Section 11. Data Collection

11   Introduction

The purpose of this document is to provide site staff with the information they need to successfully complete and submit MTN-042 Case Report Forms. For questions about this section or about general data collection policies, procedures, or materials, please contact the SCHARP Clinical Data Manager for the study as listed below.

The SDMC (Statistical and Data Management Center) for this study is SCHARP (the Statistical Center for HIV/AIDS Research and Prevention). SCHARP is located in Seattle, USA, and is in the US Pacific Time (PT) time zone. The SCHARP MTN-042 team members, along with their job role and e-mail address, are listed below.

Job Role	Name	Email Address
Protocol Statistician	Barbra Richardson	barbrar@uw.edu
Protocol Epidemiologist	Jennifer Balkus	jbalkus@uw.edu
Statistical Research Associate	Danny Szydlo	dszydlo@scharp.org
Lead Clinical Data Manager	Tanya Harrell	tharrell@scharp.org
Clinical Programmer	Radhika Etikala	retikala@scharp.org
Clinical Safety Associate	Ning Jiang	njiang2@scharp.org
Lab Data Coordinator	Stacy Russ	sruss@scharp.org

11.1 Medidata Rave Overview

Medidata Rave is the data management system used by SCHARP to receive and manage study data collected at study sites. Each site completes study electronic case report forms (eCRFs) by entering data into the Medidata Rave 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), or entered into the study database based on other non-CRF source documents (e.g., lab reports, testing logs, chart notes, etc.).

The MTN-042 study database in Medidata Rave may be accessed at www.imedidata.com.

When using Medidata Rave, the internet browser chosen and its connectivity quality will be the most critical factors affecting functionality, as Medidata is accessed via a URL using a web browser. Users using outdated browsers will see a new warning banner on the log-in page of iMedidata. This warning will inform them that their browser does not support security features that are being implemented in future iMedidata releases and to upgrade their browser. Users will see this warning banner if they use any of the following browsers:

- Internet Explorer - Versions older than 8.0
- Chrome - Versions older than 30.0
- Firefox - Versions older than 24.0
- Safari - Versions older than 7.0
- Opera - Versions older than 17.0.

Each site's Data Management SOP designates the site staff members responsible for entering data into the study database. SCHARP grants designated site staff access with specific user permissions to the study database. They are required to complete eLearning modules in Medidata, as assigned by SCHARP, before access is granted and data can be entered into the study database. For more detailed information, see the iMedidata Access Guide, posted on the MTN-042 Atlas webpage: https://atlas.scharp.org/cpas/project/MTN/042/begin.view

Detailed guidance on data collection, entry, navigation and general use of Medidata Rave is provided in the Medidata Rave Electronic Data Capture (EDC) Training Manual, which is posted on the MTN-042 Atlas web page: https://atlas.scharp.org/cpas/project/MTN/042/begin.view

Site staff should contact the study Clinical Data Manager with any questions related to study data collection and management. A representative from Medidata Solutions may be contacted (see contact information below) any time a site has technical questions or problems related to access or use of the Medidata Rave software.

For service in English	
Toll-free	**Direct number**
1-866-MEDIDATA (633-4328)	1-973-659-6780
Toll-free fax	**Direct fax**
1-877-743-2350	1-973-954-5621
Email	
helpdesk@mdsol.com	
Hours	
24 hours a day, 7 days a week	

11.2 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 Medidata Rave (e.g., denoting incomplete or inconsistent data).

- Review may be required for certain forms and/or fields by the SCHARP Clinical Data Manager and/or Clinical Safety Associate, and manual data queries may be placed.

- Review may be required for certain forms and/or fields by the site monitor (i.e., PPD), and data queries may be placed.

- MedDRA coding will be required for AE Log CRFs, and coding queries may be placed.

- WHO coding will be required for the Concomitant Medication Log CRF and coding queries may be placed.

- AE-EAE reconciliation will occur and inconsistency queries may be placed.

- QCs are listed in the Medidata Rave Task Summary on the study home page of designated site users. Designated site staff members are responsible for routinely checking the Task Summary and correcting/updating study data to resolve any outstanding queries.

- When site staff correct/update study data and/or enter a query response to address a manual or coding query, SCHARP staff review the updated data and/or response, and resolve the query or re-query, as needed.

- When site staff correct/update study data and/or enter a query response to address a monitoring query, the site monitor (i.e., PPD) reviews the updated data and/or response, and resolves the query or re-queries as needed.

- In the rare event that a site utilizes paper CRFs as source documents, any changes to the paper CRFs **must** be entered into the Medidata Rave study database.

11.3   Electronic Signatures by Investigators

Each site investigator or designee is expected to complete a single sign-off of a participant's study data (one sign-off for each participant at his/her site) once the participant terminates from the study and site staff have resolved all data queries for the given participant. SCHARP will inform site investigators when investigator sign-off of participant data should be completed at the end of the study. By completing this participant-level sign-off in the Medidata Rave study database, the investigator or designee attests that the data has been reviewed and is deemed to be accurate. iMedidata users will use their login credentials as their electronic signature (see Figure 1 below). Please refer to the "Electronic Signature" section of the Medidata Rave Electronic Data Capture (EDC) Training Manual and/or the Investigator e-Learning module for specific instructions.

Figure 11-1: Example of Investigator of Record or Designee Sign-off Pop-Up Window

11.4   CRF Completion

11.4.1   General Guidelines

- To the extent possible, site staff should utilize direct data entry into the Medidata Rave 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, such as behavioral and product use data.

