UCI Committee Review Applicability

Committee	When is it needed?	How does it impact IRB review?	Who can I contact if I have a question?
Clinical Research Finance Assessment **(CRFA)**	UC Irvine Health has established the Clinical Research Billing (CRB) process to assure appropriate billing of clinical services delivered in a research study, when the study takes place in a clinical environment which interfaces with the hospital or physician billing systems. The functions of the CRFA (Clinical Research Finance Assessment) office are now a component of CRB. CRB processes include correctly identifying, coding, and recharging and/or billing all technical and professional services provided; ensuring regulatory/contractual documents are consistent with the Medicare National Coverage Determination (NCD); advising on appropriate cost language in informed consent forms; and providing quotes for research rates to be included in proposed budgets.	*Obtaining coverage analysis and registration of the research protocol is required and remains the responsibility of the Lead Researcher prior to initiating any clinical services. The CRFA/CRB requirement applies to research protocols involving both minimal risk and greater than minimal risk.*	Paula Hilbert: 714-456-3922, philbert@uci.edu Lila Moulton: 714-456-7618, lmoulton@uci.edu
Conflict of Interest Oversight Committee **(COIOC)**	Reviews all human subjects' research studies where an investigator and/or research team member has disclosed financial interests related to a research project conducted at UCI or using UCI resources or facilities that involve the use of human subjects. COI review and management plan(s) are shared with the IRB so that the IRB can make the final determination about the COI as it pertains to human subjects research.	*FOR CPAS AND MODS, COIOC review is required prior to IRB review. Documentation of COIOC review, including the COIOC report and suggested consent language must be provided to the IRB at the time of their review.* *EXCEPTION: In an effort to facilitate the regulatory review process, FOR NEW STUDIES ONLY, IRB review may run concurrent with COIOC review. However, if the COIOC report and suggested consent language are not available at the time IRB review, the IRB must "T" the new study pending this information. Once the report is available, the new study must return to the full IRB for final review and approval.*	Nadia Wong: 949-824-0012, nadiaw@uci.edu Amy Green: 949-824-9015, acgreen1@uci.edu
Epidemiology and Infection Prevention **(EIP)** Committee	Research protocols involving the study of devices, biologic products, or infectious agents in humans on the UCIMC campus or any UCI-affiliated clinical site (including clinical sites on campus or external affiliated sites) require review by the EIP Committee.	*Securing EIP Committee approval is the responsibility of the LR and is required before clinical research procedures can be initiated.*	For additional information about the EIP Committee call the Health Epidemiology and Infection Prevention Program at: 714-456-5221.
Human Stem Cell Research Oversight **(hSCRO)**	Reviews all research or clinical investigations that involve the use of human stem cells. Applies to the use of human pluripotent stem cells.	*hSCRO approval is required before IRB review. hSCRO comments, including hSCRO approval must be provided to the IRB at the time of their review.*	Cathryn Lucas: 949-824-7735, cathryn.lucas@research.uci.edu
Institutional Biosafety Committee **(IBC)**	Responsible for providing institutional oversight of recombinant DNA research. In addition, the IBC oversees all activities using infectious agents, human and non-human primate blood, bodily fluids and tissues in accordance with CDC guidelines.	*When the research involves rDNA activities or activities involving the introduction of genetically engineered micro-organisms or infectious agents into human subjects, IBC approval is required before IRB review. IBC findings and approval must be reviewed by the IRB prior to granting approval.* *Securing IBC approval for biosafety issues (e.g., blood draws, specimens transferred from clinic to UCI lab, etc.) is the responsibility of the LR and is required before clinical research procedures are initiated.*	Alice Lee: 949-824-8024, ibc@uci.edu
Laser Safety Committee **(LSC)**	Laser Safety Committee Review: If research involves the use of an investigational laser or the use of an FDA approved laser off label, Laser Safety Committee review or consultation may be appropriate.	*Securing LSC review or consult is the responsibility of the LR and is recommended before clinical research procedures are initiated.*	For lasers with a biomedical, clinical or therapeutic focus, contact John Gratzle at: jgratzle@uci.edu. For other research use of lasers on campus contact Bryan Ruiz at: btruiz@uci.edu. For more info, please refer to the following link at: http://www.ehs.uci.edu/radsafe.html

