MATRIX Good Documentation Practices (GDP) Policy

OVERVIEW

This document describes the regulations, policies and guidelines relevant to the timely, proper and thorough creation and maintenance of study records documenting study management and data collection activities within MATRIX: A USAID Project to Advance the Research and Development of Innovative HIV Prevention Products for Women.

APPLICABLE REGULATIONS AND GUIDELINES

MATRIX is funded by the U.S. Agency for International Development (USAID). As such, all project activities must be conducted in accordance with applicable sections of the U.S. Code of Federal Regulations (CFR) (http://www.ecfr.gov):

- 2 CFR 200: Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards
- 2 CFR 225: Human Subjects Protection
- 2 CFR 700: Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards

Good Clinical Practice Guidelines (ICH E6 GCP)

In addition to the above U.S. federal regulations, MATRIX specifically requires that all human subjects research activities be conducted in accordance with the International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) (or ICH E6 GCP for short): http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219488.htm. Additional guidance can be found at: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/gcp1.pdf, and https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf.

Investigational New Drug (IND) and Investigational Device Exemption (IDE) Studies

Furthermore, all MATRIX human subjects research activities conducted under an Investigational New Drug (IND) application will be subject to additional regulation by the U.S. Food and Drug Administration (FDA) and must be conducted in accordance with the following (http://www.ecfr.gov):

- 21 CFR 11: Electronic Records, Electronic Signatures
- 21 CFR 50: Protection of Human Subjects
- 21 CFR 54: Financial Disclosure by Clinical Investigators
- 21 CFR 56: Institutional Review Boards
- 21 CFR 312: Investigational New Drug Application
- 21 CFR 314: Applications for FDA Approval to Market a New Drug

Human subjects research activities conducted under an Investigational Device Exemption (IDE) will also be subject to regulation by the FDA and must be conducted in accordance with 21 CFR 812, Investigational Device Exemptions and 21 CFR 814, Premarket Approval of Medical Devices, in addition to the above.

Health Insurance Portability and Accountability Act (HIPAA)

The HIPAA Privacy Rule establishes U.S. standards to protect individuals' medical records and other personal health information. The rule applies to health plans, health care clearinghouses and those health care providers that conduct certain health care transactions electronically. The rule requires appropriate safeguards to protect the privacy of personal health information and sets limits and conditions on the uses and disclosures that may be made of such information without the patient's authorization. HIPAA also gives patients' rights over their health information, including the rights to examine, obtain a copy of, and request corrections to their health records.

The HIPAA Privacy Rule is located at 45 CFR Part 160 and Subparts A and E of Part 164 (https://www.ecfr.gov). All applicable U.S.-based organizations participating in MATRIX human subjects research activities must comply with CFR Title 45, Parts 160 and 164, Standards for Privacy of Individually Identifiable Health Information, which include subparts related to the following:

- Standards for use and disclosure of protected health information (PHI)
- Authorizations to use and disclose PHI or waivers of authorization
- Tracking of PHI uses and disclosures

MATRIX GOOD DOCUMENTATION PRACTICE REQUIREMENTS

Essential to establishing the integrity and reliability of clinical (biomedical and/or behavioral) research results, the timely, proper and thorough creation and maintenance of study records documenting study management and data collection activities is an ICH E6 GCP requirement (see ICH E6 GCP for guidance, especially Sections 4.9, 5.5 and 8.0).

The pharmaceutical and medical device industries have adopted standards, referred to as "Good Documentation Practices" (GDP), for creating and maintaining clinical research documentation. While not law, compliance with these standards is expected by the World Health Organization (WHO), the European Medicines Agency (EMA) and most if not all regulatory agencies with marketing application approval authority (e.g., U.S. FDA, South African Health Products Regulatory Authority [SAHPRA], etc.). Failure to adequately and properly document a study in compliance with GDP can significantly and negatively impact a regulatory agency's acceptance of the study in support of a marketing application.

Therefore, records documenting clinical research study development, management, communication, conduct, analysis and reporting must be created and maintained by each implementing partner

organization within MATRIX according to the MATRIX GDP Policy. This policy sets minimum standards for GDP compliance, though each implementing partner organization may have additional, specific requirements.

