Section 18. Bone Mineral Density Substudy

This section describes study-specific procedures for MTN-003B, Bone Mineral Density Substudy of MTN-003. MTN-003B will be conducted at study sites in Harare and Kampala only. Therefore, the Harare and Kampala sites must maintain this section of the Study-Specific Procedures (SSP) Manual in its entirety. All other sites are not required to maintain this section of the manual. For clarity of documentation, however, all sites should maintain a reference copy of Version 1.0 of this page (18-1), dated 7 August 2009, in their manuals.

Note: For clarity of terminology and referencing, throughout this section MTN-003 is referred to as "VOICE" and MTN-003B is referred to by its study number.

Note: MTN 003B will continue after VOICE. The final VOICE SSP should be maintained and referenced as appropriate, even after VOICE is closed.

18.1 Introduction

Please refer to Section 1 of this manual. All information contained in that section applies to MTN-003B.

18.2 Protocol

A complete reference copy of the MTN-003B protocol is provided in Section Appendix 18-1. As of the date of this section, the following document reflects current protocol specifications: protocol Version 2.0, dated Aug, 29, 2011.

To ensure that this manual continues to reflect current protocol specifications in the future:

- Upon receipt of any protocol clarification memos, add a copy of the memo to Section Appendix 18-1.
- Upon receipt of any letters of amendment, add a copy of the letter of amendment to Section Appendix 18-1.
- Upon receipt of any full protocol amendments, replace the contents of Section Appendix 18-1 with the amended protocol.

Further information on the content and required handling of protocol clarification memos, letters of amendment, and full amendments is available in Section 9.2 of the MTN Manual of Operations.

18.3 Documentation Requirements

Please refer to Section 3 of this manual. The general documentation principles, policies, instructions, and guidelines contained in that section also apply to MTN-003B. The remainder of this section provides information related to the specific documentation requirements of MTN-003B.

18.3.1 Essential Documents

Please refer to Section 3.1 of this manual. Sites conducting MTN-003B must establish essential documents files for this study, consistent with the DAIDS policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials*. Section Appendix 18-2 presents a suggested filing structure.

18.3.2 Participant Case History Documentation

Please refer to Section 3.2 of this manual. Guidance provided in that section on the concept of source documentation; use of chart notes, visit checklists, DataFax forms; document organization; and standard operating procedures (SOPs) for source documentation and data management also applies to MTN-003B. It is recommended that each site address source documentation and data management issues relevant to VOICE and MTN-003B in combined SOPs for both studies.

If sites maintain MTN 003B and VOICE files together, they should either be separated once VOICE closes or a memo should be maintained in the VOICE regulatory binder explaining the location of these files.

For VOICE, it is expected that participant case history records will consist of the following source documents:

- Narrative chart notes
- Clinic randomization envelopes and prescriptions documenting participants' random assignments
- Pharmacy randomization envelopes and investigational product dispensing and chain of custody records (maintained in the study site pharmacy)
- Visit checklists and/or other site-specific flowsheets
- Local laboratory testing logs and result reports
- DataFax and Non-DataFax forms provided by the MTN Statistical and Data Management Center (SDMC)
- Other source documents (e.g., site-specific worksheets, non-study medical records)

For MTN-003B, in addition to the source documents listed above, electronic DXA scan data are considered source data and print-outs of DXA scans will serve as source documents.

Each site's SOP for source documentation must specify the use of the above-listed documents as source documents. Although it is the responsibility of each site to determine the most appropriate source document for each required case history element, Section Appendix 18-3 provides a guide that sites may follow for MTN-003B. Section Appendix 18-4 indicates which MTN-003B DataFax and non-DataFax forms may serve as source documents.

18.3.3.1 Study Product Accountability, Chain of Custody and Dispensing Documentation

Please refer to Section 3.3 of this manual. There are no additional study product documentation requirements for MTN-003B.

18.3.4 Record Retention Requirements

Please refer to Section 3.4 of this manual. The requirements specified in that section also apply to MTN-003B. However, since MTN-003B will include an additional year of follow-up, it is expected that those records will need to be maintained for one year past the VOICE record retention requirement.

18.4 Participant Accrual

This section provides information on requirements and procedures for recruiting, screening, and enrolling participants in MTN-003B. Informed consent considerations are provided in Section 18.5.