UCI Committee Review Applicability

Committee	When is it needed?	How does it impact IRB review?	Who can I contact if I have a question?
OR/Procedural Services Committee	LRs conducting human subjects research in the surgical units must notify the UCIMC OR/Procedural Services Committee before study procedures can be initiated. A copy of the protocol must be provided to the Committee.	*Notifying the OR/Procedural Services Committee is the responsibility of the LR and is required before clinical research procedures can be initiated in the surgical units.*	For notification, email Ms. Laura Bruzzone at: lbruzzon@uci.edu
The Chao Family Comprehensive Cancer Center (Cancer Center) Protocol Review and Monitoring Committee **(PRMC)**	Prior to initial and continuing IRB review and approval, all research protocols that involve participants with cancer, at risk for cancer, any active intervention (e.g. behavioral or pharmacological) involving cancer or pre-cancerous participants, or participants of a study involving a specific cancer focus (e.g. program evaluations, quality of life survey health education, etc.) must be submitted to and cleared by the UCI Chao Family Comprehensive Cancer Center (cancer center) Regulatory Affairs Office for facilitation through the Protocol Review and Monitoring Committee (PRMC) review process. **Note**: This is a School of Medicine requirement for all cancer related research protocols. PRMC clearance is not required for cooperative group studies and protocols which have received prior PRMC exemption from review.	*PRMC review is required (with documentation of clearance from the PRMC) prior to IRB review if the research meets the following criteria:* • *Investigator-authored research;* • *Involves biomedical/clinical research including clinical investigations;* • *Involves greater than minimal risk to subjects (i.e., requires full board review); and* • *Has not received peer review for scientific merit.* *PRMC review prior to IRB review is NOT required for:* • *Research involving no more than minimal risk to subjects (i.e., Exempt and Expedited categories of research).* • *Research that is industry-authored (i.e., for-profit pharmaceutical or medical device entities)* • *Research that is federally-sponsored or sponsored by other non-profit entities (e.g., private foundation, other academic institutions) with documentation of peer review for scientific merit.* Note: The UCI IRB reserves the right to require scientific merit review prior to IRB review or prior to approval for any research.	Researchers should contact the PRMC at: CancerCenter_Committees@health.uci.edu or (714) 456-6550 for assistance in handling this requirement. Researchers may obtain the required PRMC forms and detailed information about the PRMC review process at the internal PRMC website. **Note**: this website is located on the UCIMC Intranet, which requires HSIS intranet access (please email the PRMC for access issues). All School of Medicine employees have access to the HSIS intranet. Upon log on to the Cancer Center website, click on "Research Assistant" to access information about the PRMC.
Radiation Safety Committee **(RSC)**	All protocols involving radiation exposure to normal subjects, and/or clinical human subjects when the exposure is not considered standard-of-care must be referred to the RSC subcommittee for review. Over 75% of the RSC reviews take place by subcommittee. If necessary, the study will be referred to a full RSC meeting for a more extensive review.	*RSC approval is required before IRB review. RSC comments, consent language and approval must be reviewed by the IRB prior to granting approval.*	John Gratzle: (714) 456-5729, jgratzle@uci.edu
Radioactive Drug Research Committee **(RDRC)**	The RDRC reviews research studies that involve the use of radioactive material in or on human subjects regardless of the amount of radioactivity. The RDRC only reviews and approves basic research studies, and does not review and approve studies intended to determine the safety and effectiveness of the drug in humans for such purposes as carrying out a clinical trial, for example.	*When the research involves radioactive materials, documentation of RDRC review, including RDRC comments and approval before the IRB can grant approval. Alternatively, documentation of an IND from the FDA is required before final IRB approval. Sufficient documentation of an IND include IND letter from FDA or IND number on Sponsor's Master Protocol, if externally sponsored.*	Cathryn Lucas: 949-824-7735, cathryn.lucas@research.uci.edu
Scientific Review	UCI's IRB assumes responsibility for scientific review in conjunction with the Biostatistics, Epidemiology and Research Design (BERD) unit in the Institute for Clinical and Translational Sciences (ICTS). Studies that meet the following criteria require scientific merit review: • UCI investigator-authored • Biomedical or clinical research • Does not involve cancer* • Involves greater than minimal risk to subjects (i.e., full board review); *and* • Research described in the IRB protocol has not been peer reviewed; *or* • IRB requires scientific review (study-by-study basis) *Studies that undergo review by the PRMC are excluded from the scientific review process through the IRB/BERD.	*Scientific review clearance for full committee protocols is required before IRB review.* *Reviewer comments, including scientific review clearance must be provided to the IRB at the time of their review.* *Exempt and Expedited level protocols DO NOT require scientific review unless mandated by the IRB Subcommittee.*	Contact HRP Staff at: http://www.research.uci.edu/compliance/human-research-protections/about-the-irb/hrp-contact-list.html