GDP Policy Requirements – Applicable Implementing Partners

While all implementing partner organizations within MATRIX are encouraged to adhere to the MATRIX GDP Policy, GDP compliance is required for the following implementing partner organizations involved in MATRIX clinical research activities:

- Prime/Clinical Trials Hub (CTH)
    - Magee-Womens Research Institute (MWRI)
    - Harare Health and Research Consortium (HHRC)
    - Wits Reproductive Health and HIV Institute (Wits RHI)
- Design to Delivery (D2D) Hub Pillar 2 – Social and Behavioral Research (SBR) in Clinical Trials
    - Centre For the Aids Programme of Research in South Africa (CAPRISA)
    - RTI International (RTI)
- Product Developers (PD)
    - CONRAD
    - Oak Crest Institute of Science (OCIS)
    - Population Council
    - University of Pittsburgh (Pitt)
- Clinical Research Sites (CRS)
    - The Aurum Institute (Aurum)
    - CAPRISA
    - HHRC
    - Kenya Medical Research Institute (KEMRI)
    - Wits RHI
    - U.S. based CRS, e.g., Pitt, Eastern Virginia Medical School (EVMS), etc.

Additionally, IND/IDE Sponsor organizations are required to maintain a Trial Master File (TMF) for all clinical studies (biomedical and/or behavioral) whose results are intended for inclusion in their IND/IDE marketing application package. It is the responsibility of the IND/IDE Sponsor organization to compile, organize and store these documents in such manner as to be readily available and accessible for potential review, inspection and/or audit by the relevant marketing application approval authorities (e.g., US FDA, EMA, SAHPRA, etc.). See next section for a sample listing of the types of documents that must be included in a TMF.

MATRIX DOCUMENTATION PROCEDURES

In general, the research records that must be created and maintained in compliance with GDP are those original documents, data, recordings, and certified copies of original records necessary for the reconstruction and evaluation of the conduct of clinical (biomedical and/or behavioral) research studies and the quality of the data produced. These records are not limited to those specifically mentioned in ICH E6 GCP, but include records documenting study development, communication, management, conduct, analysis and reporting at the operational level.

The MATRIX Prime/CTH, site monitor(s), and/or (if applicable) IND/IDE Sponsor will assist, as needed, each implementing partner organization to determine which records are critical to this process.

Essential Study Documents

Essential study documents serve to demonstrate the compliance of all parties (e.g., investigators, sponsors, and monitors) with the standards of ICH E6 and all applicable regulatory requirements. The following is a sample listing of the types of study documents considered essential:

- Internal policies & procedures
- Personnel qualification, financial disclosure, and training records
- Regulatory submissions (Institutional Review Board/Independent Ethics Committee [IRB/IEC], drug regulatory agency [DRA], including US FDA if applicable)
- All documents or materials submitted for regulatory review/approval, e.g., informed consent forms, participant recruitment materials, questionnaires, interview guides, logs, forms, checklists, etc.
- Regulatory approvals (IRB/IEC/DRA, including "Study May Proceed" document[s] from US FDA if applicable)
- Communications with regulatory bodies[1]
- Communications with product developers (if not the IND/IDE Sponsor)[1]
- Communications with MATRIX Scientific Advisory Group (SAG), USAID, Prime/CTH, and other MATRIX implementing partners[1]
- Contracts (all)
- Communications with non-MATRIX sub-contractors[1]
- Investigator brochures & notices of receipt
- Study Protocols, Amendments and Clarification Memos
- Statistical Analysis Plans
- Study-specific policies and procedures
- Relevant documentation pertaining to personnel training and certification/validation of facilities
- Relevant documentation pertaining to study-specific staff responsibilities, e.g., FDA Form 1572 or MATRIX IoR Form as applicable, Delegation of Authority/Duties/Responsibilities (DoA/DoD/DoR) Log
- Documentation of monitoring visits, e.g., summary reports
- Study product shipment, accountability, dispensation, and destruction records
- Meeting minutes[1]
- Study safety review decisions, e.g., query responses
- All specimen and assay data, including repeat or reanalysis performed for a test sample[2]
- All clinical and behavioral endpoint data source documents, e.g., case report forms (CRF), chart notes, (if applicable) audio recordings and transcripts from in-depth interviews (IDI), etc.
- Relevant documentation pertaining to participant eligibility, enrollment and (if applicable) randomization, e.g., completed checklists/logs, signed informed consent forms, etc.
- Reports prepared for or resulting from study monitoring or safety reviews

[1] Relevant to significant decisions regarding study development, management, conduct, analysis and/or reporting.

