

INVESTIGATOR OF RECORD RESPONSIBILITIES

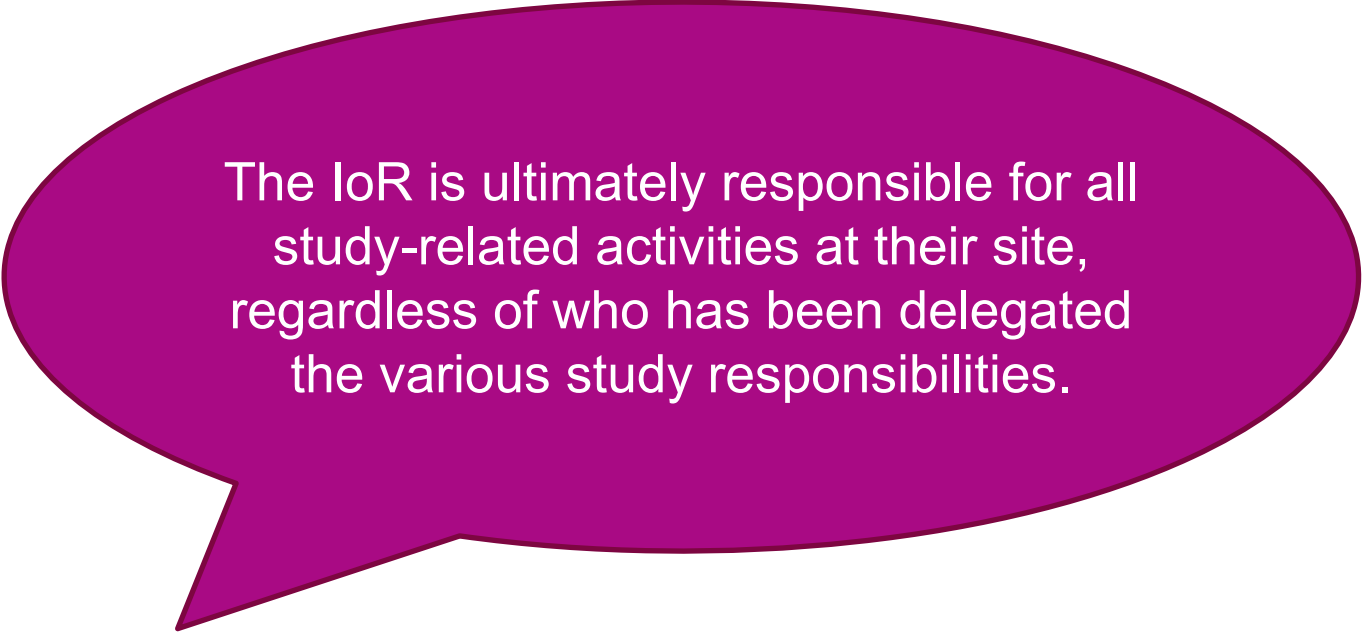


Objectives

Review and Discuss:

- Responsibilities of the clinical research site (CRS) Investigator of Record (IoR) as per relevant regulations and guidelines
- Responsibilities and commitments associated with signing
 - Form FDA 1572 – Investigational New Drug [IND]/ Investigational Device Exemption [IDE] studies
 - MATRIX IoR Form – non-IND/IDE studies
- Financial disclosure (FD) requirements
- Impact of protocol noncompliance
- Oversight responsibilities related to the informed consent process, drug accountability, safety monitoring, maintaining essential study documents and delegation of responsibilities

IoR Responsibilities



The IoR is ultimately responsible for all study-related activities at their site, regardless of who has been delegated the various study responsibilities.

What Does This Mean?