Regulatory Documents

Regulatory Documents

- Protocol and Amendments
- Informed Consent Documents
- IRB Documentation
- IRB Approvals and Correspondence
- Investigator Qualification Documentation
- Clinical Investigator's Brochure
- FDA Documents
- Study Communication
- Signed Consent Documents
- Laboratory Certifications
- Specimen Tracking Log
- Serious Adverse Events (SAE) Documents

More Regulatory Documents

- Protocol Deviation Form or Memo
- Clinical Site Monitoring Visits
- Sponsor Correspondence
- Data Safety and Monitoring Documents
- Other necessary approvals (e.g. Radiation Safety Committee)
- Certificates of Confidentiality
- Literature or publications
- Correspondence from the FDA, NIH, & etc.
- Other general correspondence

Monitoring Reports, Log, and Correspondence

ICH Guidance: E6 Good Clinical Practice (GCP) Sections:1.38, 1.39, 4.1.4, 5.18 , 5.18.6), 8.2.19 & 8.2.20, 8.3.10, 8.4.5, 21 CFR 312.56 21 CFR 812.46

- The reports document the findings of the monitor, usually a written report to the sponsor after each site visit or other trial-related communication.
- A monitoring log can document visits to the site, and may be used to track all outside visitors who review the study and who have had access to confidential study materials and when.
- The log can document whether the monitor provided a report to the site, and whether the report was provided to the IRB.

Delegation Log

*ICH Guidance: E6 GCP Sections: 4.3.1, 4.1.5, 5.18.4h, *FDA Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects Section III, A, 1*

- The overall responsibility for a clinical trial rests with the Principal Investigator. The Principal Investigator can delegate specific responsibilities to various members within the team. These responsibilities should be formally assigned.
- A delegation log can help keep track of the responsibilities of the various team members.

Delegation Log

- Any individual to whom a task is delegated should be qualified to perform the delegated task. A protocol may specify the qualifications of the individuals who are to perform certain protocol-required tasks, in which case the protocol must be followed even if individuals with different qualifications may otherwise be permitted to perform the task.

- An investigator should maintain separate lists for each study conducted by the investigator, so delegation logs should be study-specific rather than maintaining a central one for all of a PI's studies.

Delegation Log

- The list or log should include the start and end dates of a team member's involvement in the study, or the start and end dates of their specific responsibilities if they change during the study.
- The regulatory binder should also identify the training that individuals have received that qualifies them to perform delegated tasks.
- The delegation log can refer to other documents (like a CV) that identify qualifications.

Signature Log

ICH Guidance: E6 GCP Sections: 8.3.24

- For GCP, to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.
- Capturing the original signature and initials of all staff members prior to start on the study may help authenticate or verify data entry if questioned, based on handwriting/signature.
- A signature log can provide an updated reference of research staff, past and present, which can be especially helpful for studies that are long in duration, have large staff number, and/or have staff turnover during the study.

Study Personnel Education

ICH Guidance: E6 GCP Sections: 2.8, 4.1.1 - 4.1.3, 4.2.4, 5.23.4, 8.2.20

- There should be adequate training for all staff participating in the conduct of a study, including any new staff members that start after the study has begun.

- Staff should be familiar with the purpose of the study and the protocol, have an adequate understanding of the specific details of the protocol and attributes of the investigational product needed to perform their assigned tasks, be aware of regulatory requirements and acceptable standards for the conduct of clinical trials and the protection of human subjects, be competent to perform or have been trained to perform the tasks they are delegated, and be informed of any pertinent changes during the conduct of the trial and receive additional training as appropriate.

Study Personnel Education

- If the sponsor provides training for investigators in the conduct of the study, the investigator should ensure that staff receive the sponsor's training, or any information (e.g., training materials) from that training that is pertinent to the staff's role in the study.

- Certification that one has completed training in human subject protection in research is required of all faculty, investigators, study coordinators and other individuals directly involved in human subject research. This means **anyone working directly with human research participants, data, or tissue that can link back to individual research participants** .