- 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 are encouraged to enter study data into the Medidata Rave study database based on the site-specific source document (in this case, the local lab results report).

- Site staff are encouraged to avoid paper CRF completion, as it represents an additional, intermediate step of data management and 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 completing an eCRF, refer to the current version of the MTN-042 CRF Completion Guidelines (CCGs) document, posted on ATLAS, for detailed instructions on data collection pertaining to the given form and fields on that form.

- Complete eCRFs as soon as possible once the data is available and has undergone internal QC review, as applicable. 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.

11.4.2   Participant Identifier and Participant Type

- For both mothers and infants, the Participant Identifier and Participant Type CRFs will be the first two CRFs completed.
- The Participant Identifier CRF is completed to generate a Participant Identifier (see section 11.5.1). This should be completed for mothers and infants at the mother's Screening visit after consent is obtained. If infant consent is not obtained at the mother's Screening visit, it should be obtained at the mother's Enrollment visit and the infant's Participant Identifier form completed at that time.
- The Participant Type CRF is completed to indicate if the participant is a mother or an infant and should be completed after the Participant Identifier CRF is completed. If the participant is a mother, the Screening, Enrollment and Ongoing Logs folders will populate upon completion of the Participant Type CRF. If the participant is an infant, the infant follow-up visit folders will populate upon completion of the Participant Type CRF.

11.4.3   Mothers: Screening and Enrollment/Randomization

- For mothers, data entry into the study database begins at the Screening Visit. Once a participant is determined to be eligible, enrolls, or fails a screening attempt, study eligibility data should be entered into the study database as follows:

- <u>For participants who screen out of MTN-042:</u> data entry is required for the Participant Type, Inclusion/Exclusion Criteria, and Informed Consent eCRFs. Other eCRFs that were completed with data collected during the failed screening attempt may remain in the study database and will not undergo QC review.

- <u>For participants who enroll in MTN-042:</u> data entry is required for the Participant Type, Inclusion/Exclusion Criteria, and Informed Consent eCRF, along with all required Screening and Enrollment Visit CRFs. All eCRFs will undergo QC review.

Randomization: Participants will be randomized to study product arm (Dapivirine Vaginal Ring or Truvada Oral Tablet) and to In Depth Interviews (IDI). Randomization to a study product arm will be

done through Medidata. Randomization to IDI group will be done outside of the Medidata Rave database. For more information regarding randomization to IDI group, please refer to SSP Section 14. The following steps outline the study arm randomization process for clinic staff:

1. Complete the **Inclusion/Exclusion Criteria CRF** with all responses indicating that the participant is eligible for study participation.

2. Navigate to the Enrollment folder and complete the **Pregnancy Assessment CRF**.

    i. For cohort 1, the response to "Estimated gestational age – weeks" must indicate that the participant is between 36 0/7 weeks and 37 6/7 weeks gestational age.

    ii. For cohort 2, the response to "Estimated gestational age – weeks" must indicate that the participant is between 30 0/7 weeks and 35 6/7 weeks gestational age.

    iii. For cohort 3, the response to "Estimated gestational age – weeks" must indicate that the participant is between 20 0/7 weeks and 29 6/7 weeks gestational age.

    iv. For cohort 4, the response to "Estimated gestational age – weeks" must indicate that the participant is between 12 0/7 weeks and 19 6/7 weeks gestational age.

3. Complete the **Randomization CRF**. To randomize a study participant, mark the "Yes" response box (see Figure 2) for the question "Is the participant ready to be randomized?" Once this response is saved, the database (via the Medidata Balance module) will assign the participant to a study arm and the Randomization Date and Time will appear automatically on the Randomization eCRF.

Note: If a CRS clinic staff attempts to randomize a participant via the Randomization CRF without having indicated that the participant is eligible on the Inclusion/Exclusion Criteria CRF or with a gestational age on the Pregnancy Assessment CRF that is outside of the allowable window for the applicable cohort, Medidata Rave will not allow the participant to be randomized, and an error message will appear.

Figure 11-2: Participant randomization via the Randomization eCRF

4. A participant is considered officially enrolled in the study once the Randomization CRF is completed and saved, as evidenced by the appearance of a Randomization Date and Time on the Randomization eCRF.

    The product arm will be auto-populated on the Enrollment eCRF in the Enrollment Visit folder (see Figure 3). Upon completion of the Randomization eCRF, the clinic staff will navigate to the Enrollment eCRF to view the participant's randomized arm and complete the MTN-042 Prescription.

Figure 11-3: Participant randomization via the Enrollment eCRF

11.4.4 Mothers: Follow-up Visits

- The Follow-up Visit Y/N - Pre-PO CRF will be auto-populated in every pre-pregnancy outcome follow-up visit (V3 – V13). The only field is "Did the participant complete this visit?"

- Select "Yes" if the participant completed this visit. Required forms will be added to the visit folder, and the next scheduled follow-up visit folder will be added to the participant's casebook.
- Select "No – Missed visit" if the participant missed the visit, but she has not yet had her pregnancy outcome. The Missed Visit CRF will be added to the visit folder and the next scheduled follow-up visit folder will be added to the participant's casebook.
- Select "No – Pregnancy outcome" if the participant had her pregnancy outcome before this visit was conducted. The V101 – PPO Visit folder will be added to the participant's casebook.

11.4.5 Infants: Data Entry

Infant data entry begins when infant consent is obtained, ideally at the mother's Screening or Enrollment visit.

