# UH Clinical Research Education

Research Certification Packet

## THE UH CLINICAL RESEARCH CENTER

The UHCRC offers a wide range of live and online seminars to educate investigators and research staff on regulatory requirements and best practices when conducting research. See the full Education Catalog for more options.

Within this packet of information, learn about different clinical research certifications you can earn.

Once you sign up to take the exam for one of the certifications, refer back to this packet as a guide to help you study.

Additional questions or clarifications?
Contact ClinicalResearch@UHhospitals.org

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# Society of Clinical Research Associates (SOCRA)
# vs
# The Association of Clinical Research Professionals (ACRP)

| | SOCRA | ACRP |
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| **Cost**<br>Check the websites to confirm payment methods. | $450 initial, recertification $350 every 3 years. | Early Bird: $485 initial except for ACRP-PM, recertification $225 every 2 years<br>Regular: $600 initial except for ACRPPM, recertification $250 every 2 years |
| **Skillset** | Clinical Research Regulatory heavy, with FDA regulations. | Specific to your role. No FDA regulations. |
| **Content of Exam**<br>This is a general overview, each exam has a manual depicting what is covered in each exam. | • The Nuremberg Code<br>• The Belmont Report<br>• The Declaration of Helsinki • 21 U.S. Code of Federal Regulations – Parts 11, 50, 56, 312, 812<br>• 45 U.S. Code of Federal Regulations - Part 46<br>• ICH Harmonised Guideline for Good Clinical Practice E6(R2), and<br>• ICH Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A) | • Guideline for Good Clinical Practice E6(R2)<br>• Definitions and Standards for Expedited Reporting E2A<br>• General Considerations for Clinical Trials E8<br>• Statistical Principles for Clinical Trials E9<br>• Clinical Trials in Pediatric Population E11<br>• The Declaration of Helsinki (DoH) |
| **Eligibility**<br>Please check the full eligibility criteria on their respective websites, this is just a general overview. | 1750 – 3500 hours of clinical research experience. | **CCRA, CCRC, & ACRP-CP:** 1500 – 3000 years of clinical research experience.<br>**CPI:** 2 years within the last 10 of clinical research experience.<br>**ACRP-PM:** Must hold a CCRA, CCRC, ACRP-CP, or CPI certification. |

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| **Credentials** | CCRP (Certified Clinical Research Professional) | CCRA (Certified Clinical Research Associate)<br>CCRC (Certified Clinical Research Coordinator)<br>CPI (Certified Principal Investigator)<br>ACRP-CP (ACRP Certified Professional)<br>ACRP-PM (ACRP Project Manager)<br>ACRP-MDP (ACRP Medical Device Professional) |

**SOCRA:**

SOCRA established the Certification Program for Clinical Research Professionals in order to create an internationally accepted standard of knowledge, education, and experience by which clinical research professionals will be recognized by the clinical research community. Those individuals so recognized may use the "Certified Clinical Research Professional" or "CCRP® (SOCRA)" designation.

**More information**

How to Apply: https://www.socra.org/certification/ccrp-certification-exam/application-and-fee/

Maintenance of Certification: You need to acquire 45 hours of Continuing Education Credits. This can be accomplished many ways, including completing UH courses with CREC associated to them. Two months before your certification expires, you will receive an email on how to renew your membership. This includes $350 to be sent to be certified for another 3 years.

What to study for the exam:

Standards of Practice include an understanding of and application of basic concepts of Good Clinical (Research) Practice, including:

- The Nuremberg Code
- The Belmont Report
- The Declaration of Helsinki
- 21 U.S. Code of Federal Regulations – Parts 11, 50, 56, 312, 812
- 45 U.S. Code of Federal Regulations - Part 46
- ICH Harmonised Guideline for Good Clinical Practice E6(R2), and
- ICH Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A)

*Besides reading, how should I prepare?*

Think about how you apply all the regulations and guidance to your everyday tasks. Most test questions will be based on your application of the regulations and guidance, with some more basic questions.

All questions are based on how you manage your day-to-day job as a clinical research professional.

You will not need to know the numbering of the sub-sections of the regulations (ie 50.23 is exceptions from general requirements). You will need to know the information in each Code of Federal Regulation. You will not be tested on specific section numberings.

Pay close attention to reporting times, special populations, and investigator roles vs sponsor roles in a clinical trial.

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**ACRP:**

The Association of Clinical Research Professionals (ACRP) supports clinical research professionals through membership, training and development, and certification. Founded in 1976, ACRP is a Washington, DC-based non-profit organization with more than 13,000 members who work in clinical research in more than 70 countries.

**More information**

How to apply: Choose your certification to apply, https://acrpnet.org/certifications/

Maintenance of Certification: Keep your designation current and continue demonstrating your competence through the Maintenance of Certification program. To maintain your credential you are required to participate in continuing education/involvement activities and report 24 contact hours/points every 2 years, or take the current Certification exam.

What to study for the exam:
The exam content is based on current practice in clinical research and was determined by an international job analysis.

The exam assesses your proficiency of the body of knowledge required and the application of that knowledge in the conduct of your job duties and responsibilities.

Professionals are expected to have proficiency in six (6) core knowledge areas found below and detailed further in the Detailed Content Outline (DCO) for their respective exam:

1. Scientific Concepts and Research Design
2. Ethical and Participant Safety Considerations
3. Product Development and Regulation
4. Clinical Trial Operations (GCPs)
5. Study and Site Management
6. Data Management and Informatics

The exam is referenced to the International Conference on Harmonization (ICH) Guidelines. Other than the ICH Guidelines, no other regulatory framework is tested. The exam does not cover country-specific (FDA, EMA, etc.) regulations.

