



MATRIX-003 Study-Specific Procedures (SSP) Manual

Section 12 – Data Collection

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12 Introduction

The purpose of this document is to provide site staff with the information they need to successfully complete and submit MATRIX-003 Electronic Case Report Forms (eCRFs). For questions about this section or about general data collection policies, procedures, or materials, please contact the MATRIX-003 Clinical Data Manager as listed below. The Data Management & Statistical Support (DMSS) team for this study is part of the MATRIX Clinical Trials Hub (CTH) located at Magee-Womens Research Institute, Pittsburgh, PA, USA, and is in the US Eastern Standard Time (EST) time zone. The MATRIX-003 CTH-DMSS team members, their job roles and e-mail addresses, are listed below.

Table 12-1: MATRIX-003 Data Management & Statistical Support Staff

Job Role	Name	Email Address
Protocol Statistician(s)	Leslie Meyn	meynla@mwri.magee.edu
Clinical Data Manager(s)	Tracy Zamborsky	zambtx@upmc.edu

12.1 REDCap Overview

Research Electronic Data Capture (REDCap) is the data management system used by the MATRIX CTH to receive and manage study data collected at study sites. REDCap (co-chair Kathryn Mngadi asking to include license number and indicate it is validated) is a secure, web-based application designed for clinical trial data collection. REDCap employs various methods to protect the data stored in the software application's backend database against data breaches.

The security settings are controlled by the REDCap system administrators at the University of Pittsburgh and therefore are not modifiable by the end users. The user passwords do not expire. After 30 minutes of inaction, the REDCap system will automatically log a user out. After five unsuccessful login attempts, the user's account will be locked and the user will need to contact the administrators to regain access to their account. A user's account will automatically deactivate after 180 days of inactivity.

All research staff who require access to enter or view data within REDCap for their site will need a REDCap user account through the University of Pittsburgh/Clinical and Translational Science Institute (CTSI). Each staff member and study monitor will need to request REDCap account access. Protocol Safety Review Team (PSRT) members maybe also request accounts but are not required to do so. CTH-DMSS will provide sites with instructions for obtaining accounts.

Each site will be responsible for getting their monitors set up with REDCap accounts and notifying the CTH Data Management & Statistical Support team to add the monitor to their Data Access Group for read-only access. Account requests should be made at least 5 business days prior to the first expected use. New employees will also need to request REDCap account access; you cannot allow a new employee to use a former employee's account. If an employee leaves the organization or moves to a different department, the CTH-DMSS should be notified so that their access to the MATRIX-003 Study REDCap database can be revoked.

User access privileges within REDCap are customizable and controlled by the data managers of the study. The research staff responsible for direct data entry are assigned privileges that allow them to create and edit participant records, but they are not able to delete or rename records. Study monitors and members of the PSRT will have read-only access so that they are unable to change any data elements. Study staff and site monitors will only have access to their site-specific data.

The CTH-DMSS team will provide sites via e-mail with a MATRIX-003 REDCap Account Access Log to complete. This will be used to track staff members' access to REDCap, including monitors. Once staff have obtained REDCap accounts, the log is to be completed, and sent back to CTH-DMSS via email. For all communications related to REDCap accounts and access, email both Leslie Meyn and Tracy Zamborsky; email addresses listed in Table 12-1. The MATRIX-003 REDCap Account Access Log should be updated and submitted to the CTH-DMSS any time there are changes (i.e. new staff are hired and need REDCap access or to revoke access for staff who have terminated employment or involvement with the study).

Each site completes study eCRFs by entering data into the REDCap study database. As specified in each site's Source Documentation SOP, data may be entered directly into the study database (i.e., eCRF is source; this is preferred method), collected first on paper case report forms (CRFs) and then entered into the study database, and/or entered into the study database based on other non-CRF source documents (e.g., lab reports, testing logs, chart notes, etc.). Refer to Appendix 1 of section 2 of the SSP "Documentation Requirements" for specific guidance on source documentation. Site staff should contact the study Clinical Data Manager with any questions related to study data collection and management.