11.4.6 Infants: Enrollment

- An infant is considered enrolled in MTN-042 if they have consent provided by a parent and is born alive. If infant consent was obtained at the mother's Screening or Enrollment visit, the infant enrollment date is equal to the infant's date of birth. If infant consent is obtained after birth, the infant enrollment date is equal to the date of infant consent.

- For infants who do not enroll in MTN-042: data entry is required for the Participant Type, Infant Inclusion Exclusion, and Informed Consent eCRFs.

11.4.7 Site Data Management SOP

As a condition for study activation, each study site must have a site or study-specific SOP for Data Management. A template Data Management SOP is available on the MTN-042 study webpage. This SOP should be reviewed and followed in combination with the information contained in the study protocol, this SSP Manual, and the site's Clinical Quality Management Plan (CQMP).

The Data Management SOP outlines site staff responsibilities and contains information on several data topics, including:

- Participant ID (PTID) assignment

- Linking Mother PTIDs with Infant PTIDs

- Participant study file organization

- Participant confidentiality

- Site data quality control (QC) processes

- Timing of data entry into the study database

- Data storage

- Data security

- Contingency plans in case of interrupted access to the study database.

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

11.5   Study-specific Data Collection Information

11.5.1   Participant Identification Numbers (PTIDs)

As described in each site's Data Management SOP, each mother who provides written informed consent to be screened in MTN-042, and each infant who is born alive, has consent provided by a parent, and attends at least one in-clinic study visit, will be assigned an MTN-042 PTID. To do this, site staff will generate in Medidata Rave a participant number (called "Subject ID" in Medidata Rave) within the electronic study and site folder; this number will serve as the participant's PTID. Refer to the "Creating Subjects" section of the Medidata Rave Electronic Data Capture (EDC) Training Manual and the CCG for specific instructions.

Each PTID is unique. It will be assigned to a single participant only at a given site, and not assigned to any other participant at any site or in any other MTN-042 cohort.

SCHARP will provide sites with a PTID-Name Linkage Log and site staff will maintain this document, which will be used to link a participant's name with her assigned PTID, her infant's assigned PTID and her infant's name. For study purposes, the act of MTN-042 PTID assignment is defined as completion of an entry on the MTN-042 PTID-Name Linkage Log for a given participant. The PTID-name link logs are essential documents, and site staff should ensure that each PTID on the link log is assigned to one participant name only. No PTID or name should appear on the log twice, and no PTID or name should appear on the log without a corresponding name or PTID, respectively.

The MTN-042 PTIDs are nine digits and formatted as "XXXYYYYYZ". The PTID consists of three parts: the site number (XXX), the participant number (YYYYY), and a numerical check digit (Z). The check digit (Z) is a number generated by SCHARP within the participant number and helps ensure that the correct PTID is recorded/entered.

11.5.2   Study Visit Timing

Mothers 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 will be scheduled to take place within 35 days of the initial Screening Visit. The date the participant is enrolled/randomized is Study Day 0 for the participant. SCHARP will provide sites with a visit window calendar tool in Microsoft Excel that can be used to calculate the allowable window for study enrollment based on the participant's screening date (i.e., date informed consent provided for the current screening attempt) and gestational age. The tool will be posted online at: https://mtnstopshiv.org/research/studies/MTN-042/MTN-042-study-implementation-materials

Screening Attempts (Re-screens)

If a participant's first screening attempt is unsuccessful, she may re-screen once if she chooses and if she will still fall within the appropriate GA range for enrollment. If she does re-screen, all screening procedures must be repeated with the exception of PTID assignment. Once a PTID is assigned to a participant that PTID is used for the re-screening procedures and forms completed for that participant (do not assign a new PTID).

If a participant re-screens, a new screening folder should be added to the participant's casebook by selecting "Mark if additional Screening folder is needed to document an additional screening" on the Inclusion/Exclusion Criteria CRF in the first screening folder. Do not update previously completed eCRFs (from the original, failed screening attempt). Data from the second screening attempt should be captured on the forms in the second Screening folder. If a participant enrolls, the Inclusion/Exclusion Criteria eCRF completed during the second screening attempt should reflect the participant's final eligibility status and enrollment into the study.

Follow-Up Visits

For each MTN-042 follow-up visit, the visit type, visit code, target visit day, and visit window are listed

in Tables 11-1, and 11-2. Target days and windows are listed in days, with the day of enrollment/randomization as study day 0.

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.

SCHARP will provide sites with a spreadsheet tool that may be used to generate individual participant follow-up visit calendars. For mothers, the pre-pregnancy outcome visit schedule will be determined by her gestational age at enrollment and the post-pregnancy outcome visit schedule will be based on the pregnancy outcome date. The spreadsheet contains multiple tabs corresponding to the different allowable gestational ages at enrollment.

For mothers, the spreadsheet requires that the participant's Enrollment (i.e., randomization) date be entered on the tab corresponding with the participant's gestational age at enrollment. Once the enrollment date is entered, the target day and visit window will appear for each required follow-up visit up prior to the pregnancy outcome.

A separate tab is used to generate the post pregnancy outcome visit schedule for mothers and infants. After the pregnancy outcome occurs, the spreadsheet requires that the pregnancy outcome date be entered. Once the pregnancy outcome date is entered, the target day and visit window will appear for each mother and infant post-pregnancy outcome follow-up visit.