The following are the only references for which the ACRP Certification exam content can be supported:

1. Guideline for Good Clinical Practice E6(R2)
2. Definitions and Standards for Expedited Reporting E2A
3. General Considerations for Clinical Trials E8

4. Statistical Principles for Clinical Trials E9
5. Clinical Trials in Pediatric Population E11
6. The Declaration of Helsinki (DoH)

Quizlet has numerous flashcard decks to review.

**SOCRA Tips from previous Examinee:**

I think anyone who takes the crash course should be within a month of taking the exam because it is a lot of information but there you can also get very confused. I agree – if you have been doing the work for a while like required for the exam – it is not too hard, but I would encourage test takers to focus on the areas they don't work in. For example, I work in regulatory, so I did not review much about IRBs/submissions etc. I focused on things like the data portion that I don't know – and recommend other do the same. When it's part of your job – don't second guess yourself and make it harder! ☺

There is definitely some repetition within the exam! Things I really noticed:

- Know the differences between investigator roles/responsibilities verse sponsor.
- Reporting timelines are BIG! There were easily over 10 questions about them. A thing I noticed, was that it's not just x days to the FDA – it connects with the previous statement about knowing the sponsor vs investigator roles. Several questions seem like the same but it may say the sponsor or the investigator but the same SAE. Also, definitely know the differences regarding device reporting compared to drug/biologic
- Several monitoring/audit questions
- A couple of questions about significant verse non-significant risks
- Understanding what the differences are between the different phases for protocols
- Several questions about consent – to include the short form
- Special populations (children 2 questions, and 2 prison questions)
- Emergency/exempt/expedited approvals and reviews

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**ACRP Tips from previous Examinees:**

I focused on studying the ICH guidelines and Declaration of Helsinki that are listed as references for the ACRP CCRC exam:

1. Guideline for Good Clinical Practice E6(R2)
2. Definitions and Standards for Expedited Reporting E2A
3. General Considerations for Clinical Trials E8
4. Statistical Principles for Clinical Trials E9 5. Clinical Trials in Pediatric Population E11, and
6. The Declaration of Helsinki (DoH).

I also used Quizlet and Brainscape flash cards to study. I temporarily paid for subscription to one (can't remember which). There are lots of ACRP CCRC exam flash card decks to study and these were so helpful.

Also, there were a few questions about drug accountability that asked us to convert metric system measurements to US imperial measurements (grams to oz) and I was glad I had memorized the conversion. I found those in one of the online flashcard decks that I studied. Of

course, each exam is different so they may not ask any questions on this, but it's a simple conversion to memorize and could make a few points difference in your score.

**Another ACRP Experience:**

I took the ACRP-CP certification exam in September 2021. I studied for about 2 months and every night for about 2-3 weeks prior to the exam. Since it was ACRP, the exam did not contain FDA guidelines. I read all the ICH guidelines listed in the certification Detailed Content Outline and made notecards out of the material. I also utilized quizlet and searched for ACRP and SOCRA exam flashcards.

The exam was challenging, but I felt well-prepared. Most questions were a 2-3 sentence scenario and then a question to apply knowledge to the situation rather than just memorization of definitions, etc.

| At a high level, sponsor and investigator responsibilities for both drug and device studies look very familiar: | | |
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| | **DRUG (IND)** | **DEVICE (IDE)** |
| **Sponsor Responsibilities** | 21 CRF 312.50<br>Ensure that the investigation is conducted in compliance with the investigational plan, the signed agreement, and the applicable regulations. | 21 CFR 812.46<br>Ensuring compliance with the signed agreement, investigational plan, applicable FDA regulations, and IRB requirements. |
| **Investigator Responsibilities** | 21 CRF 312.60<br>Ensure that the investigation is conducted according to the signed investigator statement and the investigational plan. | 21 CRF 812.110<br>An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA. |
| **Conversely, 21 CFR 312 (drug) and 21 CFR 812 (device) regulations have the following differences:** | | |
| | **DRUG** | **DEVICE** |
| **Product information** | Investigators Brochure, package insert | Device manual, instruction for use, package insert |
| **Agreements** | FDA Form 1572 required. | No specific form required.<br>However, must sign commitment to conduct study as outlined in 21 CRF 812.110. |
| **Training** | Focus on protocol requirements, mechanism of action of drug, and possible side effects. | Must include hands-on device training in addition to protocol training. |

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| **Product Reimbursement** | Mostly provided free of charge to clinical sites and patients. | Can be expensive to produce, so charges and reimbursements vary. |
| **Adverse Events** | All AEs need to be captured and analyzed as potentially related to the drug. | Not all AEs are reportable due to local effect of the device. |

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# 9 BASIC ELEMENTS - INFORMED CONSENT FORM

1. **Voluntary Participation and Right to Withdraw**
   - Completely voluntary; and refusal or discontinuation to participate will not result in any penalty or loss of benefits to which is otherwise entitled.