[2] Applicable to MATRIX-affiliated laboratories and clinical research sites

Acceptable Use of Electronic Systems – Data Management

The use of electronic systems/software to create, transfer, sign, date, and/or store study records is permitted by MATRIX if there are adequate safeguards/mechanisms in place to ensure:

- Data integrity, e.g., restricted access, clear and consistent version numbering, tracking of changes, etc.
- Privacy/confidentiality, e.g., password protection, file transfer encryption, removal of PHI, etc.
- Study documentation will be attributable, legible, contemporaneous, original, accurate, complete consistent, enduring, available (ALCOA+), and unquestionably reliable

The use of Laboratory Data Management System (LDMS), Laboratory Information System (LIS), OpenClinica, and Research Electronic Data Capture (REDCap) for clinical and quantitative behavioral data collection and management, for example, is permitted by MATRIX. The use of FileZilla and Dedoose for qualitative behavioral data transfer and analysis is also permitted by MATRIX, as is the use of Microsoft Office software such as Word, Excel, SharePoint and Teams for collaborative decision-making and development/sharing of documents by study team members. Other systems may be used for data collection, management, transfer and/or analysis with prior approval by MATRIX Prime.

For IND/IDE studies, all electronic systems/software relevant to the rights, safety, and well-being of study participants and/or the quality and integrity of study data and results must be validated for compliance with the requirements of 21 CFR Part 11. Each proposed system will be individually evaluated and approved by the applicable implementing partner organization according to their written, internal policies and procedures.

NOTE: Qualitative behavioral data collected as part of IND/IDE studies will only contribute towards exploratory endpoints, not towards primary or secondary endpoints. Given this data is not meant for inclusion in clinical study reports (CSR) or other documents required for future regulatory approval, an FDA 21 CFR Part 11 compliance waiver may be requested from MATRIX Prime to use the above mentioned electronic systems/software (e.g., FileZilla and Dedoose) for qualitative behavioral data transfer and analysis.

Acceptable Use of Electronic Systems – Document Signatures

The use of DocuSign (or equivalent application such as Adobe Sign) for signing/dating essential study documents is permitted by MATRIX. Implementing partner organizations that opt to use DocuSign (or equivalent application) should follow the steps described below:

- For essential study documents collected by Prime/CTH prior to and during a study, send document(s) to MATRIX Regulatory (matrixregulatory@lists.matrix4prevention.org) for processing of electronic signature/date. Essential study documents collected by Prime/CTH include but are not limited to:
    - Personnel qualification and training records, including curriculum vitae (CV) and (if applicable) Investigator of Record (IoR) training
    - Financial disclosure forms per 42 CFR 50 and (if applicable) 21 CFR 54
    - FDA Form 1572 or MATRIX IoR Form, as applicable
    - DoA/DoD/DoR Log
    - Investigator Signature Page
- For essential study documents generated by Prime/CTH, D2D Hub Pillar 2, and (for placebo studies not under an IND/IDE) the PD, send document(s) to MATRIX Regulatory

(matrixregulatory@lists.matrix4prevention.org) for processing of electronic signature/date. Essential study documents generated by Prime/CTH, D2D Hub Pillar 2, and PDs include but are not limited to:
    - Safety review reports
    - Data analysis reports
    - Data monitoring reports that are relevant to significant decisions regarding study development, management, conduct, analysis and/or reporting
    - Manuals, standard operating procedures (SOP), and policies
    - Training records
    - Memos and Notes to File
    - Meeting minutes that are relevant to significant decisions regarding study development, management, conduct, analysis and/or reporting
- (If applicable) For essential study documents collected and/or generated by the IND/IDE Sponsor for their TMF, except those already being collected by Prime/CTH as listed above, send document(s) to the IND/IDE Sponsor for processing of electronic signature/date. Essential study documents collected and/or generated by the IND/IDE Sponsor for their TMF include but are not limited to:
    - Data analysis reports
    - Data monitoring reports that are relevant to significant decisions regarding study development, management, conduct, analysis and/or reporting
    - Manuals, SOPs, and policies
    - Training records
    - Memos and Notes to File
    - Meeting minutes that are relevant to significant decisions regarding study development, management, conduct, analysis and/or reporting
    - See list of essential study documents at the start of this section for additional examples
- MATRIX Regulatory or (if applicable) IND/IDE Sponsor staff will upload the document(s) to DocuSign (or equivalent application), add signature and date fields as needed, and send the document(s) back to the implementing partner via email for their signature(s)/date(s).
- Once all relevant parties have signed/dated the document(s), any signature certificate(s) generated by DocuSign (or equivalent application) should be stored along with the respective signed/dated document(s) in the relevant implementing partner organizations' essential study files.
    - Combining each electronically signed/dated document with its respective signature certificate into one PDF file is recommended to ensure they "travel together" should files be moved or reorganized later.