Study Personnel Education

- Typically this includes all individuals listed on a research protocol, including those whose work is limited to chart/medical record reviews, database inquiries, discarded biological specimens, and data analysis or statistical support if they can link back the data.
- HIPAA training specific for human subject research is also required.
- Submit proof of human subject protection training and HIPAA training to the IRB, and update every 3 years.

Curriculum Vitae, medical licenses, professional certifications

ICH Guidance: E6 GCP Sections: 2.7, 3.1.2, 4.1.1, 4.3.1, 8.2.10, 8.3.5

- Maintain the CV and/or other relevant documents indicating the qualifications and eligibility of investigators and other key personnel to conduct a trial and/or to provide medical supervision of subjects
- Valid licenses & certifications for all professional study staff (e.g., medical or nursing license)
- Current professional certifications that verify staff eligibility to perform clinical procedures (e.g. phlebotomy, vital signs, ECG)

Curriculum Vitae, medical licenses, professional certifications

- Available for all investigators and other members of the study team, including any new staff members that start after the study has begun.
- Monitor expiration dates so those nearing expiration can be promptly updated.
- Update/revise CVs as needed with significant changes such as affiliation, education, and responsibilities. It is recommended to sign, date, and update CVs every 2 years to verify that the information is accurate and current.

Curriculum Vitae, medical licenses, professional certifications

- For IND studies, maintain appropriate documents for the investigator listed in section #1 of the FDA 1572 Form, as well as those individuals listed in section #6.
- Keep all CVs, licenses, and certifications from the start of the study, even those that have expired or have been replaced, to maintain an audit trail.

Investigator Statements/Agreements

21 CFR 312, 21 CFR 312.53c, 1 CFR 812.43c

- A Statement of Investigator, *Form FDA 1572*, is an agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic. It is used for clinical investigations being conducted under an investigational new drug application (IND).
- The list of individuals named on the1572 should be consistent with the protocol submitted to the IRB.
- The site should maintain a signed investigator agreement for device studies.

Financial Disclosure

21 CFR 54, 21 CF 312, 21 CFR 54.2(d) and 54.4 FDA Guidance: Financial Disclosure by Clinical

- Disclosure statement to: Certify that there is no financial interest or Disclose specific financial interests
- Proper procedure for institutional disclosure forms should be followed per IRB and institutional policies. Generally, a study-specific financial disclosure form is requested from each individual during the initial IRB application and at each continuing review.

Financial Disclosure

- For IND studies, maintain appropriate disclosure statements for the investigator listed in section #1 of the FDA 1572 Form, as well as those individuals listed in section #6. Make sure the list of individuals named on the1572 is consistent with the protocol submitted to the IRB so that disclosure information submitted to the sponsor and to the IRB are consistent.

- For studies considered covered clinical studies by FDA, maintain signed and dated copies of all Forms FDA 3454 and 3455.

Financial Aspects of the Trial

ICH Guidance E6 GCP: Section 4.9.6, 8.2.4

- Document the financial aspects of the trial and the financial agreement between the investigator/institution and the sponsor for the trial (may be part of the CTA)

Public Registration of Research Studies

FDAAA; U.S. Public Law 110-85, Title VIII, 42 U.S.C. § 282(j)(1)(A), Fact Sheet: Clinicaltrials.gov Fact Sheet

- All research studies that are applicable clinical trial must be registered at www.clinicaltrials.gov as per the International Committee of Medical Journal Editors (ICMJE), the FDA Amendment Act of 2007, and institutional policy.
- Maintain the registration receipt for initial registration and for any updates.
- For commercially funded, multi-center studies, public registration is typically handled by the study sponsor or CRO.

FDA Documents: Regulatory approval or authorization; FDA correspondence log

ICH Guidance: E6 Good Clinical Practice (GCP) Sections: 8.2.9, 8.3.4

- Include letter indicating IND acknowledgment or IDE acknowledgment, as well as other correspondence with FDA.
- Include Form 1571 for Investigator initiated INDs
- Considered an essential document per GCP

Screening, Enrollment, and Randomization Logs

ICH Guidance: E6 GCP Sections: 4.7, 8.2.18, 8.3.20, 8.3.22, OHRP continuing review guidance

- Document identification of subjects who entered pretrial screening
- Document chronological enrollment of subjects by number
- Screening and enrollment/randomization logs may be separate or combined
- May include reasons for screen failures
- If you need to enroll more subjects than initially expected, obtain IRB approval before enrolling the additional subjects.