12.1.1 Data Entry/Quality Control

Once an eCRF is completed and saved in the study database, the following may occur:

- A system query may be automatically triggered in REDCap (e.g., denoting incomplete, inconsistent, or out-of-range data).
- Review may be required for certain forms and/or fields by the MATRIX-003 Clinical Data Manager, and manual data queries may be placed.
- Review may be required for certain forms and/or fields, as identified by the site monitor.
- Quality Control (QC) queries will be emailed no less than bi-weekly to site staff. Designated site staff members are responsible for reviewing the queried data elements and correcting/updating study data to resolve the queries, as applicable.
- When site staff correct/update study data and/or enter a query response to address a manual or coding query, the Clinical Data Manager will review the updated data and/or response, and resolve the query or re-query as needed.
- If a site utilizes paper CRFs as source documents, any changes to the paper CRFs that result from a query must be entered into the REDCap study database.

12.1.2 Electronic Signatures by Investigators

Once the study is complete, and all the study data have been entered and meet all the specified logical checks, the final complete study data files will be locked. CTH-DMSS will coordinate this process with the site Investigators of Record (IoRs). Each site IoR or their designee will review each eCRF for each participant for completeness and accuracy. Once this review is complete, each site IoR will write a Note to File stating that they have reviewed the eCRFs for their site, that they have ensured the accuracy and completeness of the data reported in the CRFs, and that their site's records can be locked. Once all sites have e-mailed their signed and dated Note to Files to the CTH-DMSS and the CTH team, the CTH-DMSS will notify the protocol chairs that the database is ready to be locked. A protocol chair will lock the records for each participant and apply an e-signature certifying that the information submitted is complete and accurate. By completing this participant-level sign-off in the REDCap study database, the protocol chairs attest that the data has been reviewed and is deemed to be accurate. This process will be completed for both the MATRIX-003 participants and MATRIX-003 Sexual Partner databases.

12.2 Case Report Forms (CRF)

CRFs have been programmed into the MATRIX-003 Participants and MATRIX-003 Sexual Partner Projects in REDCap for direct data entry. PDFs of the CRFs are available to view or download within the MATRIX-003 Project in REDCap. In some cases, the downloadable PDF will not provide the most accurate view of the CRF as it would appear for direct entry. The eCRFs in REDCap have skip patterns programmed, as well as visit-based logic, allowing some questions to only appear when entering data for the relevant visits. Paper CRFs that are a better representation of the eCRF view have been created. They highlight relevant

skip patterns and offer better guidance than those available in REDCap. PDFs of these CRFs are available to download on the matrix4prevention.org website. Staff should consult the CRF Completion Guidelines for direct data entry as well as when utilizing a paper CRF.

12.3 CRF Completion

12.3.1 General Guidelines

To the extent possible, site staff should utilize direct data entry into the REDCap study database so that the eCRF serves as the source document. Direct data entry is especially encouraged for data collection based on participant self-report. Paper CRF completion requires an intermediate step of data management and quality assurance (QA/QC) review into site data management workflows. In addition, paper CRF completion introduces the risk of data transcription errors and could contribute to database data entry errors. When paper CRFs are utilized, they are to be retained in the participant's paper chart/file.

When direct data entry is not possible due to the nature of the source data - for example, when the source data is a local lab results report - site staff should enter study data into the REDCap study database based on the site-specific source document.

When paper forms are used as source, data should be entered into the appropriate REDCap eCRF as soon as possible. Ideally, completion of all required eCRFs for a given visit will occur within 1–2 business days of the visit, though up to 7 days is acceptable.

The REDCap dashboard shows a list of forms that are available at each study visit. Most forms linked with a visit are required, some have the prefix of "PRN" and are only to be used as needed. Forms have a blank radio button until they are completed as described below.