- The US FDA's focus is on the Principal Investigator listed on Form FDA 1572
- For MATRIX trials, this is the “Investigator of Record” or IoR
- **The IoR is responsible for the oversight and execution of the protocol at their site**

IoR Responsibilities

- Ensure that the clinical investigation is conducted according to the approved protocol and in compliance with all relevant sections of
 - U.S. Code of Federal Regulations (CFR)
 - International Conference for Harmonization Guideline for Good Clinical Practice (ICH E6) standards
 - In-country regulations and guidelines
- Protect the rights, safety and welfare of study participants
- Control drugs, biological products and devices under investigation

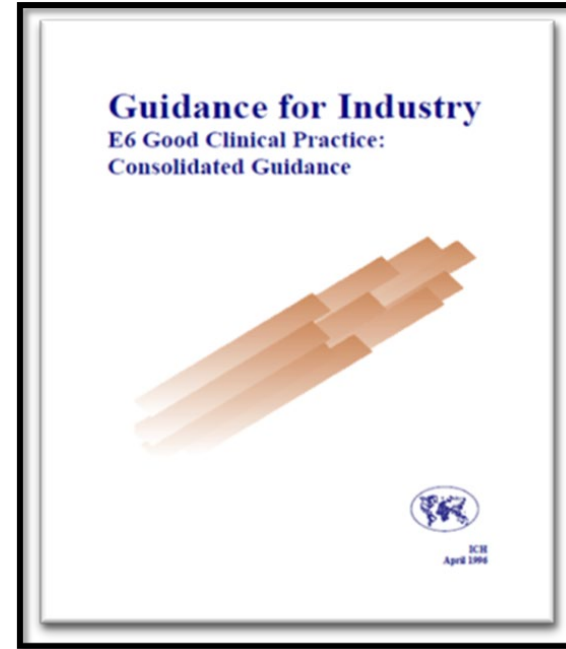
IoR Responsibilities: Regulations and Guidance

IoR responsibilities are specifically described in:

- ICH E6 (Sections 4.0 and 8.0)
- U.S. Code of Federal Regulations (CFR) Title 21
- U.S. FDA Guidance – Investigator Responsibilities (October 2009)
- U.S. FDA Guidance – Q&A Form FDA 1572 (May 2010)
- Form FDA 1572 / MATRIX IoR Form

ICH E6: Good Clinical Practice: Consolidated Guideline

Objective: to provide a unified standard for the EU, Japan, U.S. to facilitate mutual acceptance of clinical data by the regulatory authorities



Published as official guidance in U.S.
Federal Register in 1997

ICH E6 GCP – Section 4.0

Investigator Responsibilities

4.1 Investigator Qualifications and Agreements

4.2 Adequate Resources

4.3 Medical Care of Trial Subjects

4.4 Communications with IRB/IEC

4.5 Compliance with Protocol

4.6 Investigational Product(s)

4.7 Randomization Procedures and Unblinding

4.8 Informed consent of trial subjects

4.9 Records and Reports

4.10 Progress Reports

4.11 Safety Reporting

4.12 Premature Termination or Suspension of a Trial

4.13 Final Report(s) by Investigator

Country-Specific Requirements

- This presentation reviews the U.S. federal requirements for the CRS IoR
- **All local and country-level requirements must also be met**
 - Contact your local IRB/IEC for additional information on these

FDA Clarification of Investigator Responsibilities

- Supervision of the conduct of the clinical investigation
- Delegation of tasks to study staff
- Training of study staff
- Supervision of staff to whom tasks are delegated
- Reporting protocol deviations
- Supervision of third parties (if applicable)
- Protection of the rights, safety and welfare of participants in clinical trials
- Provision of reasonable medical care
- Provide reasonable access to medical care

Review of Form FDA 1572

- One of the US requirements for Principal Investigators conducting an IND clinical study is completion of Form FDA 1572