The calendars can be printed, added to the participant's study notebook, and updated as needed.

Split Visits

Whenever possible, all required follow-up visit evaluations should be completed on the same day. In those cases where this is not possible, the participant may come back and complete the remaining evaluations on another day, as long as that day is within the visit window. The Enrollment Visit may not be split. (Refer to the Study Procedures section of this manual for more information regarding visit procedures and timing). For example, a participant comes in on her V4.0 - Week 2 2-week visit target day and completes most of the required evaluations. She comes back the next day and completes the remaining required procedures. While not ideal, this is allowed as needed, and is referred to as a "split" visit; meaning, the participant completed all required visit evaluations on two separate days, both days being in the visit window.

Note that for split visits, the "Visit Date" on the Follow-up Visit Summary form within the applicable visit folder is the date of the first part of the split visit. See Section 11.3.3 for more information on assigning visit codes to split visits.

Table 11-1: Visit Timing Requirements for Mothers in Cohort 2

Visit	Target Day	Window Opens	Window Closes
Visit 1 - Screening	N/A	N/A	
Visit 2 - Day 0 Enrollment	0	Up to 35 days after screening informed consent date	
Visit 3 - Week 1 Phone Contact	7	6 days prior to target	2 days after target
Visit 4 - Week 2 2w Visit	14	4 days prior to target	4 days after target
Visit 5 - Week 3 Phone Contact	21	2 days prior to target	2 days after target

Visit	Target Day	Window Opens	Window Closes
Visit 6 - Week 4 4w Visit	28	4 days prior to target	4 days after target
Visit 7 - Week 5 Phone Contact	35	2 days prior to target	2 days after target
Visit 8 - Week 6 Bi-weekly Visit	42	4 days prior to target	4 days after target
Visit 9 - Week 7 Phone Contact	49	2 days prior to target	2 days after target
Visit 10 - Week 8 Bi-weekly Visit	56	4 days prior to target	4 days after target
Visit 11 - Week 9 Phone Contact	63	2 days prior to target	2 days after target
Visit 12 - Week 10 Bi-weekly Visit	70	4 days prior to target	4 days after target
Visit 13 - Week 11 Phone Contact	77	2 days prior to target	2 days after target
Visit 101 - PPO Visit	as soon after the PO as possible	Pregnancy Outcome	14 days after target
Visit 102 - 1-Week PPO Phone Contact*	7 days after PO	6 days prior to target	7 days after target
Visit 103 - 6-Week PPO Visit/SEV	42 days after PO	13 days prior to target	13 days after target

*The 1-Week PPO Phone Contact may be skipped if the PPO Visit occurs within the visit window for this phone contact

Table 11-2: Visit Timing Requirements for Infants

Visit	Target Day	Window Opens	Window Closes
V201 - PPO Visit	as soon after the PO as possible	Pregnancy Outcome	14 days after target
V202 - 1-Week PPO Phone Contact	7 days after PO	6 days prior to target	7 days after target
V203 - 6-Week PPO Visit	42 days after PO	13 days prior to target	13 days after target
V204 - 6-Month PPO Visit	183 days after PO	28 days prior to target	28 days after target
V205 - 12-Month PPO Visit	365 days after PO	28 days prior to target	28 days after target

*The 1-Week PPO Phone Contact may be skipped if the PPO Visit occurs within the visit window for this phone contact

Missed Visits

In those cases where a participant is not able to complete any part of a required follow-up visit within the visit window, the visit is considered "missed". For example, an enrolled participant does not report to the clinic (nor complete any phone contacts) until 25 days after enrollment. Per Table 11-1 above, Visits 3, 4, and 5 have been missed. The missed visits are documented by completion of a Missed Visit CRF for each missed visit.

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, an interim visit may occur via a phone contact if the participant reports a new AE. Required follow-up visit procedures are not done, either because the required follow-up visit has already been completed, the participant is in between visit windows, or it is too early in the visit window to complete the required visit.

- Required study visit procedures are conducted outside the visit window, either to make up certain procedures from a missed visit, or to conduct an Early Termination Visit procedures.

All interim visits/contacts with the participant should be documented in a chart note. Additionally, if the interim contact results in at least one newly-completed eCRF, the interim visit is assigned an interim visit code (visit number ending in something other than ".0"). All phone contacts that meet interim visit criteria as specified above are also assigned interim visit codes. See section 11.3.3 for information on how to assign visit codes to interim visits.

For MTN-042, an Interim Visit Summary CRF is completed for interim visits/contacts as needed.

The following are some examples of interim visits:

1. A participant completes all required evaluations for her on the V102 – 1 week PPO phone contact target day. She then returns to the clinic 4 days later to report a Social Impact.

   Why is this an interim visit? The participant has already completed all Visit 102 procedures, and it is too early (and not in the visit window) for Visit 103 to be conducted. This is an interim visit, conducted between Visits 102 and 103, and is assigned an interim visit code as new CRFs will be completed.

2. A participant completes her Visit 3 – week 1 phone contact as scheduled. Her Visit 4 – week 2 2-week visit window opens on July 13, and she is scheduled to complete Visit 4 on July 14. The participant reports to the clinic unexpectedly on July 13 to report new genital AE symptoms.

   Why is this an interim visit? The participant is in the Visit 4 visit window, but site staff decide not to conduct Visit 4 visit procedures for this participant on July 13th (e.g., the participant already has Visit 4 scheduled for the next day (on the target date) and has a history of reliably showing up for scheduled study visits, and/or there is limited staff time availability on July 13). An interim visit code is assigned as new CRFs will be completed (Interim Visit Summary, AE Log, others as needed).