At the bottom of each eCRF is a standard Form Status Section with the question: "Complete?", which simply means "Is this form complete?" The options for selection are: Incomplete, Unverified, and Complete (with "Incomplete" being the default entry). These options are each associated with a color that shows up in the bubble for the form on the study record dashboard (incomplete is red, unverified is yellow, complete is green; a blue dot shows when repeatable CRFs have multiple instances with varying completion status). A form is only to be marked "Complete" once it is finished and you do not expect to add or modify any data on it. For forms that require data to be entered later, mark them as "Incomplete". If a form needs to be reviewed by another staff member, mark it as "Unverified". This process is dependent on each individual site's SOP.

12.3.2 Screening and Enrollment/Randomization

Screening: Data entry into the study database begins at the Screening Visit. Once a participant has signed the informed consent form (ICF), screening data may be entered into the database. No data is to be entered until after the ICF is signed. The participant must be assigned a PTID immediately following obtaining Informed Consent using the PTID Assignment Log. Once the PTID is assigned, then staff can select and activate the assigned PTID in REDCap and enter data. All participants who are screened for the study will have demographic data collected, regardless of whether they are eligible.

Enrollment/Randomization:

Prior to site activation, the MATRIX-003 CTH-DMSS will provide each site with a set of 36 sealed randomization envelopes and a Randomization Envelope Assignment Log via courier service. Since the enrollment target at each site is 20 participants, provision of 36 envelopes will allow for flexibility in the number of enrollments among sites should a particular site experience accrual difficulty. Each MATRIX-003 randomization envelope will be labeled with the randomization envelope number, CRS name and CRS location. Each envelope set (one set per site) will be numbered sequentially, and authorized site staff will assign envelopes in sequential order using the Randomization Envelope Assignment Log as outlined below:

- Eligibility must be determined and confirmed by the site IoR/designee prior to randomizing a participant.
- Prior to opening the next available Randomization Envelope in the sequence, the PTID and the Randomization Envelope number is documented on the Randomization Envelope Assignment Log along with randomization date and staff initials.
- Authorized site staff opens the Randomization Envelope which contains one Participant Randomization Assignment Record. Each Participant Randomization Assignment Record is pre-populated with the corresponding Randomization Envelope number and the study product sequence of use assignment, along with the CRS name, location, and site code.
- Site staff completes the Participant Randomization Assignment Record with the participant's PTID, date and time of randomization (time of randomization is the time the randomization envelope was opened).
- Site staff prints their name, signs, and dates the Participant Randomization Assignment Record.
- The participant is now considered enrolled in the study.
- The Participant Randomization Assignment Record is used to obtain the assigned product for the enrollment visit from the site's study pharmacist(s). See study product considerations for further details.
- The information from the Participant Randomization Assignment Record is entered into the REDCap Randomization eCRF.

12.3.3 Replacement Participant

Replacement participants will be considered in consultation with the Protocol Statistician and study Management Team if loss to follow-up is higher than expected, per Protocol section 10.3. If it has been determined that a participant needs to be replaced, additional participants will be screened until the required number of evaluable participants has been reached.

12.3.4 Clinical Site Data Management SOP

As a condition for study activation, each study site must have a site or study-specific SOP for data management. This SOP should be reviewed and followed in combination with the information contained in the study protocol and this SSP Manual. The data management SOP should include site staff responsibilities and contain information on several data topics, including:

- Participant's paper chart/file
- Participant confidentiality
- Site data QC processes
- Timing of data entry into the study database
- Contingency plans in case of interrupted access to the study database

- Management of site user accounts and permissions for access to the study database

12.4 Study-Specific Data Collection Information

12.4.1 Participant and Sexual Partner Identification Numbers (PTID)

MATRIX-003 Participant PTIDs and Sexual Partner PTIDs have been pre-populated in REDCap with specific coding for each site. The CTH-DMSS will distribute to each site via email a "MATRIX-003 PTID Assignment Log" and a "MATRIX-003 Sexual Partner PTID Assignment Log", which the site will print and store in a secure location with limited access as per site standards.