18.4.1 Study Accrual Plan and Site-Specific Accrual Targets

All VOICE participants randomized to oral study product will be offered enrollment into MTN-003B. Depending on VOICE enrollment at each site, this could equal up to 540 women. Each site will be required to submit the reasons why any eligible VOICE participant did not enroll into MTN-003B with their weekly enrollment numbers submitted to CORE (FHI 360).

For each site, accrual will begin after all applicable approvals are obtained and a site-specific study activation notice is issued by the MTN Coordinating and Operations Center (CORE) at FHI 360. It is expected that accrual for MTN-003B will begin concurrent with accrual for VOICE. Once accrual is initiated, study staff will report the number of participants enrolled in MTN-003B to the CORE (FHI 360) on a weekly basis. Based on this information, the CORE (FHI 360) will distribute a weekly consolidated cross-site accrual report to the Protocol Team. In addition, the MTN SDMC will post reports on their ATLAS portal listing the number of participants enrolled in the study based on data received and entered into the study database. See Section 18.15 for more information on the study reporting plan.

Throughout the study accrual period, the Protocol Team will review accrual and other performance data from each site to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently and to determine when to discontinue accrual at each site. Findings and recommendations from these reviews will be communicated to all sites, and all sites will adjust their accrual efforts accordingly. Similar adjustments may be made after MTN Study Monitoring Committee reviews.

Study staff are responsible for establishing study-specific participant accrual plans and updating these plans and recruitment efforts undertaken if needed to meet site-specific accrual goals. It is recommended that each site establish a combined accrual plan for both VOICE and MTN-003B. See Section 4.1 of this manual for more information on the elements that should be included in site accrual plans.

18.4.2 Assignment of Participant ID Numbers

Participant ID numbers (PTIDs) will not be assigned for MTN-003B. The same PTIDs assigned for VOICE will be used for MTN-003B, including MTN003B follow-up after the VOICE PUEV. For more information on assigning PTIDs for VOICE, please refer to Section 14.3.1 of this manual.

18.4.3 Screening: Definition and Procedures

The term “screening” refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN-003B. The study eligibility criteria are listed in protocol Sections 5.2 and 5.3 and in Figure 18-1.

Figure 18-1
MTN-003B Eligibility Criteria

Inclusion Criteria
• Randomized to oral study product in VOICE within the past 14 days • Able and willing to provide written informed consent for participation in MTN-003B
Exclusion Criteria
• Pregnant at screening and enrollment visit • Has a medical condition known to effect bone (e.g. hyperparathyroidism, bone cancer) or taking any medication known to affect bone (e.g. glucocorticoids, heparin, wafarin, cyclosporine, ~~medroxyprogesterone acetate~~, cancer drugs, and thyroid hormone) • Permanently discontinued from oral study product in VOICE prior to the MTN-003B screening and enrollment visit • At enrollment, any other condition that, in the investigator's opinion, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achievement of the study objectives

Note: Protocol Version 1.0 incorrectly listed medroxyprogesterone acetate as an exclusionary medication; as shown above in strikethrough, protocol Clarification Memo #01 corrected this error. Use of medroxyprogesterone acetate is not exclusionary for MTN-003B.

Protocol Section 7.2 lists the procedures required to be performed at MTN-003B screening and enrollment visits. Among these, the following are screening procedures:

- Informed consent for screening and enrollment
- Urine collection and pregnancy testing (if not already done on the same day for VOICE)
- Eligibility determination

Written informed consent must be obtained before any screening procedures are performed. However, it is expected that study staff will perform pre-screening procedures among enrolled VOICE participants to determine which VOICE participants to recruit for MTN-003B. For VOICE participants who appear presumptively eligible for MTN-003B based on pre-screening, the MTN-003B informed consent process will be conducted and, for consenting participants, eligibility will then be determined.

It is the responsibility of the site Investigator of Record (IoR) and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled in MTN-003B. Each site must establish an SOP that describes how study staff will fulfill this responsibility. This SOP minimally should contain eligibility determination procedures, eligibility verification procedures, and staff responsibilities. Should study staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should contact the VOICE study management team (mtn003mgmt@mtnstopshiv.org).

The Screening and Enrollment Visit Checklist (see Section Appendix 18-6) and the MTN-003B Eligibility case report form (see Section Appendix 18-7) are designed to document the outcome of pre-screening and screening procedures. A Screening and Enrollment Visit Checklist and an MTN-003B Eligibility case report form should be completed for each VOICE participant who is assigned to oral study product — regardless of whether the participant enrolls in MTN-003B.