Form FDA 1572

| | | | |
|--|-----------------------|--|--------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION | | Form Approved: OMB No. 0910-0014 Expiration Date: March 31, 2025 <i>See OMB Statement on Reverse.</i> | |
| STATEMENT OF INVESTIGATOR (TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312) (See instructions on reverse side.) | | NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)). | |
| 1. NAME AND ADDRESS OF INVESTIGATOR | | | |
| Name of Clinical Investigator | | | |
| Address 1 | | Address 2 | |
| City | State/Province/Region | Country | ZIP or Postal Code |
| 2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED (<i>Select one of the following.</i>) | | | |
| <input type="checkbox"/> Curriculum Vitae | | <input type="checkbox"/> Other Statement of Qualifications | |
| 3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED | | CONTINUATION PAGE for Item 3 | |
| Name of Medical School, Hospital, or Other Research Facility | | | |
| Address 1 | | Address 2 | |
| City | State/Province/Region | Country | ZIP or Postal Code |

By Signing Form FDA 1572...

- The IoR is agreeing that he or she will personally conduct or supervise the described investigations
- To do this, the IoR must be intimately involved with the study. Depending on the size of the staff, the qualifications of the staff members, and the complexity of the protocol(s), this involvement may vary according to the site and protocol
- The IoR must have a full understanding of the protocol, as well as stay informed of all participant and site issues
- The IoR should ensure procedures are established to escalate issues quickly when needed

Form FDA 1572:

Eight Investigator Commitments

- Maintain protocol adherence
- Personally conduct or supervise
- Ensure informed consent of study participants
- Report adverse experiences
- Provide training to sub-investigators
- Ensure adequate and accurate recordkeeping
- Ensure proper IRB/IEC review and reporting
- Comply with all regulatory requirements

Who Should be Listed as a Sub-Investigator on the 1572?

- The decision to list an individual as a sub-investigator depends on their level of responsibility and whether they perform significant clinical, investigation-related duties
- In general, an individual directly involved in the performance of procedures required by the protocol and the collection of data should be listed on the 1572
 - It is not necessary to include someone with only an occasional or ancillary role
- For MATRIX studies, this will typically mean the study clinicians
 - Other site staff (lab, pharmacy, site coordinators) would only need added if they regularly conduct AE assessment, collection of participant safety information, confirmation of participant eligibility, and/or prescription of study product

When to Update the 1572? (U.S. Federal Regulation)

- According to U.S. federal regulation, the Form FDA 1572 must only be updated when a new protocol has been added to the IND or a new Investigator is added to the study. However, ...

When to Update the 1572? (MATRIX Policy)

Within 30 days of any change in the following information

- Change of IoR at the site
- A sub-investigator is added to or removed from the study
- At the time of continuing IRB/IEC review (if required by the local IRB/IEC)
- A laboratory is added, removed or changed
- Site location added, removed or changed

MATRIX IoR Form

- For non-IND studies, an IoR Form is completed instead of a Form FDA 1572
 - The information on the IoR Form is similar to the 1572 (i.e., items to complete, investigator commitments)
- For MATRIX non-IND studies, site IoRs should follow the same guidelines as listed previously for the 1572
 - How to complete the IoR Form
 - When to update the IoR Form
 - Who should be listed as a sub-investigator

Investigator of Record Form



MATRIX INVESTIGATOR OF RECORD FORM

Any Investigator participating in a Non-IND clinical trial supported and/or sponsored by USAID through MATRIX should complete this form and submit a copy to the Product Developer, the MATRIX Clinical Trials Hub, and their respective IRBs/IECs.

1. Name and address of Investigator of Record (IoR):

2. Education, training, and experience that qualifies the investigator to conduct this study. Please indicate which of the following is attached.

☐ Curriculum Vitae ☐ Other Statement of Qualifications (e.g., biosketch)

3. Name and address of Clinical Research Site(s) where the study will be conducted:

4. Name and address of any clinical laboratories to be used in the study (Specify none if no lab will be utilized for this study) ☐ None

Financial Disclosure Requirement: Reporting Financial Interests

- Goal: Preserve objectivity of clinical research and the protection of human subjects
- Regulation
 - 21 CFR 54 (IND studies only)
- Requirement: Each applicable investigator must disclose any financial interests that may be affected by the outcome of the research or attest to the absence of relevant significant financial interests