2. **Research Statement**
   - Involves research
   - Purpose
   - Duration
   - Procedures
   - What part is experimental
   - Why you are being asked to join

3. **Risks and Discomforts**
   - Reasonably foreseeable realistic risks/discomforts

4. **Benefits**
   - Presumed positive outcome of trial is not a benefit

5. **Alternatives**
   - Disclosure of subjects' alternatives to research participation, including possibly advantageous alternative procedures

6. **Confidentiality**
   - Extent of confidentiality of identifiable records
   - For FDA regulated research, a statement disclosing that the FDA may inspect records

7. **Compensation**

8. **Contact Person**

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9. ***One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:***
   - *A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or*
   - *A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.*

*Source: 21 CFR 50; 45 CFR 46.116;*

# ADDITIONAL ELEMENTS - INFORMED CONSENT FORM

When appropriate (*) one or more of the following elements of information must also be provided to each subject:

1. **Unknown Risks to Participants**
2. **Termination of Participation**
3. **Costs**
4. **Consequences of Withdrawal**
5. **New Findings Will Be Given to Subjects**
6. **Number of Participants**

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7. ***Biospecimens may be used for commercial profit***
8. ***Disclosure of clinically relevant research results***
9. ***Whether biospecimens will or may be used for whole genome sequencing***

*All applicable to Clinical Trials, i.e. required by the FDA

- GINA: Genetic Information Nondiscrimination Act
- GWAS: Genome-Wide Association Studies
- Conflict of Interest (COI)

Sponsor and/or Funding Agency requirements

- Injury language
- Payment for procedures
- Access and Disclosure of information (HIPAA)

***All Research participants receive a copy of the signed inform consent***

*Source: 21 CFR 50; 45 CFR 46;*

## Determining whether an AE is Expected or Unexpected

UADEs – Unanticipated Adverse Device Effects. Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a 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), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Caused or contributed means that death/injury was/may have been attributed to a medical device or a medical device may have been a factor in a death/injury, in event of: failure, malfunction, improper or inadequate design, manufacture, labeling, or user error.

## Determining whether an AE is Serious or Non-serious

Serious injury means an injury or illness that:

1) Is life-threatening,
2) Results in permanent impairment damage of a body function or permanent damage to a body structure, or
3) Necessitates medical or surgical intervention to preclude permanent impairment of a body or permanent damage to a body structure

Permanent – irreversible impairment to body structure/function, excluding trivial damage.

## Grades of Severity

***Mild***: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.

***Moderate***: Events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.

***Severe***: Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

## Reporting Requirements

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| Report to FDA if:<br>1) Serious,<br>2) Unexpected, and<br>3) An Adverse Experience | Timeframe for Reporting to FDA: 10 Days | Identify whether the AE is:<br>1) Device-Related<br>2) Possibly Related, or<br>3) Unrelated |
| Report to IRB if:<br>1) Serious,<br>2) Unexpected, and<br>3) Implications for Study Conduct* | Timeframe for Reporting to IRB: 10 Days | |

*The regulatory requirement is not to inform IRBs of all "unanticipated problems". An individual adverse event (AE) occurrence ***ordinarily*** does not meet these criteria because, as an isolated event, its implications for the study cannot be fully understood.

# *FDA Forms relevant to clinical research*

| Form | Title | Regulation Reference | Description |
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| Form FDA 482 | Notice of Inspection | 21 CFR Part 1.374(a) | Official FDA inspection form, completed by FDA investigators, and presented to the senior most responsible person (such as the PI) at the site being inspected at the start of any inspection. |
| Form FDA 483 | Inspectional Observations | | Official FDA inspection form, used by FDA investigators to note deviations, if any, and is presented to the most senior responsible person (such as the PI) at the inspected site at the end of the inspection. |
| Form FDA 1571 | Investigational New Drug Application (IND) | 21 CFR Part 312 | 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. |
| Form FDA 1572 | Statement of Investigator | 21 CFR Part 312 | The 1572 is a federal form and is the statement of the investigator that he will abide by the federal guidelines set forth in the Code of Federal Regulations for the use of drugs in an investigational setting. |
| Form FDA 3454 | Certification – Financial Interests and Arrangements of Clinical Investigators | 21 CFR Part 54 | The regulations require that the applicant submit one completed Form 3454 for all clinical investigators certifying to the absence of financial interests and arrangements. |
| Form FDA 3455 | Disclosure – Financial Interest and Arrangements of Clinical Investigators | 21 CFR Part 54 | For any clinical investigator for whom the applicant does not submit the certification, the applicant must submit a completed Form 3455 disclosing the financial interests and arrangements and steps taken to minimize the potential for bias. |
| Form FDA 3500 | For Voluntary Reporting of Adverse Events and Product Problems | | MedWatch form – The FDA Safety Information and Adverse Event Reporting Program<br>To be used for VOLUNTARY reporting of adverse events |
| Form FDA 3500A | For Use by Sponsors, Distributors, and Manufacturers for Mandatory Reporting | | MedWatch form – The FDA Safety Information and Adverse Event Reporting Program<br>To be used for MANDATORY reporting of adverse events |

# Record Retention

| Entity | What to maintain | How | How long |
|---|---|---|---|
| DHHS (Department of Health and Human Services)<br><br>IRB Records<br><br>45 CFR 46.115 | Copies of research proposals reviewed and any respective scientific evaluations, approved sample consent forms, Investigator progress reports, and subject injury reports.<br><br>IRB Meeting Minutes detail inclusive of attendance, actions taken, tallies of voting, logic for requiring changes in or disapproving research, and a written summary of discussions of controverted issues and their resolution.<br><br>Records of continuing review activities, correspondence between the IRB and Investigators, a list of IRB members per 46.108(a)(2), written procedures for the IRB, and statements of significant new findings provided to subjects.<br><br>Added in 2018:<br>Rationale for an expedited reviewer's determination under §46.110(b)(1)(i) that research appearing on the expedited review list described in §46.110(a) is more than minimal risk.<br><br>Documentation specifying the responsibilities that an institution and an organization operating an IRB each will undertake to ensure compliance with the requirements of this policy, as described in §46.103(e). | Format – The Institution or IRB may maintain the records in printed form, or electronically.<br><br>All records shall be accessible for inspection and copying by authorized representatives of the Federal department or agency at reasonable times and in a reasonable manner.<br><br>Retention of multiple copies of each record is not required. | Three (3) years after completion of research. |
| FDA (Food and Drug Administration)<br><br>IRB Records<br><br>21 CFR 56.115 | Documentation of IRB activities.<br><br>Copies of research proposals reviewed and any respective scientific evaluations, approved sample consent forms, Investigator progress reports, and subject injury reports.<br><br>IRB Meeting Minutes detail inclusive of attendance, actions taken, tallies of voting, logic for requiring changes in or disapproving research, and a written summary of discussions of controverted issues and their resolution.<br><br>Records of continuing review activities, correspondence between the IRB and Investigators, a list of IRB members per 46.108(a)(2), written procedures for the IRB, and statements of significant new findings provided to subjects. | Format - Silent (Default to DHHS requirements).<br><br>Must be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner. | The records required by this regulation shall be retained for at least 3 years after completion of the research. |