The PTID Assignment Log includes participant's full name, screening attempt, staff initials, date and time of entry. When establishing a new screening participant, the steps to obtain a unique participant identification (PTID) number are outlined below:

- Immediately after obtaining informed consent and prior to accessing REDCap, site staff assigns the next available sequential number on the PTID Assignment Log.
- Site staff completes the log with participant's full name, screening attempt, initials of staff completing the log, date and time of entry.
- Once the PTID Assignment Log is completed, site staff activates the pre-populated PTID by choosing the corresponding PTID "Establish PTID" eCRF in the MATRIX-003 REDCap database.
- In the event of a re-screen attempt, the participant is assigned a new PTID and is re-entered into the PTID Assignment Log following re-consent.

The Sexual Partner PTID Assignment Log includes sexual partner's full name, the main participant's PTID (for linkage purposes), staff initials, date, and time of entry. When establishing a new sexual partner participant, the steps to obtain a unique sexual partner participant identification (PTID) number are outlined below:

- Immediately after obtaining informed consent and prior to accessing REDCap, site staff assigns the next available sequential number on the Sexual Partner PTID Assignment Log.
- Site staff completes the log with sexual partner's participant's full name, the main participant's PTID, initials of staff completing the log, date, and time of entry.
- Once the Sexual Partner PTID Assignment Log is completed, site staff will activate the pre-populated Sexual Partner PTID by choosing the corresponding PTID "Establish PTID" eCRF in the MATRIX-003 Sexual Partner REDCap database. The Sexual Partner Demographics CRF will capture the main participant's PTID, linking the partners within the two databases.

12.4.2 Study Visit Timing

12.4.2.1 Screening and Enrollment

The initial screening visit is defined as the day the participant provided written informed consent to be screened for the study. The Enrollment Visit should be scheduled to take place within 45 days of the initial Screening Visit date. The date the participant is enrolled/randomized is considered Study Day 0.

12.4.2.2 Screening Attempts (Re-Screens)

If a participant's first screening attempt is unsuccessful, they may re-screen once if they choose (depending on the reason for the unsuccessful first attempt). If a participant re-screens, a new PTID is assigned. The site staff will indicate on the "Establish PTID" form that this is a rescreen attempt and indicate the original PTID number associated with the initial screening attempt.

12.4.2.3 Follow-up Visits

For each MATRIX-003 follow-up visit, the visit type, visit code, and target visit day are listed in Table 12-2. Target days and windows are listed in days, with the day of enrollment/randomization as study Day 0.

12.4.2.4 Target Days and Visit Windows

Whenever possible, visits should be completed on the target day. If it is not possible to complete the visit on the target day, the visit should be completed within the visit window as detailed in Study Procedures SSP section (5.5.1). The MATRIX CTH will provide sites with a Participant Visit Calendar Tool that may be used to generate individual participant follow-up visit calendars. The spreadsheet requires that the participant's Enrollment (i.e., randomization) date be entered. Once the enrollment date is entered, the target date and visit window for each required follow-up visit through Visit 5 will appear. The window for Visit 6 is then 7 to 21 days past Visit 5. The timing of Visits 7 through 9 is dependent on the date of Visit 6. Once the actual Visit 6 date is entered into the Tool, the target dates and visit window ranges for Visits 7, 8 and 9 will populate. The calendar can be printed and added to the participant's study chart/folder.

12.4.2.5 Split Visits

The preference is to complete all follow-up evaluations on the same day. In the event that a participant must split a visit, all procedures must be completed within the window period to be considered complete. If the entire visit is completed within the visit window, the first day that a study procedure was completed will be considered the Visit Date. If all visit procedures are not completed within the visit window, a protocol deviation should be submitted.

12.4.2.6 Missed Visits

In cases where a participant is not able to complete a required follow-up visit, the visit is considered "missed." For example, an enrolled participant is not contacted for V3 and the window period for V4 has started. In this case, the missed V3 is documented by completing the PRN Missed Visit CRF.. While this is a Protocol Deviation, the protocol deviation CRF will not need to be completed. The Missed Visit CRF will capture the deviation.