Specific Requirement: 21 CFR 54

- Per 21 CFR 54, each clinical research Investigator and sub-investigator (i.e., anyone listed on the Form FDA 1572 during the study) is required to disclose the aggregated financial interests of themselves, their spouse and dependent children, as they relate to the study sponsor and/or study product(s)
- Per 21 CFR 312.53, financial disclosures must be completed prior to study involvement

Demonstrating Compliance: 21 CFR 54

- Individual FD forms must be completed, signed and dated by each IoR/sub-investigator **before** the relevant Form FDA 1572 to which they are being added is finalized, signed and dated
- The 1572 must be finalized, signed, and dated **before** the IoR/sub-investigator adds their signature and start date to the Delegation of Duties (DoD) Log

Note: The IoR's/sub-investigator's DoD start date must be no sooner than the signature dates on their 21 CFR 54 FD form and corresponding 1572

Reporting Time Points: 21 CFR 54

- **Before** an IoR or sub-investigator begins study activities (i.e., before final sign off by the IoR on the Form FDA 1572)
- Within thirty (30) days of discovering that relevant changes to their significant financial interests have occurred during their study involvement and for one year following the end of their study involvement

Note: The PD/IND holder may require completion of FD forms at additional timepoints (e.g., at or after study end)

How to Report Financial Disclosure:

21 CFR 54

- Blank, study-specific FD Forms can be found on the MATRIX website under "Resources" (www.matrix4prevention.org)
- Definition of reportable financial interests (as per 21 CFR 54) and instructions for completion of the form will appear in the form itself



USAID
FROM THE AMERICAN PEOPLE



MATRIX FINANCIAL DISCLOSURE/CERTIFICATION FORM – 21 CFR 54

| | |
|--|--|
| Please complete all of the information below, including providing your signature where indicated. Once complete, scan the document and email it as instructed to the study sponsor. Retain the original form in your central files. | |
| 1. Name and Address of Study Sponsor: | |
| 2. Protocol Name: | |
| 3. Protocol Number: | |
| 4. Study Start Date (mm/dd/yyyy): | |
| 5. Principal Investigator (as listed on FDA Form 1572): | |
| 6. Your Name: Institution Name and Address (including phone number): | |
| 7. Are you listed as the Principal Investigator on the FDA Form 1572? Yes <input type="checkbox"/> No <input type="checkbox"/> | |
| 8. Indicate by marking YES or NO if any of the financial interests or arrangements of concern to US FDA (as described below) apply to you, your spouse, or dependent children. If you respond "yes" to any of the items, please provide the details of the interest or arrangement. Attachments to this document are permitted. | |
| YES <input type="checkbox"/> | NO <input type="checkbox"/> Financial arrangements whereby the value of the compensation could be influenced by the outcome of the study. This could include, for example, compensation that is explicitly greater for a favorable outcome or compensation to the investigator in the form of an equity interest in the sponsor or in the form of compensation tied to sales of the product, such as a royalty interest. If yes, please describe: _____ |
| YES <input type="checkbox"/> | NO <input type="checkbox"/> Significant payments of other sorts, excluding the costs of conducting the study or other clinical studies. This could include, for example, payments made to the investigator or the institution to support activities that have a monetary value greater than \$25,000 (i.e., a grant to fund ongoing research compensation in the form of equipment, or retainers for ongoing consultation of honoraria). If yes, please describe: _____ |
| YES <input type="checkbox"/> | NO <input type="checkbox"/> A proprietary or financial interest in the test product, i.e., patent, trademark, copyright, or licensing agreement. If yes, please describe: _____ |
| YES <input type="checkbox"/> | NO <input type="checkbox"/> A significant equity interest in the sponsor of the study. This would include, for example, any ownership interest, stock options, or other financial interest whose value cannot be easily determined through reference to public prices, or an equity interest in a publicly traded company exceeding \$50,000. If yes, please describe: _____ |
| In accordance with 21 CFR § 54.1 to 54.6, I declare that the information provided on this form is, to the best of my knowledge and belief, true, correct, and complete. Furthermore, if my financial interests and arrangements, or those of my spouse and dependent children, change from the information provided above during the course of the study or within one year after the last participant has completed the study as specified in the protocol, I will complete a new Financial Disclosure/Certification Form to document this change and notify the study sponsor. | |
| 9. Signature: | 10. Date: |