| Entity | What to maintain | How | How long |
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# Record Retention

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| FDA (Food and Drug Administration)<br><br>Investigational Devices<br><br>21 CFR 812.140 | Accurate, complete, and current records relating to the participation in an investigation.<br><br>All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.<br><br>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. The names of all persons who received, used, or disposed of each device. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.<br><br>Records of each subject's case history and exposure to the device. 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. Such records shall include: Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.<br><br>The protocol, with documents showing the dates of and reasons for each deviation from the protocol.<br><br>Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation. | Format - Silent (Default to DHHS requirements).<br><br>Must be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner. | An investigator shall maintain the records required during the investigation and for a period of 2 years after the latter of the following two dates:<br><br>The date on which the investigation is terminated or completed.<br><br>OR<br><br>The date that the records are no longer required for purposes of supporting a premarket approval application, a notice of completion of a product development protocol, a humanitarian device exemption application, a premarket notification submission, or a request for De Novo classification. |

# Record Retention

| Entity | What to maintain | How | How long |
|---|---|---|---|
| FDA (Food and Drug Administration)<br><br>Investigational Drugs<br><br>21 CFR 312.62 | Records of the disposition of the drug, including dates, quantity, and use by subjects.<br><br>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.<br><br>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.<br><br>The case history for each individual shall document that informed consent was obtained prior to participation in the study. | Format - Silent (Default to DHHS requirements).<br><br>Must be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner. | For 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated.<br><br>OR<br><br>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. |

# Record Retention

| Entity | What to maintain | How | How long |
|---|---|---|---|
| GCP E6R2 – Guidance for Industry (Good Clinical Practice)<br><br>Essential Documents<br><br>Sections 4.9.0, 4-5, 8.1 | Trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by applicable regulatory requirement(s).<br><br>The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.<br><br>The minimum list of essential documents that has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: (1) before the clinical phase of the trial commences, (2) during the clinical conduct of the trial, and (3) after completion or termination of the trial.<br><br>The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.<br><br>The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial. | Recorded, handled, and stored in a way that allows accurate reporting, interpretation, and verification.<br><br>When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.<br><br>Accurate, legible, contemporaneous, original, attributable, and complete. | The investigator/institution should take measures to prevent accidental or premature destruction of essential documents.<br><br>Essential documents should be retained until at least 2-years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region.<br><br>OR<br><br>At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.<br><br>These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor.<br><br>It is the responsibility of the sponsor to inform the investigator/institution as to when these |

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| | | | documents no longer need to be retained. |

# Record Retention

| Entity | What to maintain | How | How long |
|---|---|---|---|
| UH<br><br>UH Policy GM- 1, Records Management | All records are maintained and retained in accordance with federal and Ohio laws and regulations. | Electronic must be backedup On site or offsite with approved vender. | Research papers, published – Permanent<br><br>Human experimentation records – 30 years<br><br>IRB documentation – 3 years<br><br>Research Reports – 10 years |
| Sponsor | Check Clinical Trials Agreement | Check Clinical Trials Agreement | Check Clinical Trials Agreement |

| Entity | Details |
|---|---|
| GCP E6R2 – Guidance for Industry (Good Clinical Practice)<br><br>IRB Documents<br><br>Section 3.4 | The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).<br><br>The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists. |

| Entity | Details |
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# Record Retention