3. A participant completes her Visit 3 – week 1 phone contact as scheduled. She gives birth two days later on July 13. The participant calls and completes her Visit 102 – 1-week PPO Phone Contact on July 19. She and her baby return to the clinic on July 31; the mother's PO data is collected, and the infant attends his first visit.

   Why is this an interim visit? The mother has missed Visit 101 and already completed all Visit 102 procedures, and it is too early (and not in the visit window) for Visit 103 to be conducted. An interim visit is conducted to capture information about her pregnancy outcome and an interim visit code is assigned as new CRFs will be completed (Interim Visit Summary, Pregnancy Outcome, others as needed).

   The infant has missed Visit 201 and Visit 202.This is an interim visit, conducted between Visits 202 and 203, and is assigned an interim visit code as new CRFs will be completed (Infant Interim Visit Summary, Infant Demographics, Physical Exam, Infant Specimen Storage, Infant Vital Signs, others as needed).

4. A participant completes all required evaluations for Visit 101 – PPO visit on September 20. She returns to the site on October 8 and informs the clinic that she wishes to withdraw from the study. As such, Visit 103 – 6 week PPO visit procedures are conducted as part of the October 8 interim visit.

Why is this an interim visit? On October 8, the participant wishes to withdraw from the study and an early termination visit is conducted. As Visit 101 has been completed, the early termination visit should be assigned an interim visit code. CRFs required at the Visit 103 – 6 week PPO visit are completed.

5. A participant goes into labor, removes her ring, and alerts site staff. Site staff visit the delivery facility, collect the participant's used ring, and store it at the clinical research site. The participant returns to the clinical research site a week later for her Visit 101 – PPO visit.

   Why is this an interim visit? The used vaginal ring was collected and stored outside of the regular visit schedule. An interim visit code is assigned as new CRFs will be completed (Interim Visit Summary, Ring Insertion and Removal, and Specimen Storage).

6. An infant completes his Visit 203 – 6 week PPO visit on the target day. The next day, the infant's mother calls the clinic to report a new mild symptom.

   Why is this an interim visit? During the phone contact, the participant's mother reported a new infant symptom which will result in completion of a new CRF (AE Log). Since new CRFs are completed (AE Log and Interim Visit Summary), an interim visit code is assigned.

11.5.3 Visit Folders and Visit Codes

The eCRFs in the study database are set up within pre-defined study visit folders, so the visit name and visit code automatically appear (and do not need to be entered for required study visits).

11.5.4 Mother Visit Folders

With the exception of the Baseline Medical History Log CRF and Pharmacy Dispensation Log CRF, all log forms (i.e., Adverse Event Y/N and Log, Non-Enrolled Infant Adverse Event Y/N and Log, Concomitant Medications Y/N and Log, Protocol Deviations Y/N and Log, Social Impact Y/N and Log, and Product Hold Y/N and Log) are housed in the "Ongoing Logs" folder within the study database.

The Product Discontinuation eCRF and Study Termination eCRF are housed within the "Discontinuations" folder; The Study Termination form is completed once for each participant to document study termination and the Product Discontinuation Log CRF is completed once when the study product is discontinued.

The Pharmacy Dispensation log CRF is housed within the "Pharmacy" folder. This form is completed at each visit when study product is dispensed. The Pharmacy folder is viewable and data can be entered by the Pharmacy role only. The CRC role (i.e., site clinic) cannot view the Pharmacy folder.

11.5.5 Infant Visit Folders

All log forms (i.e., Adverse Event Y/N and Log, Concomitant Medications Y/N and Log, and Protocol Deviations Y/N and Log) are housed in the "Ongoing Logs" folder within the study database.

The Study Termination eCRF is housed within the "Infant Discontinuations" folder; The Study Termination form is completed once for each participant to document study termination.

Tables 11-3 and 11-4 below lists the visit codes assigned to each required follow-up visit.

Table 11-3: Mother Cohort 2 Visit Code Assignments for Required Visits

Visit	Visit Code
V1.0 - Screening	1.0
V2.0 - Enrollment	2.0

V3.0 - Week 1 phone contact	3.0
V4.0 - Week 2 2w Visit	4.0
V5.0 - Week 3 Phone Contact	5.0
V6.0 - Week 4 4w Visit	6.0
V7.0 - Week 5 Phone Contact	7.0
V8.0 - Week 6 Bi-weekly Visit	8.0
V9.0 - Week 7 Phone Contact	9.0
V10.0 - Week 8 Bi-weekly Visit	10.0
V11.0 - Week 9 Phone Contact	11.0
V12.0 - Week 10 Bi-weekly Visit	12.0
V13.0 - Week 11 Phone Contact	13.0
V101.0 - PPO Visit	101.0
V102.0 - 1w PPO phone contact	102.0
V103.0 - 6w PPO visit	103.0

Table 11-4: Infant Visit Code Assignments for Required Visits

Visit	Visit Code
V201.0 - PPO Visit	201.0
V202.0 - 1w PPO phone contact	202.0
V203.0 - 6w PPO visit	203.0
V204.0 - 6m PPO visit	204.0
V205.0 - 12m PPO visit	205.0

Visit codes for Split Visits

See Section 11.5.2 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 will differ between some of the CRFs. For example, a participant comes in on her Visit 4 - Week 2 2-week visit target day of 23-NOV-19 and completes all required visit evaluations except vital signs. She returns on 24-NOV-19 (still within the visit window) and her vital signs are collected. All CRFs dated 23-NOV-19 and 24-NOV-19 are assigned the same visit code of "4.0" and are housed within the Visit 4 - Week 2 2-week visit folder in the study database.