18.4.4 Definition of Enrollment

Participants will be considered enrolled in MTN-003B after they have provided written informed consent, study staff have determined them to be eligible for the study, and study staff have completed an MTN-003B Eligibility form documenting their enrollment.

18.4.5 Screening and Enrollment Timeframe

Enrollment in MTN-003B may take place on the day of enrollment in VOICE or up to 13 days after the VOICE enrollment date. For example, as shown in Figure 18-2, a potential participant enrolled in VOICE on 8 July 2009 could be enrolled in MTN-003B on any day up to and including 21 July 2009.

Figure 18-2
Sample Screening and Enrollment Time Frame for MTN-003B

JULY 2009						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	2	3	4
5	6	7	8 Randomized in VOICE	9	10	11
12	13	14	15	16	17	18
19	20	21 Last day to enroll in MTN-003B	22	23	24	25

As a second example, consider a potential participant randomized to oral study product in VOICE on 12 November 2009. This participant could be enrolled in MTN-003B on any day up to and including, 25 November 2009.

Measurement of participant height and weight is required at the MTN-003B screening and enrollment visit. If, however, these measurements have been completed and documented for VOICE within 14 days (inclusive) of the MTN-003B screening and enrollment visit, the VOICE measurements may be used for MTN-003B.

18.4.6 Screening and Enrollment Logs

The *DAIDS policy on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* requires study sites to document screening and enrollment activity on screening and enrollment logs. It is recommended that sites combine their VOICE and MTN-003B screening and enrollment logs. A sample combined log is available in the Study Implementation Materials section of the MTN-003B web page.

18.5 Informed Consent

Please refer to Section 5 of this manual. The general principles, policies, instructions, and guidelines contained in that section also apply to MTN-003B.

MTN-003B Protocol Version 1.0 involves a single informed consent process for screening and enrollment in the study. Informed consent must be obtained before performing any MTN-003B procedures. For participants who do not consent, no MTN-003B procedures should be performed.

Once version 2.0 of the protocol and Informed Consent Form (ICF) is approved by all of a site's IRBs/ECs and regulatory authorities, the site will need to reconsent its MTN003B participants to Protocol Version 2.0 before conducting MTN003B post-PUEV visit procedures. Only MTN-003B participants who completed follow-up through the VOICE PUEV will be asked to reconsent under Protocol Version 2.0. MTN-003B participants who withdrew consent, terminated the study prior to the VOICE PUEV, or continued in the study but refused DXA scans will not be asked to reconsent under Protocol Version 2.0.

At each site, the informed consent process for MTN-003B will be conducted according to site SOPs. It is recommended that each site specify its procedures in a combined SOP that addresses informed consent for both VOICE and MTN-003B. For sites wishing to use a comprehension checklist as part of their informed consent process, a sample checklist is provided in Section Appendix 18-5. The checklist is also available as a separate electronic file in the Study Implementation Materials section of the MTN-003B web page.

18.6 Participant Follow-up

This section provides information on requirements and procedures for participant follow-up in MTN-003B.

18.6.1 Follow-up Visit Scheduling

MTN-003B participants will complete a screening and enrollment visit, multiple semi-annual follow-up visits, and possibly an additional final MTN-003B follow-up visit.

Under Protocol Version 1.0, follow-up visits for MTN-003B should be completed semi-annually (approximately every six months) for the duration of VOICE. Additionally, participants will complete MTN-003B procedures at the VOICE PUEV, or at the Early Termination Visit (ETV) for early terminators, if at least 90 days have passed since the last completed semi-annual follow-up visit.

Under Protocol Version 2.0 of MTN-003B, follow-up will continue semi-annually for an additional 12 months beyond the VOICE PUEV. The visit schedule will reset for these additional 12 months. If a participant decides to terminate early, prior to the 12-month post-PUEV visit, she will be asked to complete an MTN-003B Early Termination Visit if at least 30 days have passed since the last completed semi-annual follow-up visit.

The number of MTN-003B follow-up visits that each participant will be expected to complete will depend on her duration of follow-up in VOICE and if she consents to Version 2.0 of the MTN 003B protocol.

- Participants are expected to complete a minimum of 12 months and a maximum of 36 months of follow-up on study product in VOICE, plus 12 months of follow-up off of study product (beyond the VOICE PUEV) under MTN-003B version 2.0. Thus, the total duration of MTN-003B follow-up for a given participant is a minimum of 24 months and a maximum of 48 months. MTN-003B follow-up visits are expected to occur every 6 months for the duration of follow-up.