Steps to Report Financial Disclosure

- **Print** the FD Form(s) from www.matrix4prevention.org
 - Study-specific 21 CFR 54 FD Form (IND studies only)
- **Complete** the FD Form(s)
 - Must be signed and dated by hand or using a 21 CFR 11 compliant electronic signature application (i.e., DocuSign)
- **Scan and email** a copy of the completed, signed/dated FD Form(s) to the applicable Product Developer(s) and MATRIX CTH Regulatory
- **File** the original, completed, signed/dated FD Form(s) in the study binder
 - 21 CFR 54 FD Forms should be filed with the associated 1572

How are Conflicts of Interest Managed?

- All financial disclosure statements will be reviewed by the MATRIX CTH Regulatory
- If potential conflicts of interest (COI) are identified, the MATRIX CTH Regulatory, in conjunction with the Investigator, will determine if steps need to be taken to minimize the potential for bias

ICH E6 GCP – Section 4.0

Investigator Responsibilities

4.1 Investigator Qualifications and Agreements

4.2 Adequate Resources

4.3 Medical Care of Trial Subjects

4.4 Communications with IRB/IEC

4.5 Compliance with Protocol

4.6 Investigational Product(s)

4.7 Randomization Procedures and Unblinding

4.8 Informed consent of trial subjects

4.9 Records and Reports

4.10 Progress Reports

4.11 Safety Reporting

4.12 Premature Termination or Suspension of a Trial

4.13 Final Report(s) by Investigator

Compliance with the protocol

- ICH E6 Section 4.5
- Form FDA 1572 / MATRIX IoR Form
- 21 CFR 312.60
- 21 CFR 812.100

Protocol Compliance

- By signing the protocol Investigator Signature Page, the IoR is expected to make every effort to ensure that the study is conducted in compliance with the protocol approved by the IRB/IEC
- By signing the 1572/IoR Form, the IoR agrees they will not make any changes in the research without IRB/IEC approval, except where necessary to “eliminate apparent immediate hazards to human subjects” (1572) or “protect the safety, rights, or welfare of study participants” (IoR Form)

Protocol Compliance

- Any departure from the protocol must be documented as a protocol deviation
- In the event you find a deviation has occurred at your site, follow the instructions provided to you in the protocol's Study Specific Procedures (SSP) Manual and the MATRIX Good Documentation Practices (GDP) Policy

Protocol Deviations

- Recognizing that protocol deviations do sometimes occur, it is important to promptly document and report them

Why is it critical that this happens?

Potential Impact of Noncompliance

- Impact on risk to the participant
- Impact on data quality
- Impact on scientific integrity and credibility
- Rejection of data by regulatory bodies
- Selection of the site for FDA inspection
- Disqualification of the IoR
- Suspension of site activities

Risks for Noncompliance

- Insufficient investigator involvement/oversight in study conduct
- Poor supervision and training of study staff
- Inappropriate delegation of study tasks to unqualified persons
- Overworked investigator and study staff (e.g., too many study participants, complex study with large data collection, too many concurrent studies)
- Failure to adequately protect study participants