12.4.2.7 Interim Visits

An interim visit is a contact with a study participant that meets one of the following criteria:

Additional study procedures and/or data collection are conducted outside of what is specified in the protocol for a required study visit. For example, a participant calls to report an AE and requires an assessment. The phone contact should be entered on the site's contact log and the participant may be scheduled for an Interim Visit. All interim contacts with the participant should be documented in a chart note. Interim Visits are repeatable events, which will be automatically numbered within REDCap.

12.4.3 Visit Folders and Visit Codes

The eCRFs in the study database are set up within pre-defined study visits on the study record dashboard, so the visit name and visit code will automatically be assigned (and do not need to be entered for required study visits). Table 12-2 below lists the visit codes assigned to each study visit.

Table 12-2: MATRIX-003 Visit Code Assignments for all Study Visits

Visit	Visit Code
Screening (V1)	1.0
Stage 1: Enrollment/Day 0 (V2)	2.0
Stage 1: Day 7 Phone Visit (V3)	3.0
Stage 1: Day 14 Clinic Visit (V4)	4.0
Stage 1: Day 28 Clinic Visit (V5)	5.0
(7-21 days of no IVR use between Stage 1 and Stage 2)	
Stage 2: Day 0 Clinic Visit (V6)	6.0
Stage 2: Day 7 Phone Visit (V7)	7.0
Stage 2: Day 14 Clinic Visit (V8)	8.0
Stage 2: Day 28 Clinic Visit/IDI (V9)	9.0

12.4.3.1 Visit Codes for Split Visits

See Section 12.4.2.5 for a definition of split visits. When split visits occur, the CRFs completed for the visit are all assigned the same visit code, even though the dates may differ between some of the CRFs. For example, a participant returns for Visit 6.0 on 20-JAN-2024 and completes all required visit evaluations except pregnancy testing. The participant returns on 21-JAN-2024 (still within the visit window) and provides a urine sample for pregnancy testing. All CRFs dated 20-JAN-2024 and 21-JAN-2024 are assigned the same visit code of "6.0" and are housed within the Visit 6.0 folder in the study database.

12.4.4 Form Supply

PDFs of the current MATRIX-003 CRFs can be found on the MATRIX-003 webpage under Study Documents (<https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents>).

The PDF files posted on the webpage represent the complete set of current study CRFs and may be used by site staff for local IRB/IEC/DRA submissions as needed, as well as for printing for a participant visit (i.e. in the event REDCap is not available).

12.4.5 CRF Completion Schedule

The MATRIX-003 REDCap database includes the electronic data forms for the study, including general and socio-behavioral (SBR) forms. A complete table of contents published along with the CRF PDFs (on the matrix4 prevention website linked above in section 12.4.4) lists the forms that are required to be completed at each study visit, as well as the forms that are completed on an "as needed" basis. The website also

includes the Socio-behavioral CRFs (see SBR SSP section 11) that are managed by the D2D team and are required for completion at the relevant linked visits.

12.4.6 Completing Interviewer-Administered Forms

In order to standardize interviewer-administered data collection from site to site and to maximize quality, it is critical that participant interviews be conducted with a non-biased, non-judgmental approach. Study staff should help a participant feel comfortable sharing personal information and opinions while asking the study questions in a consistent manner from participant to participant.

Site staff are encouraged to use direct data entry when administering the interviewer-administered forms (i.e., Demographics), to the extent possible, so that the eCRFs serve as the source documents. Skip patterns are documented in the CRF Completion Guidelines (CCG) document, which site staff should reference when administering the forms. The CCG will be posted on the MATRIX-003 webpage under Study Documents (<https://www.matrix4prevention.org/activity-hubs/clinical-trials/matrix-003/matrix-003-study-documents>) along with the complete set of study CRFs. The skip patterns are also programmed into the data checks within the study database. System queries will be generated in real-time, as data is saved within the database, if required items are missed or an entered value is out of range. This real-time feedback will allow the interviewer to clarify participant responses and update/correct participant self-reported data during the participant interview, yielding accurate, consistent, and complete study data. Site staff who conduct the participant interviews and complete the interviewer-administered behavioral and product adherence forms are encouraged to practice conducting the interviews, and to familiarize themselves with the eCRF questions, skip patterns, and system queries prior to conducting actual participant interviews.