Split Visits: If a participant is not able to complete all required MTN-003B visit procedures on one day, she may come back and complete the remaining procedures on another day. As long as the procedures are completed within the same visit window, the visit will be considered a split visit and all case report forms will be assigned the same visit code corresponding to the visit window in which the visits take place.

See Figures 18-7a and 18-7b for a complete listing of visit codes for VOICE and MTN-003B, and see Sections 14.3.3 and 18.14.3 of this manual for more information on assigning visit codes. See Figures 18-8a and 18-8b for several examples illustrating split visits for VOICE and MTN-003B.

Interim Visits: It is not expected that any interim visits will occur specifically for MTN-003B, unless a participant terminates early and completes one final study visit outside of any visit window (applies to post-PUEV visits only).

- *If a participant is still in VOICE follow-up,* any interim contact during her MTN-003B participation should be conducted as a VOICE interim visit (see Section 14.3.2 of this manual for more information on VOICE interim visits).
- *If a participant has completed her VOICE participation,* any interim contact should be chart-noted only, **unless**:
    - the participant is co-enrolled in another trial, in which case the interim contact should be documented per the other trial's requirements, or
    - the participant has consented to Protocol Version 2.0, then decides to terminate early (that is, after the VOICE PUEV but prior to the 12 Months Post PUEV Visit) **and** completes a final study visit outside of any allowable visit window. See Figure 18-4b for examples.

There may be times when additional DXA scans need to be done after a scheduled MTN-003B visit has been completed. In these cases, please contact the MTN SDMC Project Manager for form completion instructions (including visit code assignment).

18.6.1.1 Follow-up Visit Scheduling During VOICE Follow Up

Target days and visit windows for MTN-003B follow-up visits are based on participants' follow-up visit schedules for VOICE. As shown in Figure 18-3a, semi-annual MTN-003B visits are targeted to occur every 168 (28*6) days following the participant's VOICE enrollment date. Visit windows open 14 days before the target date and close 13 days after the target date. Even if a participant enrolls in MTN-003B several days after she enrolls in VOICE, the VOICE enrollment date is used to establish follow-up visit target days and visit windows for both VOICE and MTN-003B. Ideally, both VOICE and MTN-003B visits will be completed on the target day. Since it is not always possible to complete both visits on the target day, a participant may complete VOICE and MTN-003B visits on different days within the visit window. See Figure 18-8a for examples.

The MTN SDMC has provided study sites with a visit scheduling tool that can be used to generate follow-up visit schedules for VOICE and MTN-003B.

Figure 18-3a
MTN-003B Target Visit Days and Visit Windows During VOICE Follow-Up

Visit	Day Visit Window Opens	Target Visit Day	Day Visit Window Closes
Screening and Enrollment	May occur on the day of enrollment in VOICE or up to 13 days after the VOICE enrollment date		
Month 6	154	168	181
Month 12	322	336	349
Month 18	490	504	517
Month 24	658	672	685
Month 30	826	840	853
Final Follow-up Visit (if applicable)*	Should occur as close as possible to the date of the VOICE PUEV but may occur up until the date of the VOICE Termination Visit		

*A final follow-up visit is required at the time of the participant's VOICE Product Use End Visit (PUEV) if the PUEV occurs at least 90 days after the last semi-annual MTN-003B visit.

Missed Visits During VOICE Follow-up (on or prior to PUEV): If a semi-annual MTN-003B visit is missed, i.e., no procedures for that visit are completed *within the visit window*, an MTN-003B Missed Visit form must be completed. All missed MTN-003B procedures should be performed as soon as possible after the participant is re-contacted. If the missed MTN-003B procedures cannot be completed within the next monthly visit window in VOICE, the procedures may be completed within the next two monthly visit windows in VOICE thereafter.

- For example, if a Month 6 MTN-003B visit is missed, the missed procedures should ideally be performed within the participant's Month 7 visit window. If the missed procedures cannot be performed within the Month 7 visit window, they may be performed within the Month 8 visit window or Month 9 visit window. When the missed procedures are performed, all case report forms documenting the procedures should be assigned the visit code corresponding to the study month when the procedures are performed. In this example, if the procedures are made up in the Month 7 visit window, all forms should be assigned the Month 7 visit code (10.0). See Figure 18-7a.

  Note: a Missed Visit form must still be completed for the Month 6 visit (visit code 9.0), since the procedures were not conducted within the Month 6 visit window.