Implementing partner organizations that do not use DocuSign (or equivalent application) must sign and date study records by hand. See next section for additional details regarding documentation procedures in the absence of acceptable electronic systems, including handwritten signatures, initials, and dates.

MATRIX Documentation Procedures in the Absence of Acceptable Electronic Systems

In the absence of acceptable (or in the case of IND/IDE studies, 21 CFR Part 11 compliant) electronic systems for use by the applicable implementing partner organization, the procedures for creating, collecting, and storing study records will be as follows:

- Creation:
  - Documents should be created with a header or footer which includes the MATRIX study title/number (where applicable), title or subject of the document, version (where applicable), date and pagination in "x of n" format.
  - All attachments should be listed by title/subject, version (where applicable), date and total number of pages.
  - Documents may be electronically created initially but must be printed and hand-signed and hand-dated by the author and, where applicable, by persons providing additional verification or authorization of the record.
    - All roles (authorship, verification, approval) must be specified.
      - An electronic image of the hand-signed and hand-dated paper copy will be created by scanning. Multiple page documents should be scanned as a single record.
  - Word documents that are created from older documents/templates originally used for non-MATRIX purposes should have the document metadata checked and (if needed) updated to reflect their current MATRIX purpose prior to finalizing.
    - To check the metadata on a Word document, open the document, select "View", select "Properties", select the drop-down "Properties" option labeled "Advanced Properties", and delete/edit the "Summary" entries as needed.

  NOTE: The above "Creation" procedures should also guide creation of documents when using acceptable electronic systems, except for the steps related to hand-signing and hand-dating.

- Corrections:
  - Hardcopy--
    - Never obscure the original entry.
    - Draw a single line through the error, provide or reference an explanation for the change (when needed), initial and date the change by hand.
  - Electronic File--
    - Never destroy or overwrite the original source file. The original file is a permanent part of the history of the study.
    - The header or footer of the revised file must be modified by giving it a new version # or by adding the word "revision" and giving it a new date.
    - Provide or reference an explanation for the change (when needed).
    - Print and collect dated signatures by hand of persons approving the change, preferably the same individual(s) who signed the document originally.

  NOTE: The above "Corrections" procedures should also guide correction of documents when using acceptable electronic systems, except for the steps related to hardcopy documents, hand-signing and hand-dating.

- Collection and Storage:
  - Source documentation should adhere to the ALCOA+ principle (attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, and available).
  - Records (both paper and electronic) will be collected and stored in a timely manner.
  - Both paper and electronic files will be maintained in secure, limited access files which are protected to the extent possible from physical damage and loss.

- Final versions of electronic files will be routinely backed up and original date/time stamps (metadata) will be maintained.
    - When retrieving electronic files from email communications or other applications, or when moving them from one location/folder to another, it is strongly recommended that, whenever possible, electronic files be copied/cut and pasted, rather than saved, to maintain the document metadata.

NOTE: The above "Collection and Storage" procedures should also guide collection and storage of documents when using acceptable electronic systems.