12.4.7 Site Review (Quality Control) of CRFs

Each site must perform QC review steps, especially for paper CRFs (if used) prior to their data entry into the study database. While paper CRFs are being reviewed, it is important that they are stored and tracked systematically.

Below are specific review guidelines that should be followed for these QC review steps.

MATRIX-003 QC Review Step #1 procedures (completed during visit)

- Review visit checklist to ensure all required procedures were completed.
- Review eligibility checklists/worksheets to ensure completeness and verify participant eligibility.
- Review completed CRFs based on participant responses to ensure completeness.
- Ensure the PTID is correct, is recorded correctly on all paper source documents (including paper CRFs, if used) and is the same on the paper source documents and the eCRFs for a given participant.
- Ensure that no participant identifiers other than the PTID are present on paper source documents, with the exception of the signed informed consent form and locator information.
- Ensure that the assigned visit code is correct and consistent between the paper source documents, including paper CRFs (if used), the eCRFs, the LDMS Specimen Tracking Sheet, and LDMS for a given participant visit.

Additional QC Review Step #2 procedures for Screening and Enrollment Visit documents:

- Review all CRFs for completeness. Refer to the CCG for guidance as needed.
- Ensure that all eCRFs used to document lab test results have the correct Collection Dates entered. If any lab tests were repeated, update the appropriate eCRF(s) to reflect the repeat test result(s).
- Review the Specimen Storage eCRF and make sure they match information documented on the visit checklist and Enrollment Visit LDMS Specimen Tracking Sheet (or local lab requisition sheet).
- If a participant screens but does not enroll in the study, make sure the Participant Disposition eCRF is completed and entered into the study database, along with all other required Screening forms as applicable. Demographics are required for all participants who have signed the ICF. Other eCRFs that were completed as part of the failed screening attempt may remain in the study database but will not be QC'd.

Additional QC Review Step #2 procedures for follow-up visit documents:

The same approach should be followed for all follow-up visits.

QC #2 procedures for paper CRFs (if used) – all visits:

- This QC review step should occur before data from the forms are entered into the study database. The goal is to correct data inconsistencies/errors prior to entering data into the study database, so that data is accurate, complete, and available at the time of data entry, thus minimizing the likelihood of data queries.
- Make sure a response has been recorded for each item, as required. Make sure skip patterns have been followed correctly, per instructions in the CCG document.
- If a response box with an "other", "specify", or "describe" line is present, ensure text is present on this line.
- Make sure text responses are clearly recorded.
- For paper CRFs that are not source documents, make sure the data recorded on the paper CRFs matches or is consistent with the source documents.

QC #2 procedures for Electronic CRFs (eCRF)

When data is entered into the study database and an eCRF is saved, system queries are automatically generated in response to inconsistent or incomplete data. Unlike the paper CRFs, which require manual review, eCRFs have the advantage of having the study database itself provide a real-time QC review to ensure data completeness and consistency. In addition, the database design and system queries ensure skip patterns are followed, per instructions in the CCG. Staff should review and verify data for eCRFs that are source (i.e., the data is directly entered into the study database, rather than entered based on a separate paper CRF or other paper source document) prior to marking the form status as "complete." REDCap eCRFs that are completed based on other source documents (e.g., paper CRFs, short message service [SMS] data, or lab reports) should be reviewed to ensure that the data entered matches or is consistent with the source documents.

12.5 Form-Specific Completion Instructions

Detailed form completion instructions for each form are provided in the CCG document. The instructions document skip patterns and include guidance on completion of eCRFs in the study database. Some items on forms are straightforward and do not require specific instructions. Therefore, you will not see all form items listed in the CCG, but rather only those items needing detailed explanation.