- If the participant is not able to make up the missed procedures within the next three monthly visit windows following the missed visit, all efforts to make up the visit should cease. In this example, if the Month 9 visit window closes before the Month 6 visit procedures can be made up, efforts to perform the missed MTN-003B Month 6 visit procedures should be discontinued and every effort should be made to complete the MTN-003B Month 12 visit within the Month 12 visit window.

Final Study Visits for Participants Who Do Not Reconsent to Protocol Version 2.0:

All participants who remain in MTN-003B follow-up through the VOICE PUEV are expected to complete MTN-003B procedures at the VOICE PUEV, if at least 90 days have passed since the last completed MTN-003B semi-annual follow-up visit. For these participants, the MTN-003B procedures conducted at the time of the VOICE PUEV will count as the participant's final study visit. If a participant's VOICE PUEV occurs less than 90 days after her last completed MTN-003B semi-annual follow-up visit, then MTN-003B procedures should not be completed at the PUEV. Rather, her last completed study visit is considered her final study visit.

Participants who terminate MTN-003B early, prior to the VOICE PUEV, will be asked to complete one final study visit – the Early Termination Visit (ETV) – if at least 90 days have passed since the last completed MTN-003B semi-annual follow-up visit. If less than 90 days have passed since her last completed MTN-003B semi-annual follow-up visit, or if at least 90 days have passed but she is unwilling to complete an ETV, then no further MTN-003B procedures will be completed. Her last completed visit will count as her final study visit.

See Figure 18-4a below for examples of final study visits.

Figure 18-4a
Scheduling Final MTN-003B Follow-up Visits
for Participants who do NOT consent to follow-up beyond VOICE PUEV

Example 1: A participant's VOICE PUEV is scheduled for Month 12. She completes semi-annual MTN-003B visits at Month 6 and at Month 12. Her Month 12 MTN-003B visit is considered her final MTN-003B follow-up visit.

Example 2: A participant's VOICE PUEV is scheduled for Month 19. She completes semi-annual MTN-003B visits at Months 6, 12, and 18. Her Month 18 MTN-003B visit is completed less than 90 days before her PUEV and is therefore considered her final MTN-003B visit (no further MTN-003B visits are required).

Example 3: A participant's VOICE PUEV is scheduled for Month 29. She completes semi-annual MTN-003B visits at Months 6, 12, 18, and 24. Her last semi-annual MTN-003B visit takes place at Month 24, which is more than 90 days before the PUEV. Therefore, an additional final MTN-003B visit should be completed at the time of the PUEV.

Example 4: A participant decides to withdraw from VOICE and MTN-003B at Month 22. Her last semi-annual MTN-003B visit took place at Month 18, which is more than 90 days before Month 22. If the participant is willing to do so, a final MTN-003B visit should be completed at Month 22.

18.6.1.2 Follow-up Visit Scheduling After VOICE Follow Up

Once the participant has completed her VOICE PUEV, the MTN-003B visit calendar resets. It is no longer based on the date of VOICE enrollment. Rather, it is based on the date the VOICE PUEV was actually completed (PUEV date=Day 0).

As shown in Figure 18-3b, two semi-annual MTN-003B visits are targeted to occur at six months and twelve months after the VOICE PUEV (that is, every 168 (28*6) days following the participant's VOICE PUEV date).Target visit windows open 14 days before the target date and close 13 days after the target date. Allowable visit windows open a month (28 days) before the target date. Allowable visit windows close 3 months (84 days) after the target date, with the exception that all study visits must be completed by 30 days after the last participant's 12-Months Post PUEV target date.

The MTN SDMC will provide study sites with a visit scheduling tool that can be used to generate follow-up visit schedules for MTN-003B post PUEV.

Figure 18-3b
MTN-003B Target Visit Days and Visit Windows After VOICE PUEV
Note: PUEV date = Day 0

Visit	Allowable Visit Window Opens	Target Visit Window Opens	Target Visit Day	Target Visit Window Closes	Allowable Visit Window Closes*
6 Months Post PUEV	140	154	168	181	252
12 Months Post PUEV	308	322	336	349	420

* All study visits must be completed by 30 days after the last participant's 12-Months Post PUEV target date.

Ideally, MTN-003B visits will be completed on their target days, or at least within their target windows. However, if necessary, MTN-003B visits may take place on any day or on different days within the specified allowable visit window. See Figure 18-8b for examples.