Screening, Enrollment, and Randomization Logs

- An enrollment log may be useful to track the number of subjects enrolled and the rate of enrollment for continuing renewal with the IRB.

- A log may keep track of the following information:
  - Number of subjects who provided consent
  - Number of subjects determined to be ineligible
  - Number of subjects currently active/on study
  - Number of subjects withdrawn at subject's request
  - Number of subjects withdrawn at the request of the investigator
  - Number of subjects withdrawn due to adverse events/unanticipated problems
  - Number of subjects lost to follow-up
  - Number of subjects no longer participating for other reasons
  - Number of subjects who have completed the study

Subject Visits and Termination

ICH Guidance: E6 GCP Sections: 4.3.4, 21 CFR 312.62(b)

- Study visits may be documented with detailed progress notes or with visit checklists that outline required study procedures and data points that must be captured for each visit.

- Progress notes, study visit checklists, or another method for documenting visits are useful in addition to documents like admission notes, history and physician records, x-rays, labs, emergency room notes, etc.

Subject Visits and Termination

- Documentation of a Study visit may include the following information:
  - ✓ Date of visit and Subject ID
  - ✓ Subject's current status
  - ✓ Changes in subject's condition or diagnosis
  - ✓ Subject's response to planned intervention
  - ✓ Unexpected Occurrences
  - ✓ Completion of required procedures or tests
  - ✓ Any concerns or questions of the subject/family
  - ✓ Information pertinent to subject/family comprehension
  - ✓ Documentation that consent was obtained prior to research procedures or that subject expressed a continuing agreement to participate

Subject Visits and Termination

- Include additional details in study visit documentation which may pertain to the subject's mood, cooperation and any questions that were discussed during the visit. Study visit documentation can provide valuable data about the conduct and understanding of the study that CRFs and other types of source documents (x-rays, labs, etc.) cannot.

- Progress notes and study visit checklists can be very useful during data analysis as questions arise. For example, if the documentation of the study visit indicates that the subject was rushed because of a transportation issue, it could help explain missing information (a potential protocol deviation).

Subject Visits and Termination

- Logs may be a useful addition to progress notes and study visit checklists.
- A subject visit tracking log can track all enrolled subjects' visits and keeps visits scheduled as per protocol. It can also note where to find additional information if a subject did not complete a test or completed a test on different date, if the subject ended the study early, etc.
- A subject withdrawal/completion log can track whether subjects completed the study, withdrew, or were terminated early, and can collect additional information about withdrawals.

Subject Visits and Termination

- Per GCP, a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, but the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.
- A log can also indicate if the subject participated in the study termination visit (which may be specified in the protocol for safety reasons).
- It can also track if any subjects were partial withdrawals. For instance, a subject may stop the investigational product because of side effects, but the investigator may ask to continue follow up research activities.

Subject Visits and Termination

- OHRP recommends that when seeking the informed consent of subjects, investigators explain whether already collected data about the subjects will be retained and analyzed even if the subjects choose to withdraw from the research.

- For HHS-conducted or supported research that is not subject to FDA regulations or the HIPAA Privacy Rule, the investigator should inform subjects whether the investigator intends to either: (1) retain and analyze already collected data relating to the subject up to the time of subject withdrawal; or (2) honor a research subject's request that the investigator destroy the subject's data or that the investigator exclude the subject's data from any analysis.

Consent Form

- Obtain signed informed consent forms in accordance with the process described in the protocol. They must be dated prior to participation of each subject in a trial. If consent is obtained the same day that study procedures start, please note the time consent is obtained.

- Changes to a consent form may be initiated by the study team, the sponsor, or the IRB. Any change to a consent form must be approved by the IRB before the revised consent form is signed by subjects. Each subject must sign a copy of the consent form with the IRB approval/expiration stamp.

Consent Form

- Be aware of the template version date, and check with the IRB regarding template revisions. Incorporate any applicable template revisions into your consent document if appropriate for the study (usually if the study is still consenting subjects). This may be done at the time of continuing review, or as indicated by the IRB for the study.

- Save all versions submitted and approved by the Institutional Review Board (IRB) in the regulatory binder. Have a method to indicate the current consent form for the study team.