Visit codes for Interim Visits

Note that interim visit codes are not used for visits/contacts between the Screening Visit and Enrollment Visit, as these contacts are considered part of the screening process.

For interim visits occurring after the Enrollment Visit and onwards, interim visit codes are assigned using the following guidelines:

- To the left of the decimal point, record the visit code of the most recently required follow-up visit, *even if the visit was missed and/or if the participant is within the next visit's window.*

- To the right of the decimal point:

  - #.01 = the first interim visit after the most recently-required visit,

  - #.02 = the second interim visit after the most recently-required visit,

  - #.03 = the third interim visit after the most recently-required visit, and so on.

The examples below are from section 11.5.2, where interim visits are defined. These examples now have visit code information added to each example.

1. A participant completes all required evaluations for her on the V102 – 1 week PPO phone contact target day. She then returns to the clinic 4 days later to report a Social Impact.

   visit code = 102.01

2. A participant completes her Visit 3 – week 1 phone contact as scheduled. Her Visit 4 – week 2 2-week visit window opens on July 13, and she is scheduled to complete Visit 4 on July 14. The participant reports to the clinic unexpectedly on July 13 to report new genital AE symptoms.

   visit code = 3.01

3. A participant completes her Visit 3 – week 1 phone contact as scheduled. She gives birth two days later on July 13. The participant calls and completes her Visit 102 – 1-week PPO Phone Contact on July 19. She and her baby return to the clinic on July 31; the mother's PO data is collected, and the infant attends his first visit.

   mother's visit code = 102.01

   infant's visit code = 202.01

4. A participant completes all required evaluations for Visit 101 – PPO visit on September 20. She returns to the site on October 8 and informs the clinic that she wishes to withdraw from the study. As such, Visit 103 – 6 week PPO visit procedures are conducted as part of the October 8th interim visit.

   visit code = 101.01

5. A participant goes into labor, removes her ring, and alerts site staff. Site staff visit the delivery facility, collect the participant's used ring, and store it at the clinical research site. The participant returns to the clinical research site a week later for her Visit 101 – PPO visit.

   visit code depends on last completed pre-PO visit.

   > *If last visit was Visit 3.0 – week 1 phone contact, interim visit code = 3.01*

   > *If last visit was Visit 6.0 – week 4 4-week visit, interim visit code = 6.01*

6. An infant completes his Visit 203 – 6 week PPO visit on the target day. The next day, the infant's mother calls the clinic to report a new mild symptom.

   visit code = 203.01

11.5.6 Case Report Form Completion Schedule

The SCHARP-provided forms for this study include all forms that are completed and entered into the study database, as well as the Pelvic Exam Diagrams, which is an optional tool sites may use to source document pelvic exam findings for data entry into the Pelvic Exam eCRF.

Some SCHARP-provided forms are required to be completed at each visit, while other forms are

required only at one visit or only when specifically indicated. The following tables (Tables 11-5 and 11-6) 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 ongoing log forms, discontinuation forms, and pregnancy forms.

Table 11-5: Cohort 2 Mothers Schedule of Forms – CRFs Required to be Completed at Each Visit

Visit	Applies to participants with GA at Enrollment	CRF
n/a		Participant Identifier
Participant		Participant Type
Visit 1 – Screening Visit	30 - 35	Baseline Medical History Y/N, Baseline Medical History Log
		Chemistry Panel
		Demographics
		Hematology
		Inclusion/Exclusion Criteria
		*Complete and submit at Screening Visit only if it is determined the participant will not enroll in MTN-042
		Informed Consent
		Obstetric Abdominal Exam
		Physical Exam
		Pregnancy History
		Screening Date of Visit
		STI Test Results
		Urine Test Results
		Vaginal Practices
		Vital Signs
Visit 2 – Enrollment Visit	30 - 35	Randomization
		Baseline Behavioral Assessement
		Chemistry Panel
		COVID-19 Behavioral Assessment
		Edinburgh Postnatal Depression Scale
		Enrollment
		Pregnancy Assessment
		Hematology
		Obstetric Abdominal Exam
		Pelvic Exam
		Ring Assessment OR Tablet Assessment
		Ring Insertion and Removal OR PrEP Provisions and Returns
		Specimen Storage
		STI Test Results
		Ultrasound Results