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| DHHS (Department of Health and Human Services)<br><br>HHS Awards<br><br>45 CFR 75.361<br>45 CFR 75.364 | Retention requirements for records.<br>Financial records, supporting documents, statistical records, and all other non-Federal entity records pertinent to a Federal award must be retained for a period of three years from the date of submission of the final expenditure report or, for Federal awards that are renewed quarterly or annually, from the date of the submission of the quarterly or annual financial report, respectively, as reported to the HHS awarding agency or pass-through entity in the case of a sub-recipient. HHS awarding agencies and pass-through entities must not impose any other record retention requirements upon non-Federal entities. The only exceptions are the following:<br>(a) If any litigation, claim, or audit is started before the expiration of the 3-year period, the records must be retained until all litigation, claims, or audit findings involving the records have been resolved and final action taken.<br>(b) When the non-Federal entity is notified in writing by the HHS awarding agency, cognizant agency for audit, oversight agency for audit, cognizant agency for indirect costs, or pass-through entity to extend the retention period.<br>(c) Records for real property and equipment acquired with Federal funds must be retained for 3 years after final disposition.<br>(d) When records are transferred to or maintained by the HHS awarding agency or pass-through entity, the 3-year retention requirement is not applicable to the non-Federal entity.<br>(e) Records for program income transactions after the period of performance. In some cases, recipients must report program incomeafter the period of performance. Where there is such a requirement, the retention period for the records pertaining to the earning of the program income starts from the end of the non-Federal entity's fiscal year in which the program income is earned.<br>(f) Indirect cost rate proposals and cost allocations plans. This paragraph applies to the following types of documents and theirsupporting records: Indirect cost rate computations or proposals, cost allocation plans, and any similar accounting computations of the rate at which a particular group of costs is chargeable (such as computer usage chargeback rates or composite fringe benefit rates).<br>(1) If submitted for negotiation. If the proposal, plan, or other computation is required to be submitted to the Federal Government (or to the pass-through entity) to form the basis for negotiation of the rate, then the 3-year retention period for its supporting records starts from the date of such submission.<br>(2) If not submitted for negotiation. If the proposal, plan, or other computation is not required to be submitted to the Federal Government (or to the pass-through entity) for negotiation purposes, then the 3-year retention period for the proposal, plan, or computation and its supporting records starts from the end of the fiscal year (or other accounting period) covered by the proposal, plan, or other computation.<br><br>Access to records.<br>(a) Records of non-Federal entities. The HHS awarding agency, Inspectors General, the Comptroller General of the United States, andthe pass-through entity, or any of their authorized representatives, must have the right of access to any documents, papers, or other records of the non-Federal entity which are pertinent to the Federal award, in order to make audits, examinations, excerpts, and transcripts. The right also includes timely and reasonable access to the non-Federal entity's personnel for the purpose of interview and discussion related to such documents.<br><br>(b) Only under extraordinary and rare circumstances would such access include review of the true name of victims of a crime. Routinemonitoring cannot be considered extraordinary and rare circumstances that would necessitate access to this information. When access to the true name of victims of a crime is necessary, appropriate steps to protect this sensitive information must be taken by both the nonFederal entity and the HHS awarding agency. Any such access, other than under a court order or subpoena pursuant to a bona fide confidential investigation, must be approved by the head of the HHS awarding agency or delegate.<br><br>(c) Expiration of right of access. The rights of access in this section are not limited to the required retention period but last as long as therecords are retained. HHS awarding agencies and pass-through entities must not impose any other access requirements upon nonFederal entities. |

# Record Retention

| Entity | Details |
|---|---|
| NIH (National Institutes of Health) and Cooperative Agreements<br><br>Grant Awards<br><br>NIH Grants Policy Statement 8.4.2 | REVISED DECEMBER 2019.<br>Recipients generally must retain financial and programmatic records, supporting documents, statistical records, and all other records that are required by the terms of a grant, or may reasonably be considered pertinent to a grant, for a period of 3 years from the date the annual FFR is submitted. For awards under SNAP (other than those to Federal institutions), the 3year retention period will be calculated from the date the FFR for the entire competitive segment is submitted. Those recipients must retain the records pertinent to the entire competitive segment for 3 years from the date the FFR is submitted to NIH. Federal institutions must retain records for 3 years from the date of submission of the annual FFR to NIH. See 45 CFR 75.361 for exceptions and qualifications to the 3-year retention requirement (e.g., if any litigation, claim, financial management review, or audit is started before the expiration of the 3-year period, the records must be retained until all litigation, claims, or audit findings involving the records have been resolved and final action taken). Those sections also specify the retention period for other types of grant-related records, including F&A cost proposals and property records. See 45 CFR Parts 75.361 and 75.364 for record retention and access requirements for contracts under grants.<br><br>These record retention policies apply to both paper and electronic storage of applicable information, including electronic storage of faxes, copies of paper document, images, and other electronic media. Institutions that rely on an electronic storage system must be able to assure such a system is stable, reliable, and maintains the integrity of the information. When storing electronic images of paper documents, the system must also assure a full, complete, and accurate representation of the original, including all official approvals.<br><br>NIH, Inspectors General, the Comptroller General of the United States, and the pass-through entity, or any of their authorized representatives, must have the right of access to any documents, papers, or other records of the non-Federal entity which are pertinent to the NIH award, in order to make audits, examinations, excerpts, and transcripts. The right also includes timely and reasonable access to the non-Federal entity's personnel for the purpose of interview and discussion related to such documents. The rights of access in this section are not limited to the required retention period but lasts as long as the records are retained. Pass-through entities must not impose any other access requirements upon non-Federal entities. |

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# Study Start Up with GCP E6 R2 Guidance

## Principles of Good Clinical Practice

1. Clinical Trials should be conducted in accordance with the ethical principles from the Declaration of Helsinki, consistent with GCP and applicable regulatory requirements.
2. Prior to initiation, risks and inconveniences should be weighed against the benefits for the participant. The study should only continue if the benefits justify the risks
3. The rights, safety and well-being of the study participants are the utmost priority and should be put over the interests of science and society
4. Non-clinical and clinical information on an investigational product should support the proposed trial
5. Trials should be scientifically sound and detailed in a protocol.
6. A trial should be conducted in compliance with the protocol after receiving IRB approval.
7. Medical care and decisions given to study participants should be the responsibility of a qualified physician
8. Each individual involved in conducting a trial should be qualified by education, training and experience to perform their delegated tasks
9. Freely given informed consent should be obtained from every study participant prior to participation
10. All clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation, and verification
11. Confidentiality of records should be protected respecting the privacy and confidentiality of participant information
12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice and in accordance with the protocol

## Investigator

The responsibility of the proper conduct of all aspects of a clinical trial (protocol adherence, investigational product, etc.) ultimately lies with the Principal Investigator.