Consent Form

- Document revisions of the trial-related documents that take effect during the trial; save any revisions to:
  - ✓ Informed consent
  - ✓ Any other written information provided to the subjects
- Retain consents obtained for screening purposes even if the subject was not enrolled in the study
- Non-English speaking subjects must be consented in a language they can understand.

Consent Form

- Changes to any other written information provided to the subjects also must be approved by the IRB before presenting the information to the subjects. Save all versions submitted and approved by the IRB in the regulatory binder. Study visit documentation should indicate what documents were presented to subjects and the dates (e.g., instructions for use on study visit #1; revised instructions on study visit #5; article addressing outcome from earlier study on study visit #14)

Consent Form

- A consent revision log can provide a reference for study staff to determine when changes were made to the consent form and may also assist in ensuring the proper version of the consent form is used during the consent process or when proposing new revisions of the consent form.

- A log can document revisions made to the consent form, as well as track proposed revisions currently pending IRB review and approval. It may be particularly helpful when there are multiple consent forms in use for a study (e.g., sub-study consents or consents for different populations), the research staff is large, or the study will enroll subjects over a long period of time.

Final Closeout Reports

ICH Guidance: E6 GCP Sections 4.13, 8.4.7

- Final report by investigator is sent to the IRB where required and, where applicable, to the sponsor and to the regulatory authorities, to document completion of the trial.

- May include the following information:
  - ✓ Disposition of the subjects
  - ✓ Location of the research records
  - ✓ Disposition of the specimens
  - ✓ Disposition of the study drugs

Investigator's Brochure (IB) and Safety Package Inserts

ICH Guidance: E6 GCP Sections: 1.3.6, 3.1.2, 7, 8.2.1, 8.3.1, 21 CFR 312.55 (sponsor)

- Document that relevant and current scientific information about the investigational product has been provided to the investigator
- Include updates to document that investigator is informed in a timely manner of relevant information as it becomes available
- Include the following:
  - ✓ The most recent version
  - ✓ Addendum
  - ✓ Safety letters

Protocol Deviations/Protocol Exceptions/Violations

ICH Guidance: E6 Good Clinical Practice (GCP) Sections: 3.3.7, 4.5, 8.3.11, 21 CFR 312.66, 21 CFR 312.53(c)(1)(vii)

- Maintain records of all protocol deviations, their resolution, and IRB reporting status.
- Protocol deviations related to individual participants may be included in the participants' study record, but there may also be a protocol deviation log where all deviations are noted for the study as a whole.
- Keep exceptions granted by the sponsor in the participant study record.
- Communications regarding protocol violations are considered an essential document per GCP

Adverse Events (AE) and Unanticipated Problems

ICH Guidance: E6 GCP Sections: 1.1, 1.2, 1.50, 1.60, 4.11, 5.16.2 & 5.17, 8.3.16, 8.3.17 & 8.3.18 , 21 CFR 312.66, 45CF 46, 21CFR50, 21CFR56, 21CFR312, 45 CFR 46.103(b)(5)

- Notification by originating investigator to sponsor of adverse events, related reports, and other safety information
- Notification by sponsor to investigators of safety information
- Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB of unexpected adverse events, unanticipated problems, and of other safety information
- Information about specific AEs should be kept in the participant's individual study record
- Considered an essential document per GCP

IND Safety Reports

21 CFR 312.32

- Sponsors are specifically required to provide written IND safety reports to all participating investigators (and FDA).
- Sponsors may instruct the investigators to submit IND safety reports to the IRB.
- IRBs are required by FDA and DHHS human subjects protection regulations to review "unanticipated problems involving risks to participants or others."

Advertising/Education/Written Materials

ICH Guidance: E6 Good Clinical Practice (GCP) Sections: 3.1.2, 8.2.3

- Include any IRB approved advertisements, recruitment flyers, written educational, or other materials provided to study participants.
- This documents that recruitment measures are appropriate and not coercive.
- Maintain all revisions to the documents. Have a method to indicate the current documents in use for the study team.

Recruitment Material

UC Irvine complies with the federal regulations of human subjects that require equitable subject selection, and with the NIH policy regarding gender and ethnic representation in human research populations.

Advertisements and recruitment materials for human research subjects (posters, flyers, paid or unpaid newspaper/magazine ads, scripts for radio/TV, e-mail, or solicitations from outside sources) are considered an extension of the informed consent and subject selection process.