- Version Control and Release:
    - Documents that are created or updated with input from multiple authors and/or through an iterative review process should have a designated person(s) to collect and collate authors'/reviewers' input into one master document.
        - The designated person(s) will track changes made to the master document and ensure version integrity is maintained during document development.
    - Any time changes or updates are made to a document, whether it is a draft or a final document, the changed document should be saved with a different filename to preserve the earlier version.
    - The document's footer and filename should reflect the document's stage of development (e.g., Version 0.1/0.2/0.3, Version 1.1/1.2/1.3, Version 1.0/2.0/3.0, draft/revised/final, etc.) and version date.
        - For documents created or updated with input from multiple authors and/or through an iterative review process, version number and date should be updated in the footer and filename after each round of document review is completed and input received is incorporated.
            - For example, a document sent for a second round of document review would be at Version 0.2 and would be changed to Version 0.3 (or to Version 1.0 if no additional review/input is expected) once all input received during the second round of review was incorporated.
        - If the changes/updates made to a document do not warrant a version number update or if more changes are expected prior to updating the version number, the version date should still be updated in the document's footer and filename to preserve the earlier version. Alternatively, some other identifier may be added to the filename (e.g., reviewer/author initials).
    - Once a document is finalized, the document should be saved as a PDF prior to filing and/or circulating, particularly if the document is meant to be posted on the MATRIX website or otherwise shared outside the group of authors/reviewers (e.g., Protocol/Management Team, Activity Hub, Product Developer, Prime, etc.) that created the document, for example, as part of IRB/IEC/DRA submissions or if requested by site monitors or other protocol-approved reviewing institutions.
        - Editable versions of finalized documents should not be circulated outside the group of authors/reviewers that created the document unless they are explicitly meant to be modified (e.g., templates) or filled out (e.g., blank forms, logs, checklists, etc.), or unless required by IRB/IEC/DRA, site monitors or other protocol-approved reviewing institutions.
        - Documents posted on the open portion of the MATRIX website may be shared freely but documents posted on the closed portion of the MATRIX website should not be shared without permission from the relevant group of authors/reviewers.

- For additional guidance about document sharing, contact the Prime at matrixprime@matrix4prevention.org.

NOTE: The above "Version Control and Release" procedures should also guide version control and sharing of documents when using acceptable electronic systems.

- Signatures/Initials:
  - Handwritten signatures (and dates) should be made using blue or black ink only. The individual's name should be hand-printed or typed underneath or next to a signature.
  - Where a Signature Log is maintained, hand-written initials and hand-written dates are sufficient in many cases, unless prohibited by institutional policies and procedures. Initials must be traceable to a single individual.
  - However, documents likely to be circulated outside the immediate group (i.e., to those without access to the relevant signature logs) should be signed rather than initialed.

- Dates:
  - Dates must be consistently recorded according to a specific format designated by the policies and procedures of the implementing partner organization.
  - The format being used should be indicated whenever possible (e.g., MM/DD/YYYY, DD/MM/YYYY or DD/MMM/YY as applicable) especially on documents likely to be circulated outside the immediate group.

NOTE: The above "Dates" procedures should also guide dating of documents when using acceptable electronic systems.

The objective of the above-described procedures is to ensure that all study documentation will be attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring, available (ALCOA+), and unquestionably reliable even in the absence of acceptable (or in the case of IND/IDE studies, 21 CFR Part 11 compliant) electronic systems.

Additional Guidance for CRS Partners – Completion of FDA Form 1572 or MATRIX IoR Form

The goal of this guidance is to reduce unnecessary administrative burden for sites, PDs, and the Prime/CTH while still meeting the basic regulatory standards set forth in US CFR and ICH E6 GCP. Specifically, the following guidance streamlines the list of laboratory facilities and site staff that should be listed in Sections #4 and #6, respectively, of both the FDA Form 1572 and the MATRIX IoR Form.

Section #4 – Name and Address of Clinical Laboratory Facilities to be Used in this Study

Per the US FDA's FAQ guidance on the FDA Form 1572 (https://www.fda.gov/media/78830/download), Section #4 of the form "is intended to identify clinical laboratories or testing facilities directly contributing to or supporting the clinical study (for example, diagnostic labs performing blood work, imaging centers, cardiology labs, etc.). This may include analytical labs that provide pharmacokinetic analysis, and laboratories supplying efficacy data for clinical investigations conducted under an IND."

The guidance above is interpreted as follows:

- For all MATRIX clinical (biomedical and/or behavioral) research studies, only those laboratory facilities that will perform primary and secondary endpoint analyses should be listed in Section #4 of the FDA Form 1572 (IND/IDE studies) or MATRIX IoR Form (placebo studies not under an IND/IDE).
    - For active product studies conducted under an IND/IDE, this will typically include:
        - Local laboratory(ies) used by the site for clinical and safety-related analyses.
        - Protocol-designated laboratory(ies) used for pharmacokinetic and efficacy-related analyses.
    - For placebo studies not under an IND/IDE, this will typically only include all local facilities used by each site for clinical and safety-related analyses.