ICH E6 GCP – Section 4.0

Investigator Responsibilities

4.1 Investigator Qualifications and Agreements

4.2 Adequate Resources

4.3 Medical Care of Trial Subjects

4.4 Communications with IRB/IEC

4.5 Compliance with Protocol

4.6 Investigational Product(s)

4.7 Randomization Procedures and Unblinding

4.8 Informed consent of trial subjects

4.9 Records and Reports

4.10 Progress Reports

4.11 Safety Reporting

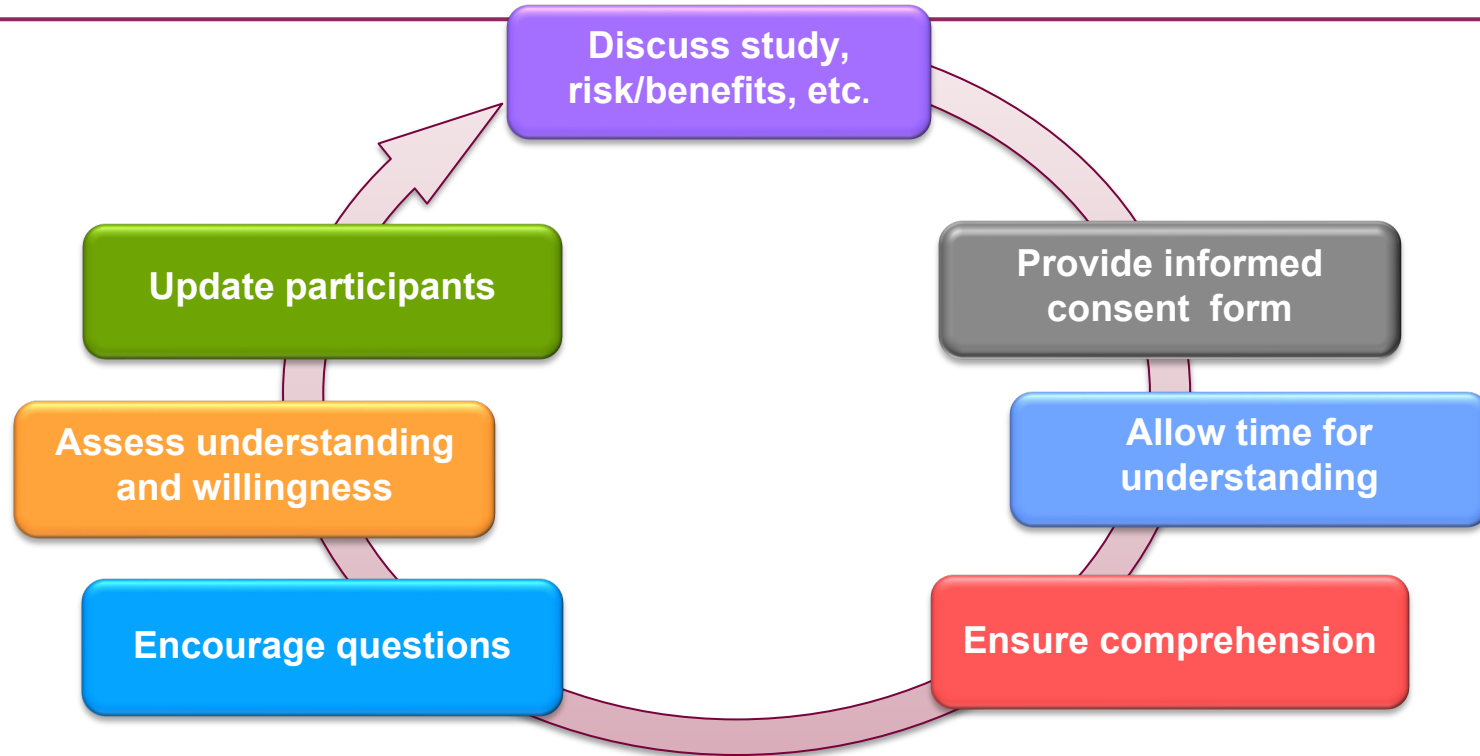
4.12 Premature Termination or Suspension of a Trial

4.13 Final Report(s) by Investigator

Informed Consent: Role of the Investigator

- Declaration of Helsinki
- ICH E6 Section 4.8
- Form FDA 1572 / MATRIX IoR Form
- 21 CFR 50