		Urine Test Results
		Pelvic Exam Diagrams (non- Medidata Rave)
Visit 3 - Week 1 Phone Contact	30 - 35	Follow-up Visit Y/N – Pre-PO, Follow-up Visit Summary
Visit 4 - Week 2 2-week Visit	30 - 35	Follow-up Visit Y/N – Pre-PO, Follow-up Visit Summary
		Obstetric Abdominal Exam
		Specimen Storage
Visit 5 - Week 3 Phone Contact	30 - 35	Follow-up Visit Y/N – Pre-PO, Follow-up Visit Summary
Visit 6 - Week 4 4-week Visit	30 - 35	Follow-up Visit Y/N – Pre-PO, Follow-up Visit Summary
		Follow-up Behavioral Assessment
		Chemistry Panel
		Hematology
		HIV Test Results
		Obstetric Abdominal Exam
		Physical Exam
		Ring Adherence Y/N OR Tablet Adherence Y/N
		Ring Assessment OR Tablet Assessment
		Ring Insertion and Removal OR PrEP Provisions and Returns
		Social Impact
		Specimen Storage
		Urine Test Results
Visit 7 - Week 5 Phone Contact	31 - 35	Follow-up Visit Y/N – Pre-PO, Follow-up Visit Summary
Visit 8 - Week 6 Bi-weekly Visit	30 - 35	Follow-up Visit Y/N – Pre-PO, Follow-up Visit Summary
		Obstetric Abdominal Exam
		Specimen Storage
Visit 9 - Week 7 Phone Contact	30 - 34	Follow-up Visit Y/N – Pre-PO, Follow-up Visit Summary
Visit 10 - Week 8 Bi-weekly Visit	30 - 33	Follow-up Visit Y/N – Pre-PO, Follow-up Visit Summary
		HIV Test Results
		Obstetric Abdominal Exam
		Ring Assessment OR Tablet Assessment
		Ring Insertion and Removal OR PrEP Provisions and Returns
		Specimen Storage
Visit 11 - Week 9 Phone Contact	30 - 32	Follow-up Visit Y/N – Pre-PO, Follow-up Visit Summary
Visit 12 - Week 10 Bi-weekly Visit	30 - 31	Follow-up Visit Y/N – Pre-PO, Follow-up Visit Summary
		Obstetric Abdominal Exam
		Specimen Storage
Visit 13 - Week 11 Phone Contact	30	Follow-up Visit Y/N – Pre-PO, Follow-up Visit Summary
Visit 101 - PPO Visit	30 - 35	Follow-up Visit Y/N, Follow-up Visit Summary
		Physical Exam

		Pregnancy Outcome
		Ring Adherence Y/N OR Tablet Adherence Y/N
		Ring Insertion and Removal OR PrEP Provisions and Returns
		Specimen Storage
		Vital Signs
Visit 102 - 1-week PPO Phone Contact	30 - 35	Follow-up Visit Y/N, Follow-up Visit Summary
Visit 103 - 6-week PPO Visit	30 - 35	Follow-up Visit Y/N, Follow-up Visit Summary
		Chemistry Panel
		COVID-19 Behavioral Assessment
		Edinburgh Postnatal Depression Scale
		Hematology
		HIV Test Results
		Post-PO Behavioral Assessment
		Social Benefits
		Social Impacts
		Specimen Storage
		STI Test Results
		Urine Test Results
As needed	30 - 35	Additional Study Procedures
		Chemistry Panel
		COVID-19 Behavioral Assessment
		Edinburgh Postnatal Depression Scale
		Follow-up Behavioral Assessment
		Hematology
		HIV Confirmatory Results
		HIV Test Results
		IDI Tracking
		Interim Visit Summary
		Missed Visit
		Obstetric Abdominal Exam
		Pelvic Exam
		Physical Exam
		Post-PO Behavioral Assessment
		PreP Provision and Return
		Ring Adherence
		Ring Assessment
		Ring Insertion and Removal
		Seroconverter Results
		Social Benefits
		Social Impact
		Specimen Storage

		STI Test Results
		Tablet Adherence
		Tablet Assessment
		Ultrasound Results
		Urine Test Results
		Vaginal Practices
		Vital Signs
		Pelvic Exam Diagrams (non-Medidata Rave)

Ongoing Logs (as needed)	30 - 35	Adverse Event Y/N
		Adverse Event Log
		Non-Enrolled Infant Adverse Event Y/N
		Non-Enrolled Infant Adverse Event Log
		Concomitant Medications Y/N
		Concomitant Medications Log
		Protocol Deviations Y/N
		Protocol Deviations Log
		Product Hold Y/N
		Product Hold Log
		Social Impact Y/N
		Social Impact Log

Discontinuations	30 - 35	Study Termination
		Discontinuation of Study Product

Pharmacy	30 - 35	Pharmacy Dispensation

Congenital Anomaly Report	30 - 35	Congenital Anomaly Review
		EAE Upload
		Photographic Survey and Congenital Anomaly Documentation

Table 11-6: Infants Schedule of Forms – CRFs Required to be Completed at Each Visit

Visit	Form Name
n/a	Participant Identifier
Participant	Participant Type
	Infant Inclusion/Exclusion
	Informed Consent
Visit 201 – PPO Visit	Chemistry Panel (required for Truvada group before LOA#1; required for all after LOA#1)
	Infant Demographics

	Infant Feeding Assessment
	Follow-up Visit Y/N, Infant Follow-up Visit Summary
	Infant Specimen Storage
	Physical Exam
	Infant Vital Signs
Visit 202 – 1-week PPO Phone Contact	Follow-up Visit Y/N, Infant Follow-up Visit Summary
	Infant Feeding Assessment
Visit 203 – 6-week PPO Visit	Chemistry Panel (required for Truvada group before LOA#1; required for all after LOA#1)
	Follow-up Visit Y/N, Infant Follow-up Visit Summary
	Infant Feeding Assessment
	Physical Exam
	Infant Vital Signs
Visit 204 – 6-month PPO Visit	Infant Ages and Stages Assessment
	Chemistry Panel (required for Truvada group before LOA#1; not required after LOA#1)
	Follow-up Visit Y/N, Infant Follow-up Visit Summary
	Infant Feeding Assessment
	Physical Exam
	Infant Vital Signs
Visit 205 – 12-month PPO Visit	Infant Ages and Stages Assessment
	Chemistry Panel (required for Truvada group before LOA#1; not required after LOA#1)
	Follow-up Visit Y/N, Infant Follow-up Visit Summary
	Infant Feeding Assessment
	Physical Exam
	Infant Vital Signs
As needed	Chemistry Panel
	Hematology
	Infant HIV Confirmatory Results
	Infant Additional Study Procedures
	Infant Ages and Stages Assessment
	Infant Feeding Assessment
	Infant Interim Visit Summary