Section #6 – Names of Sub-Investigators

Per the US FDA's FAQ guidance on the FDA Form 1572 (https://www.fda.gov/media/78830/download), Section #6 of the form is intended "to capture information about individuals who, as part of an investigative team, will assist the investigator and make a direct and significant contribution to the data. The decision to list an individual in Section #6 depends on his/her level of responsibility (i.e., whether he/she is performing significant clinical investigation-related duties). In general, if an individual is directly involved in the performance of procedures required by the protocol and the collection of data, that person should be listed on the 1572… Staff who provide ancillary or intermittent care but who do not make a direct and significant contribution to the clinical data, do not need to be listed individually. It is not necessary to include in this section a person with only an occasional role in the conduct of the research".

The guidance above is interpreted as follows:

- For all MATRIX clinical (biomedical and/or behavioral) research studies, only site staff regularly involved in the source documentation of safety data or are delegated to perform critical trial related procedures (e.g., adverse event assessment, confirmation of participant eligibility, prescription of study product) should be listed in Section #6 of the FDA Form 1572 (IND/IDE studies) or MATRIX IoR Form (placebo studies not under an IND/IDE).
    - This will typically mean the study clinicians. Other site staff (e.g., nurses, pharmacists, laboratory staff, 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.

NOTE: The guidance in this section only applies to the FDA Form 1572 and MATRIX IoR Form. For other documents that may require a listing of laboratory facilities (e.g., Materials Transfer Agreements [MTA], informed consent forms, etc.) or a listing of site staff (e.g., DoA/DoD/DoR Log), implementing partners should follow the applicable local, national and/or institutional regulations, policies, and procedures.

Additional Guidance for CRS Partners – Completion of Delegation of Authority/Duties Log

The Prime/CTH will provide a template DoA/DoD/DoR Log for sites to complete prior to study activation. Sites are encouraged to edit/modify the category labels listed in the "Significant Research-Related Duties Key" section of the template DoA/DoD/DoR Log as needed to fit their specific staffing nomenclature.

NOTE: Guidance regarding addition of laboratory staff to sites' DoA/DoD/DoR Logs can be found in the MATRIX Laboratory Policy at www.matrix4prevention.org/resources.

Prior to study activation, sites need to assign responsibility to all staff members involved in the study and fill out all the columns in the "Investigator of Record (IoR)" and "Site Staff" sections except for the last columns labeled "End Date" and "Stop Date and Investigator/IoR Confirm Delegation End/Date", respectively. Those will be completed at the end of the staff members' study involvement or at the end of the study (i.e., database lock), whichever comes first.

NOTE: Dates and signatures and initials of staff members and the IoR need to be handwritten. The other columns can be typed in.

The DoA/DoD/DoR Log is a running document and as such may need to be updated during the study as staff members and/or responsibilities change. The IoR will only sign and date the "Investigator's/IoR's End of Study Declaration" section of the DoA/DoD/DoR Log at the end of the study.

If you have any questions about completing the DoA/DoD/DoR Log, contact the MATRIX CTH at matrixcthub@matrix4prevention.org.

Guidance on Long-Term Storage and Destruction of Study Records

All study records, including paper files, electronic study data, electronic documents, and audio files of interviews, will be maintained on-site for the entire period of study implementation and for an extended period after study completion or discontinuation as stipulated by the Sponsor and/or in-country regulatory authorities. During such time, study records must be available and accessible for possible inspection, review and/or audit by the following entities or their designees: USAID, MATRIX, IND/IDE Sponsor (if applicable), and applicable local, national, and international regulatory agencies.

Study records must be maintained on-site for the entire study implementation period. No records are permitted to be relocated off-site without prior written authorization from the MATRIX Prime and, if applicable, the IND/IDE Sponsor. To relocate study records, the following requirements must be met:

- All MATRIX study records must be maintained throughout the study close-out process
- All MATRIX study records must be maintained in accordance with protocol-specified protections of participants' confidentiality and with site IRB/IEC/DRA policies and procedures
- All MATRIX study records must be filed in a safe, secure and confidential storage area (physical or electronic) that is easily accessible for prompt retrieval of records if needed

When the above conditions are met, the study primary investigator (PI) will contact the Prime to request approval to relocate study records. Following approval, the Prime will notify the study PI that MATRIX approves sites' record relocation. All approvals for relocation of long-term storage of study records will be documented according to the MATRIX GDP Policy described in the previous sections.