The Consenting Process



Key Points of the Informed Consent Process

Translation

Role of the witness

Timing

Signing and Dating

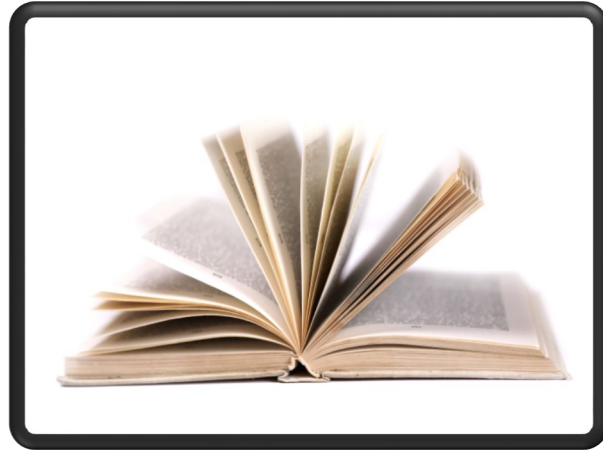
Version

Re-signing the consent



Consenting a Vulnerable Population: Illiterate Participants

- What are the consenting challenges?
- What strategies could you use to mitigate challenges?



Illiterate Participants

- Including illiterate participants is protocol specific
- Sites should follow their written SOP for including and consenting illiterate participants, as applicable
- Considerations:
 - Ask potential participants to read the informed consent form (ICF) out loud
 - Test writing skills
 - Read the informed consent form to the participant
 - Ask participant to “teach back”

ICH E6 GCP – Section 4.0

Investigator Responsibilities

4.1 Investigator Qualifications and Agreements

4.2 Adequate Resources

4.3 Medical Care of Trial Subjects

4.4 Communications with IRB/IEC

4.5 Compliance with Protocol

4.6 Investigational Product(s)

4.7 Randomization Procedures and Unblinding

4.8 Informed consent of trial subjects

4.9 Records and Reports

4.10 Progress Reports

4.11 Safety Reporting

4.12 Premature Termination or Suspension of a Trial

4.13 Final Report(s) by Investigator

Investigational Study Product(s)

- ICH E6 Section 4.6
- 21 CFR 312.57(a)
- 21 CFR 312.62(a)

Investigational Study Product(s)

- Responsibility for investigational product accountability at each site lies with the IoR
- Some or all of these duties can be delegated to the site pharmacist or other individual who is under the supervision of the IoR
- The investigational product(s) should be stored as specified in the approved protocol and related SSP and/or Pharmacy Manual(s), and in accordance with local and national regulatory requirements

Investigational Study Product(s)

- The IoR or designee should ensure investigational products are only used in accordance with the approved protocol and related SSP and/or Pharmacy Manual(s)
- The IoR or designee should explain the correct use of the investigational product(s) and continue to remind participants throughout the study as applicable

Product Accountability Records

- These records should include the following information:
 - Product delivery to the study site
 - Inventory at the study site
 - Proper storage
 - Use by each study participant
 - Return to the Product Developer or alternative disposition of unused product
 - Dates, quantities, batch/serial numbers, expiration dates (if applicable), unique code assigned to the product and study participant

ICH E6 GCP – Section 4.0

Investigator Responsibilities

4.1 Investigator Qualifications and Agreements

4.2 Adequate Resources

4.3 Medical Care of Trial Subjects

4.4 Communications with IRB/IEC

4.5 Compliance with Protocol

4.6 Investigational Product(s)

4.7 Randomization Procedures and Unblinding

4.8 Informed consent of trial subjects

4.9 Records and Reports

4.10 Progress Reports

4.11 Safety Reporting

4.12 Premature Termination or Suspension of a Trial

4.13 Final Report(s) by Investigator

Medical Care of Trial Participants and Safety Reporting

- ICH E6 Sections 4.3 and 4.11

Medical Care of Trial Participants

- A qualified physician must be responsible for all study-related medical decisions and ensure medical care is provided for any adverse events (AE) related to the trial
- The IoR or designee should attempt to find the reason for premature withdrawal of participation in the study when appropriate, while respecting the participant's rights