**Qualifications**

- Investigators should be qualified by education, training and experience with evidence to support it to assume responsibility and proper conduct of the study.
- Investigators should maintain a list of all study team members and their delegated tasks along with their qualifications and allow monitoring and auditing by regulatory authorities.

**Adequate Resources**

- The investigator should be able to demonstrate sufficient time, number of qualified staff, and facilities to properly conduct the study

- All study team members should be properly trained on the protocol, products and trialrelated duties
- The investigator should be able to demonstrate the potential for recruiting proper number of subjects for the trial
- The Principal Investigator (PI) is responsible for supervising staff with delegated tasks and any services the PI retains

## Sponsor

**Contract Research Organization (CRO)**

- A sponsor may transfer any of the sponsor's related duties and functions to a CRO however the ultimate responsibility for the conduct of the trial still resides with the sponsor and in turn should still ensure oversight of the duties and functions carried out on their behalf

**Medical Expertise**

- The sponsor should designate appropriately qualified medical personnel that are readily available to advise on trial-related medical questions or problems

**Investigator Selection**

- The sponsor is responsible for selecting qualified investigators ○ If it is a multi-site trial and a coordinating committee is organized, the sponsor is responsible for their selection

## Clinical Trial Protocol and Amendments

The following is information that should be included in the protocol:

**General Information/ Background Information**

- This section should include: Protocol title, id number, and date,
- Name and title of: person authorized to sign the protocol, the investigator conducting the trial,
- Name, Title, Address and telephone number of: the medical expert, qualified physician responsible for medical decisions
- Name and Address of: the sponsor and monitor, the clinical laboratories and other medical or technical departments involved in the trial.
- Name and description of the investigational product
- Summary of nonclinical studies that may have clinical significance and any known or potential risks
- Description of the route of administration, dosage and regimen, treatment period, and population studied
- References to literature and data that are relevant to the trial and provide background

**Trial Objects, Purpose, and Design**

- Detailed description of the objectives and the purpose of the trial
- Statement on the primary endpoints

- Description about: the trial design, schematic diagram of the design, randomization and blinding procedures or other measures taken to minimize bias, trial treatment and discontinuation criteria
- Expected duration of the subject participation
- Accountability procedures for the investigational product including the placebo
- Maintenance of trial treatment randomization codes and procedures • Identification of any data to be recorded directly on the CRFs

**Selection and Withdrawal of Subjects**

- Subject inclusion and exclusion criteria,
- Withdrawal criteria: when and how to withdraw subjects, type and timing of the data to be collected, whether and how subjects are replaced, follow-up for subjects withdrawn

**Treatment of Subjects**

- Treatment to be administered: name of all products, the doses, dosing schedule, route of administration and the treatment period, follow-up period for each trial group
- Medication/treatments permitted before, during, and after the trial
- Procedures for monitoring subject compliance

**Assessment of Efficacy and Safety**

- Specification of the efficacy parameters and methods/timing for assessment of the parameters
- Specification of the safety parameters and methods/timing for assessment of the parameters ○ Procedures for editing reports of adverse events and intercurrent illnesses and the type, and duration of follow up after adverse events

**Statistics**

- Description of statistical methods to be used, number of subjects, level of significance, criteria for termination, procedures for accounting for missing/unused/sparious data
- Procedures for reporting any deviations from the original plan
- Selection of subjects to be included in the analyses (randomized subjects, dosed subjects, etc.)

**Direct Access to source data/documents/Ethics**

- Sponsor should ensure that its specified in the protocol that the investigator allows trial monitoring, audits, IRB review, and regulatory inspections and provides direct access to all source data A description of ethical considerations relating to the trial

**Financing and Insurance/Publication Policy** •
If not addressed in a separate agreement

# Investigator's Brochure

Investigator's Brochure is a compilation of the clinical and nonclinical data on the investigational product that are relevant to the study of the products in human subjects.

**Purpose**

- To provide the investigators with the information to facilitate their understanding of the rationale for and the compliance with the protocol.
- Provides insight to support clinical management of the study subjects during the course of the clinical trial
- Extent of the information in the IB will depend on the stage of development
- Generally the sponsor is responsible for ensuring up-to-date information and the investigator is responsible for relaying the information to the IRB

**What to include in the Investigator Brochure**

- Title page & Confidentiality statement
- Summary
- Introduction – brief statement that contains the chemical name and highlighting significant physical, chemical, pharmaceutical, pharmacological, toxicology, pharmacokinetic, metabolic, and clinical information
- Nonclinical studies ○ Introduction- The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic and metabolism should be summarized including any possible unfavorable or unintended effects in humans
    - Pharmacology
    - Pharmacokinetics/product metabolites in animals ○ Toxicology
- Clinical studies ○ Introduction- thorough discussion of known effects in humans including pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities
    - Pharmacokinetics and product metabolism in humans ○ Safety and efficacy ○ Marketing Experience
- Summary of Data and Guidance for the Investigator – provide an overall discussion of the nonclinical and clinical data and should summarize the information from the various sources on different aspects of the product
- The overall aim is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of specific tests/observations/precautions that may be needed for a clinical trial. The understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxilogical, and clinical information on the product