Under no circumstances will any study record located at a site be destroyed without prior written authorization from the MATRIX Prime and, if applicable, the IND/IDE Sponsor. The destruction of study records may proceed provided the following requirements are met:

- All MATRIX study records must be maintained in accordance with protocol-specified protections of participants' confidentiality and with site IRB/IEC/DRA policies and procedures. Site staff should follow the strictest retention requirements to which a study record is subject, including national or local laws, regulations, or policies.
- All study records of MATRIX studies conducted under an IND/IDE application must be retained for at least two years after the FDA's marketing product approval or disapproval, IND/IDE withdrawal or study discontinuation as per 21 CFR 312.62 (c). Requirements stipulated by other drug regulatory authorities (such as SAHPRA for sites operating in South Africa) may also apply.
- All study records of MATRIX studies that are not conducted under an IND/IDE must be retained for at least three years after completion of research as per 22 CFR 225.115 (b).

When the above conditions are met, and after confirming that study records will no longer be needed for analyses, the study PI will contact the Prime to request approval to destroy study records. Following approval, the Prime will notify the study PI that MATRIX approves sites' record destruction. However, study sites will be reminded to confirm with their institutions and regulatory bodies whether any in-country or local requirements stipulate that study records must be retained for longer periods of time. All approvals for destruction of study records will be documented according to the GDP guidelines described in the previous sections.

MATRIX GDP TRAINING PROCEDURES

While GDP training is not specifically named by any federal U.S. regulatory bodies, GDP is an integral part of ICH E6 GCP and is essential to establishing the integrity and reliability of clinical research results.

MATRIX is committed to protecting the safety and confidentiality of study participants and producing high quality research. To achieve this goal, all lead/key implementing partners involved in clinical (biomedical and/or behavioral) research must have current (i.e., completed within three years) training in ICH E6 GCP relevant to their scope of work (i.e., biomedical or behavioral) prior to start of study accrual activities and, at minimum, complete ICH E6 GCP training every three years while study activities are ongoing.

GCP Training Requirements – Applicable Implementing Partner Personnel

The following is a list of lead/key persons responsible for the design, conduct, analysis and/or reporting of MATRIX-funded human subjects research, and for whom ICH E6 GCP training is required (individual persons may be represented in more than one category):

- MATRIX Executive Director and Deputy Director
- MATRIX Prime/CTH and D2D Hub Pillar 2 Co-PIs
- MATRIX Prime/CTH key staff
    - Protocol Safety Physicians
    - Independent Safety Physician

    - Pharmacy Consultant
    - Clinical Research Managers
    - Data Management and Statistical Support lead
    - Laboratory Support lead
    - Protocol Development lead
- D2D Hub Pillar 2 key staff
    - Project Management leads
    - Research Epidemiologist
- Protocol Chairs/Co-Chairs
- Site IoR* and co-PIs listed in Protocol Team Rosters
- Site sub-Investigators listed in FDA Forms 1572 (IND/IDE studies) or MATRIX IoR Forms (placebo or behavioral studies not under an IND/IDE)
- PD PIs/co-PIs and key staff listed in Protocol Team Rosters
- Protocol Statisticians not already represented in above categories

Additional implementing partner staff may need to complete GCP training if required by their respective organizations, and additional GCP or GDP training may be required of implementing partners by their respective organizations. Implementing partners will ensure compliance with these additional requirements according to their internal policies and procedures.

*Site IoRs are required to take additional training related to their IoR responsibilities for MATRIX studies, including as relates to GCP. The Prime/CTH developed a training presentation that site IoRs must review prior to starting data collection activities and every three years thereafter. Upon reviewing the training materials, site IoRs will document this training by completing the IoR training documentation form and sending the completed form to MATRIX Regulatory (matrixregulatory@lists.matrix4prevention.org). Both the IoR training presentation and documentation form can be found at https://www.matrix4prevention.org/resources/regulatory-documents.

GCP Training Resources

Acceptable GCP training certification may be obtained from many sources given the diverse training delivery methods accessible to implementing partners from their respective institutions, e.g., online courses, in-person sessions, etc. Furthermore, specific courses may be required of implementing partners by their respective institutions (e.g., focusing on local country regulations), roles (e.g., Sponsor or Investigator), or fields of study (e.g., biomedical or behavioral).