Recruitment Material

Accordingly, such materials are governed by federal regulations for the protection of human research subjects and require IRB review and approval. If not submitted with the initial application, ads should be submitted with requests for protocol modification once a study is approved.

Investigational Product Management
FDA-Regulated Human Research

Investigational Drug and Device

- Investigator Brochure
- FDA Form 1571 (IND Application)
- FDA Form 1572 (Statement of the Investigator)
- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071073.htm

Investigational New Drug (IND) Application

- IND means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.
- A filing is required with the FDA when a new drug, biologic, or significant risk device is the object of the research
- Affirms a body of knowledge about the manufacturing, pharmacology, and toxicology of the drug to support its use in human research

Investigational New Drug (IND) Application

- The IND exemption is granted for purposes of clinical investigation (research)
- Requires that the clinical investigation(s) be performed in accordance with Good Clinical Practices
- The investigation is intended to be reported to the FDA as a well-controlled study in support of a new indication or a significant change in the labeling of the drug
- The clinical investigation is intended to support a significant change in advertising for the product

21 CFR Sec. 312.6 Labeling of an investigational new drug.

(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."

(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.

21 CFR Sec. 312.6 Labeling of an investigational new drug.

(c) The appropriate FDA Center Director, according to the procedures set forth in 201.26 or 610.68 of this chapter, may grant an exception or alternative to the provision in paragraph (a) of this section, to the extent that this provision is not explicitly required by statute, for specified lots, batches, or other units of a human drug product that is or will be included in the Strategic National Stockpile.

Investigational Device Exemptions (IDE) Process

- *Investigational device* means a device, including a transitional device, that is the object of an investigation.
- An approved investigational device exemption (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device.
- An IDE and IRB approval are required before a device study can begin
- The sponsor must determine, with supporting documentation to the FDA, that the device represents a significant risk (SR) or a non-significant risk (NSR)

Investigational Device Exemptions (IDE) Process

- A formal IDE application must be filed with the FDA for a device with a SR determination
- A device with a NSR determination is considered by the FDA to have an approved IDE when documentation is sufficient to substantiate the finding of NSR as reviewed and approved by an IRB
- The IRB must have SOP's and supporting documentation as to how the risk determination was made

Investigational Device Exemptions (IDE) Process

- Under an IND or IDE the FDA may permit a sponsor, when requested, to charge for an investigational device, investigational drug or biologic under certain circumstances.
- The charge should not exceed an amount that is necessary to recover the costs associated with the manufacture, research, development, and handling of the investigational device, investigational drug or biologic.

21 CFR Sec. 812.5 Labeling of investigational devices.

- An investigational device or its immediate package shall bear a label with the following 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 precautions.

- 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 subjects."

Investigational Product/Study Drug Accountability

ICH Guidance: E6 GCP Sections: 4.6, 5.13, 5.14, 8.2.14, 8.2.15, 8.2.16, 8.3.8, 8.3.9, 8.3.23, 8.4.1, 8.4.2, 21 CFR 312.57, 21 CFR 312.62, 21 CFR 812.140

The PI is responsible for the following with respect to investigational drugs/devices:

- Maintain records of investigational product delivery to the study site. Include dates, quantities received, batch/serial numbers, and expiration dates.
- Maintain an inventory of the investigational product at any site. Inventory control records should be updated, signed, and dated in a timely manner.

Investigational Product/Study Drug Accountability

- Record/track use of the investigational product by each participant. Documentation should verify that dosing/device use was in accordance with the approved protocol. Maintain an accountability log that records when the participant(s) received the drugs/device and the specific dosage/device the participant(s) received.
- Return/dispose of unused investigational product as specified by the sponsor. Maintain documentation of return/disposal.

Investigational Product/Study Drug Accountability

- Store the investigational product. The storage area should be locked/secure with access limited to approved study staff only. Drugs/devices should not be stored with standard clinical inventory.
- This should be done in collaboration with the research pharmacy.
- Considered essential documents per GCP

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/

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

References

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.

Dr Thomas Bart. "Comparison of Electronic Data Capture with Paper Data Collection – Is There Really an Advantage?". *Business Briefing, Pharmatech*. Retrieved 2013-02-25.

https://clinicaltrials.georgetown.edu/common-regulatory-documents

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https://intranet2.ha.uci.edu/Compliance/research/Default.htm

Have a nice day!

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

UC Irvine Health