	Infant Specimen Storage
	Missed Visit
	Physical Exam
	Seroconverter Results
	Infant Vital Signs

	Adverse Event Y/N
	Adverse Event Log
Infant Ongoing Logs (as needed)	Concomitant Medications Y/N
	Concomitant Medications Log
	Protocol Deviations Y/N
	Protocol Deviations Log

Infant Discontinuations	Study Termination

	Congenital Anomaly Review
Congenital Anomaly Report	EAE Upload
	Photographic Survey and Congenital Anomaly Documentation

11.5.7 Site Review (Quality Control) of CRFs

As described in the site's Data Management SOP [and referenced in the site's Clinical Quality Management Plan, (CQMP)], each site must perform Quality Control (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.

MTN-042 QC Review Step #1 (completed during visit)

- Review visit checklist and pelvic exam checklist (if used) to ensure all required procedures were completed

- For mothers, review eligibility checklists/worksheets to ensure completeness and verify participant eligibility

- Review LDMS Specimen Tracking Sheets to ensure completeness and accuracy

- Review completed CRFs based on participant responses to ensure completeness:

  o Screening Visit: Demographics, Baseline Medical History Log, Concomitant Medications Log

  o Enrollment Visit: Inclusion/Exclusion Criteria, Baseline Medical History Log, Concomitant Medications Log, Ring Insertion and Removal or PrEP Provisions and Returns, Ring Assessment or Tablet Assessment, Edinburgh Postnatal Depression Scale, Vaginal Practices, and Baseline Behavioral Questionnaire (cohorts 2 – 4 only)

- Mother follow-up visits, when present: Adverse Event Log, Non-Enrolled Infant Adverse Event Log, Concomitant Medications Log, Edinburgh Postnatal Depression Scale, Follow-up Behavioral Questionnaire (cohorts 2 – 4 only), Ring Assessment or Tablet Assessment, Ring Adherence or Tablet Adherence (cohorts 2 – 4 only), Social Benefits, Social Impacts
  - Infant follow-up visits, when present: Adverse Event Log, Concomitant Medications Log, Infant Ages and Stages Assessment

MTN-042 QC Review Step #2 (completed after visit)

General QC #2 procedures for all visits:

- Review visit checklist to ensure all required procedures were completed

- 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, including paper CRFs (if used).

- Ensure that the assigned visit code is correct, and is 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 #2 procedures for Screening and Enrollment Visit documents:

- Review the Chemistry Panel, Hematology, Obstetric Abdominal Exam, Ring Insertion and Removal, PrEP Provision and Return, Pelvic Exam, Physical Exam, Vital Signs, Pregnancy Assessment, Pregnancy History, STI Tests, Ultrasounds Results, and Urine Test Results forms, and ensure that medical conditions are recorded appropriately on the Baseline Medical History Log. Refer to the CCG for further guidance.

- Ensure that all eCRFs used to document lab test results have the correct Specimen 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 and the Ring Insertion and Removal (if applicable) eCRFs 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 Inclusion/Exclusion Criteria eCRF is completed and entered into the study database. Other eCRFs that were completed as part of the failed screening attempt may remain in the study database, but will not undergo QC review.

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

- Concomitant Medications Log CRF: if a medication is taken for an AE, select the on the Concomitant Medications Log eCRF, and ensure the AE Log CRF for the AE has "Medication(s)" entered for "Other action(s) taken".

QC #2 for Paper CRFs (if used)

This QC review step should occur before forms are data-entered into the study database. Ideally, this review will happen once all lab results are available, so that all forms for a particular visit can be reviewed for consistency across documents.

The goal, as outlined in the site's Data Management SOP, 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.

QC #2 procedures for <u>paper CRFs</u> - all visits:

- Make sure a response has been recorded for each item, as required. Make sure skip patterns have been followed correctly, per instructions in the CRF Completion Guidelines (CCG) document.

- If a response box with "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 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.

No additional QC #2 review steps are required 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).

Electronic CRFs that are completed based on other source documents (e.g., paper CRFs or lab reports) should be reviewed to ensure that the data entered matches or is consistent with the source documents. The site's Data Management SOP provides additional details, and specifies which staff members will perform this review.

11.6   Form-Specific Completion Instructions

Detailed form completion instructions for each form are provided in the CRF Completion Guidelines (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.

The current version of the MTN-042 CCGs is located on the MTN-042 ATLAS webpage:

https://atlas.scharp.org/cpas/project/MTN/042/begin.view?

11.7   Case Report Forms

SCHARP will post a CRF (pdf) file, representing output from the study database eCRFs, on the following MTN-042 Atlas web page:

https://atlas.scharp.org/cpas/project/MTN/042/begin.view?

The pdf file represents the current and complete set of study CRFs, and may be used by site staff for local IRB submission as needed. Should the Medidata Rave study clinical database become unavailable (i.e., offline) during the study, the Rave CRF pdf should be used to perform paper CRF completion.