# Essential Documents – Before the Trial

- Documents that are individually and collectively permit evaluation of a trial and the quality of data produced
- Demonstrates the compliance of the investigator, sponsor, and monitor
- Below are the essential documents that should be stored before the trial has begun:

| Document | Investigator | Sponsor |
|---|---|---|
| Investigator Brochure | Yes | Yes |
| Signed protocol and amendments (if any) and sample case report form | Yes | Yes |
| Information given to trial subject informed consent form | Yes | Yes |
| Any other written information | Yes | Yes |
| Advertisement for subject recruitment | Yes | Yes |
| Financial aspects of the trial | Yes | Yes |
| Insurance statement | Yes | Yes |
| Signed agreement between involved parties | Yes | Yes |
| Dated, Documented approval/favorable opinion of institutional review board of the following:<br>- Protocol and amendments<br>- CRF<br>- ICF<br>- Any written information provided to participants<br>- Advertisements<br>- Subject compensation<br>- Any other documents approved by the IRB | Yes | Yes |
| IRB composition | Yes | Yes |
| Regulatory authorities' authorization | Yes | Yes |
| CV and other documents evidencing qualifications of investigator and sub-investigators | Yes | Yes |
| Normal value/ranges for any procedures/tests/labs included in the protocol | Yes | Yes |
| Medical/laboratory/technical procedures/tests (certification or accreditation or established quality control or other validation) | Yes | Yes |
| Sample of labels attached to investigational product container | | Yes |
| Instructions for handling of investigational products and trial related materials | Yes | Yes |
| Shipping records for investigational product and trial related materials | Yes | Yes |
| Certificate of analysis of investigational product shipped | | Yes |
| Decoding procedures for blended trials | Yes | Yes |
| Master randomization list | | Yes |
| Pre-trial monitoring report | | Yes |
| Trial initiation monitoring report | Yes | Yes |

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# Study Implementation with GCP E6 R2 Guidance

Investigator

**Medial Care of Trial Subjects**

- A PI or Sub-Investigator should be responsible for all trial related medical decisions
- Investigators should ensure subjects have adequate care for any AE's or abnormal lab values and inform subjects of any intercurrent illness that may need care

**Communication with the IRB**

- All documents used during the conduct of the trial should be approved prior to use by the IRB including but not limited to the protocol, consents, and the investigator brochure

**Compliance with the Protocol**

- The investigator should conduct the trial in compliance with the protocol that is agreed upon by all parties and approved by the IRB
- Any deviations should be reported and approved prior to being implemented ○ Unless patient safety is at risk, then the deviation can occur prior to approval but should be approved as soon as possible by the sponsor, IRB and any other regulatory bodies

**Records and Reports**

- Data should be attributable, legible, contemporaneous, original, accurate, and complete ○ Any Changes that are needed should be dated, initialed, explained, and not obscuring the original entry
- Essential documents should be retained for a minimum of 2 years after the last approval ○ Documents may need to be stored longer depending on the regulatory requirements, the agreement with the sponsor or the IRB
- Summaries should be provided to the IRB at least on an annual basis

## Sponsor

**Quality Management**

- A system should be implemented to manage quality throughout all stages of the trial to ensure human subjects protections
- Sponsor is responsible for determining which risks to mitigate and implanting activities within the study design and by establishing quality tolerance limits which should be summarized in the clinical study report along with any deviations from the predefined limits

**Trial Management, Data Handling, and Record Keeping**

- An independent data monitoring committee could be established to assess the progress of the study
- When using electronic systems ensure the same requirements are met as paper systems and maintain SOPs for the systems
  - SOPs should consist of startup, installation, and use
  - The electronic system should allow any changes to be compared to the original data and observations
- Essential documents should be retained for at least 2 years after the last approval and sponsors should notify the investigators in writing when the records are no longer needed

**Financing**

- Financial aspects of the trial should be documented in an agreement between the investigator and the sponsor

**Confirmation of Review by IRB/IEC**

- Sponsor should obtain from the investigator:
  - The name and address of the investigator's IRB
  - A statement obtained from the IRB that it operates per GCP and applicable regulations ○ Documentation of approval of the trial by the IRB and a copy of the approved documents if applicable
- If the trial is conditionally approved by the IRB upon changes to any part of the trial, the sponsor should obtain a copy of the modifications with approval dates given by the IRB.

## Informed Consent

- Prior to consent, the study participant should be given ample opportunity to inquire about details of the trial and receive answers prior to deciding if they would like to participate in the trial
- The witness should sign and date the consent form after the information has been provided to study participant, and they have orally consented to the participation in the trial (and if capable has signed and dated the consent)
- For a study participant who can only be enrolled by a legally authorized representative, the study participant should be informed about the trial to the extent compatible with the participants understanding and if capable, should also sign the consent

## Investigational Product

- The sponsor should ensure that sufficient safety and efficacy data from nonclinical studies or clinical trials are available to support human exposure by the route, at the dosages, and in the trial population to be studied
  - As new data becomes available, the investigator brochure should be updated by the sponsor
- Manufacturing, Packaging, Labeling and Coding investigational products ○ The sponsor should ensure the product is:
    - characterized as appropriate to the stage of development,
    - manufactured in accordance with good manufacturing practice
    - coded and labelled in a manner that protects the blinding and comply with regulatory requirements
  - Sponsor should determine acceptable storage temperature and storage conditions, storage times, reconstitution fluids and procedures, and devices for product infusion and inform all parties of the determinations
  - In blinded trials, the coding system for the product should include a mechanism that permits rapid identification of the product in case of emergency
- Supplying and handling investigational products
  - Sponsor is responsible for supplying the investigator with the product
  - Sponsor should not supply an investigator with the product until the sponsor obtains all required documentation including IRB approval