However, at minimum, GCP training courses must cover the following topics:

- Investigator Roles and Responsibilities (ICH E6, section 4)
- Relevant topics in Sponsor Roles and Responsibilities (ICH E6, section 5), including Investigator Selection, Confirmation of Review by IRB/EC, Data Handling and Recordkeeping, Quality Assurance and Quality Control (QA/QC), and Adverse Event Reporting
- Essential Documents (ICH E6, section 8)
- Source Documents (ICH E6, section 8)

For implementing partners conducting IND/IDE studies, GCP training courses should also cover the following topics relevant to US FDA-regulated research:

- 21 CFR Part 11 Electronic Records and Signature
- 21 CFR Part 312 Investigational New Drug Application with particular attention to Sections 312.53 (FDA Form 1572) and 312.60-70 (Investigator's Responsibilities)
- 21 CFR Part 50 Protection of Human Subjects
- 21 CFR Part 54 Financial Disclosure by Clinical Investigators
- 21 CFR Part 56 Institutional Review Boards

The following is a partial listing of GCP training delivery methods, including virtual and in-person courses, that meet the above minimum criteria and provide certification of completion for a course in which basic GCP knowledge is demonstrated in order to receive the certificate:

- Collaborative Institutional Training Initiative (CITI) Program online modules
- National Institutes of Health (NIH) GCP e-learning courses, such as those offered through the National Institute of Allergy and Infectious Diseases (NIAID) or the Society of Behavioral Medicine
- National Institute on Drug Abuse (NIDA) Clinical Trials Network courses
- Pharmaceutical Product Development (PPD, now part of Thermo Fisher Scientific) courses
- Certification from a recognized clinical research professional organization, such as Association of Clinical Research Professionals (ACRP) or Society of Clinical Research Associates (SOCRA)
- Other courses provided/facilitated/sponsored by the implementing partner's institution and/or local regulatory agencies which are designed to meet "the minimum criteria for ICH GCP investigator site personnel training identified by TransCelerate BioPharma as necessary to enable mutual recognition of GCP training among trial sponsors" (e.g., BCompliant, Global Health Training Centre, Clinical Research Education and Development [CREDE], Task Academy, Academic Advance, etc.)

Additional GCP or GDP training may be required of implementing partners by their respective organizations. Implementing partners will ensure compliance with these additional requirements according to their internal policies and procedures.

Documenting GCP Training

All relevant implementing partner organization staff (see list of "lead/key persons" in Page 10 of this policy) must have documentation of training in ICH E6 GCP completed less than three years before study start and, at minimum, every three years until study end.

NOTE: For purposes of this policy, "study start" either refers to the date a person is added to their site's FDA Form 1572 or MATRIX IoR Form (for Site IoRs and Sub-Investigators only) or to the first site activation for a study (for all other "lead/key persons" listed in Page 10 of this policy).

NOTE: Except for Site IoRs and Sub-Investigators, who must provide documentation of GCP training prior to being added to their site's FDA Form 1572 or MATRIX IoR Form, any "lead/key persons" who begin their study involvement after study start must provide documentation of GCP training within 60 days of joining a study.

NOTE: For purposes of this policy, "study end" either refers to completion of participant follow-up at their site (for Site Sub-Investigators only) or database lock (for all other "lead/key persons" listed in Page 10 of this policy, including Site IoRs).

In collaboration with the relevant implementing partners, the Prime/CTH will identify which persons are required to receive GCP training and solicit certification documentation for those individuals accordingly. Documentation of training should include trainee name(s), date(s) of training, name/affiliation of trainer, and course title. Course outline/syllabus should also be included if available, particularly if it is unclear whether the training meets the minimum criteria as described in the previous section.

Upon completion of training, implementing partners will file the certification document(s) with their essential documents and email an electronic copy of the document(s) to MATRIX Regulatory (matrixregulatory@lists.matrix4prevention.org). Any paper generated training certificate(s) should be scanned and then emailed.

NOTE: If needed, implementing partners will also print a hard copy of any electronically generated training certificate(s) and file it with their essential study documents per the guidance described in the "MATRIX Documentation Procedures in the Absence of Acceptable Electronic Systems" section of this policy.

The Prime/CTH will maintain records of GCP training dates for documentation and tracking purposes. The Prime/CTH will monitor the relevant implementing partners' GCP training completion dates and request completion of renewal/refresher training as necessary to ensure their certification remains current (i.e., completed every three years) throughout their involvement in study activities.

As with other essential study documents, implementing partners should maintain training records and make them available and accessible for possible inspection, review and/or audit by the following entities or their designees: USAID, MATRIX, IND/IDE Sponsor (if applicable), and applicable local, national, and international regulatory agencies.

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