Safety Reporting

- AEs should be reported according to the requirements of the protocol
- All serious adverse events (SAE) should be promptly entered into the database
 - PTIDs (not names or other unique identifiers) should be used in any uploaded reports
- The IoR must follow the site's IRB/IEC requirements regarding reporting AEs, SAEs and unanticipated problems to the IRB/IEC

ICH E6 GCP – Section 4.0

Investigator Responsibilities

4.1 Investigator Qualifications and Agreements

4.2 Adequate Resources

4.3 Medical Care of Trial Subjects

4.4 Communications with IRB/IEC

4.5 Compliance with Protocol

4.6 Investigational Product(s)

4.7 Randomization Procedures and Unblinding

4.8 Informed consent of trial subjects

4.9 Records and Reports

4.10 Progress Reports

4.11 Safety Reporting

4.12 Premature Termination or Suspension of a Trial

4.13 Final Report(s) by Investigator

Essential Documents

- ICH E6 Section 4.9 and 8.0

Essential Study Documents

- ICH E6 GCP Section 8.0 provides a clear presentation of those documents required to be kept on-file at the study site by the IoR
- Individually and collectively, these documents permit evaluation of the conduct of the study and the quality of the data produced

Essential Study Documents

- Filing essential documents at the study site in a timely manner can greatly assist in the successful management of a study by the IoR
- These documents may be audited by the Product Developer's independent audit function and inspected by regulatory authorities

ICH E6 GCP – Section 4.0

Investigator Responsibilities

4.1 Investigator Qualifications and Agreements

4.2 Adequate Resources

4.3 Medical Care of Trial Subjects

4.4 Communications with IRB/IEC

4.5 Compliance with Protocol

4.6 Investigational Product(s)

4.7 Randomization Procedures and Unblinding

4.8 Informed consent of trial subjects

4.9 Records and Reports

4.10 Progress Reports

4.11 Safety Reporting

4.12 Premature Termination or Suspension of a Trial

4.13 Final Report(s) by Investigator

Site Oversight

- IoRs may delegate tasks, but the IoR is ultimately responsible for the conduct of the study at their site

How is Oversight Assessed?

- Were those to whom tasks were delegated qualified to do the tasks?
- Did staff receive adequate training to perform the delegated tasks?
- Is there evidence demonstrating the ongoing involvement of the IoR?
- Was there adequate supervision of any third parties?

Demonstrating Adequate Oversight (MATRIX Policy)

- Investigator qualification (IQ) documents for all sub-investigators listed on the 1572/IoR Form
 - Availability of CVs and clinical licenses
 - Maintenance of staff training records, including GCP and Human Subjects Protection (HSP)
- Timely signature/initials/date of IoR on study documents
- Delegation of Duties Log (DoD)
 - Note: IQ and training documents for site staff not listed on the 1572/IoR Form should be collected and maintained according to their site's institutional policy(ies)*
- Complete and accurate study product accountability records

Study Delegation of Duties Log



MATRIX DELEGATION OF DUTIES LOG



| | |
|---|--|
| Protocol Title: | |
| Study Number: | |
| Investigator of Record (IoR) Name: | |
| Clinical Research Site (CRS) Name: | |



*THIS FORM IS TO BE COMPLETED BY ALL STUDY STAFF AND OTHERS TO WHOM THE INVESTIGATOR/IoR HAS DELEGATED SIGNIFICANT RESEARCH-RELATED DUTIES, AFTER THEY HAVE BEEN TRAINED TO CONDUCT THE ACTIVITIES AND PRIOR TO TAKING PART IN ANY STUDY ACTIVITIES.

References

- ICH E6 Sections 4.0 and 8.0
- Form FDA 1572
- MATRIX IoR Form
- US Code of Federal Regulations (CFR) Title 21
- US FDA Guidance – Investigator's Responsibilities (October 2009)
- US FDA Guidance – Q&A Form FDA 1572 (May 2010)