- Sponsor should ensure that written procedures include instructions that the investigator should follow for the handling and storage of the products.
  - Procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects and return of the product to the sponsor (or alternative disposition)
- Sponsor should
  - Ensure timely delivery of the product to the investigator
  - Maintain records that document shipment/receipt/disposition/return and destruction of the product
  - Maintain a system for retrieving products and documenting the retrieval
  - Maintain a system for the disposition of unused product and document the process
  - Take steps to ensure the products are stable over the period of use
  - Maintain sufficient quantities of the product used in the trials to reconfirm specifications, 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 requirements- whichever is the longer retention period

## Monitoring

**Selection and Qualifications**

- Monitors should be appointed by the sponsor
- Monitors should have documented training and have scientific or clinical knowledge needed to monitor accurately
- Monitors should be thoroughly familiar with the protocol, informed consent document, any other IRB approved documents and investigational products to confirm compliance with the sponsor's SOPs, GCP, and all applicable regulatory requirements

**Extent and Nature of Monitoring**

- The Sponsor is responsible for ensuring adequate monitoring and for determining the appropriate extent and nature of monitoring by developing a risk-based approach to the plan in which on-site or centralized monitoring may be appropriate
- Two main types of monitoring: ○ On-Site Monitoring: performed on site where trial is being conducted
  ○ Centralized Monitoring: performed remotely focused mainly on identifying missing or inconsistent data, data outliers, examining data trends, evaluating systematic or significant errors in data collection and reporting, analyzing site characteristics and performance metrics, selecting sites and/or processes for targeted on-site monitoring visits

**Monitor's Responsibilities**

- Monitor should ensure that the trial is conducted and documented properly by:
  - Acting as the main line of communication between the sponsor and investigator
  - Verifying the investigator has adequate qualifications and resources to conduct the trial, receives all current relevant documents, and has submitted all reports/notifications/applications/submissions

- Verifying the investigator and staff is qualified, adequately licensed and trained as well as conducting the trial per protocol and in accordance with GCP and other regulatory requirements, and ensuring no tasks are delegated to unauthorized individuals
- Verifying investigational product for proper: dispensation, storage, patient eligibility, proof of instructions given to participants, receipt/use/return of and disposition of the product
- Verifying informed consent is obtained prior to participation and only eligible participants are enrolled
- Verifying all study documents are accurate, complete, kept up-to-date, and maintained and also report the subject recruitment rate, informing the investigator of any errors and
- Determining if all adverse events are appropriately reported per all regulations and all essential documents are being maintained by the investigator
- Verifying all deviations are communicated to the investigator and IRB and documentation of plan to eliminate recurrence of the deviation

**Monitoring Report**

- A written report should be submitted after each visit including a summary of what the monitor reviewed, the monitor's statements concerning the findings, and the actions that should be taken to secure compliance
- The review and follow up by the study team to resolve issues identified by the monitor should also be verified and documented

## Auditing

**Selection and Qualification of Auditors**

- Appoint individuals who are independent of the trial and are qualified by training and experience with appropriate documentation

**Auditing procedures**

- Conducted in accordance with the sponsor's written procedures on what to audit, how to audit, frequency, and form of the audit. Audit plan and procedures should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects, type and complexity of the trial, the level of risks to the trial subjects, and any identified problems. Observations and findings should be documented.
- When required by applicable law or regulation, the sponsor should provide an audit certificate

**Noncompliance**

- Noncompliance with the protocol, SOPs, GCP, and applicable regulatory requirements by an investigator or by the members of a sponsors staff should lead to:
  - prompt action by the sponsor to secure compliance
  - root cause analysis and implement appropriate corrective and preventative actions and be verified by the auditor
  - termination of the investigator's participant in the trial and the sponsor should notify the regulatory authorities

# Essential Documents – During the Clinical Trial

The following documents should be kept, in addition, to the documents that were required prior to study initiation:

| Title of Document | Investigator | Sponsor |
|---|---|---|
| Investigator Brochure updates | yes | yes |
| Any Revision to:<br>- Protocol/CRF<br>- Informed Consent Form<br>- Any other written information to subjects<br>- Advertisement for subject recruitment | yes | yes |
| Dated, documented, approval from IRB of IRB:<br>- Protocol amendments - Revisions of: ○ Any other written information to be provided to the subject ○ Advertisements for subject recruitment<br>- Any other documents given approval/favorable option - Continuing review of the trial | yes | yes |
| Regulatory authorities authorizations/approvals/notifications where required for protocol amendments and other documents | yes | yes |
| Curriculum vitae for new investigators and sub investigators | yes | yes |
| Updates to normal values for tests included in the protocol | yes | yes |
| Updates of tests:<br>- Certifications or<br>- Accreditation or<br>- Quality control procedures<br>- Other validations | yes | yes |
| Documentation of investigational products and trial related materials shipment | yes | yes |
| Certificate of analysis for new batches of investigational products | | yes |
| Monitoring reports | | yes |
| Relevant communications other than site visits:<br>- Letters<br>- Meeting notes<br>- Notes of telephone calls | yes | yes |
| Signed informed consent forms | yes | |
| Source documents | yes | |
| Signed, dated and completed case report forms | yes | yes |
| Documentation of CRF corrections | yes | yes |
| Notification by originating investigator to sponsor of serious adverse events and related reports | yes | yes |
| Notification by sponsor and investigator where applicable to regulatory authorities and IRB of unexpected serious adverse drug reactions and other safety information | yes | yes |
| Notification by sponsor to investigators of safety information | yes | yes |
| Interim or annual reports to IRB and authorities | yes | yes |
| Subject screening log | yes | yes |
| Subject identification code list | yes | |
| Subject enrollment log | yes | |

| | | |
|---|---|---|
| Investigation products accountability at site | yes | yes |
| Signature sheet | yes | yes |
| Record of retained body fluids/samples | yes | yes |