Missed Visits After VOICE PUEV: A semi-annual MTN-003B visit is considered missed if no procedures for that visit are completed within the allowable visit window. Once the allowable visit window has closed for a given visit, the visit procedures cannot be made up; the visit will be considered "missed" and an MTN-003B V2 Missed Visit form will be required to document the missed visit. Site staff should focus their efforts on contacting the participant to ensure that she can come in to complete her next scheduled MTN-003B visit, if applicable.

Final Study Visits for Participants Who Reconsent to Protocol Version 2.0:

Participants who reconsent to Protocol Version 2.0 are expected to complete the 12 Months Post-PUEV Visit, which will count as the final study visit. If a participant decides to terminate the study early; that is, after the VOICE PUEV but prior to the 12 Months Post-PUEV Visit, then the participant will be asked to complete one final study visit – the Early Termination Visit (ETV) – *if* at least 30 days have passed since the last completed MTN-003B semi-annual follow-up visit. If less than 30 days have passed since her last completed MTN-003B semi-annual follow-up visit, or if at least 30 days have passed but she is unwilling to complete an ETV, then no further MTN-003B procedures will be completed. Her last completed visit will count as her final study visit.

See Figure 18-4b below for examples of final study visits.

Figure 18-4b
Scheduling Final MTN-003B Follow-up Visits
for Participants who consent to follow-up beyond VOICE PUEV

Example 1: A participant completes her 12 Months Post-PUEV Visit within the visit window. It is considered her final MTN-003B follow-up visit and is assigned visit code 93.0.

Example 2: A participant completes her 6 Months Post-PUEV Visit. At the end of the visit, she says that she will no longer be able to participate in the study, as she is moving to another country for work in two weeks. Since less than 30 days have passed since her last completed study visit (the 6 Months Post-PUEV Visit), no further MTN003B procedures should be conducted for the participant. The 6 Months Post-PUEV Visit will count as her Early Termination Visit (ETV) and final study visit. Complete an MTN003B V2 Termination CRF to indicate that the participant has terminated from the study.

Example 3: A participant completes her 6 Months Post-PUEV Visit. She contacts site staff four months later to report that she is moving out of town and will no longer be able to participate in the study. Since at least 30 days have passed since her last MTN-003B visit (the 6 Months Post-PUEV Visit), site staff ask her if she would be willing to complete one final study visit.

- If the participant is willing to complete one final study visit within the 12 Months Post PUEV visit window, then the visit will count as the 12 Months Post-PUEV Visit. The participant will have completed the expected follow-up in MTN003B and will not considered an early terminator.
- If the participant is willing to complete one final study visit and the visit is conducted before the 12 Months Post-PUEV visit window opens, then the visit will count as an ETV. Assign the visit interim visit code 92.1. Complete an MTN003B V2 Termination CRF to indicate that the participant has terminated from the study.
- If the participant is unwilling or is unable to complete one final study visit, then no further MTN-003B procedures are conducted. Her last completed visit, the 6 Months Post-PUEV Visit, will count as her ETV and final study visit. Complete an MTN003B V2 Termination CRF to indicate that the participant has terminated from the study.

Example 4: A participant reconsents to Protocol Version 2.0. She then presents to the site 5 months after her PUEV and states that she would like to withdraw from the study. Despite several staff attempts to dissuade the participant, she refuses further participation. Since at least 30 days have passed since her last MTN-003B visit (around the time of her PUEV), site staff ask her if she would be willing to complete one final study visit – her ETV.

- If the participant is willing to complete one final study visit within the 6 Months Post-PUEV visit window, then the visit will count as the as the 6 Months Post-PUEV Visit and ETV. Complete an MTN003B V2 Termination CRF to indicate that the participant has terminated from the study.
- If the participant is willing to complete one final study visit and the visit is conducted before the 6 Months Post-PUEV visit window opens, then the visit will count as an ETV. Assign the visit interim visit code 91.1.
- If the participant is unwilling or is unable to complete one final study visit, then no further MTN-003B procedures are conducted. Her last completed MTN003B visit (around the time

of the PUEV) will count as her ETV and final study visit. Complete an MTN003B V2 Termination CRF to indicate that the participant has terminated from the study.

Example 5: A participant reconsents to Protocol Version 2.0 at her PUEV. A month later, she contacts the site to state that she is moving out of the area and will no longer be able to participate in MTN-003B.

- If at least 30 days have passed since her last semi-annual MTN-003B visit, ask the participant if she would be willing to complete one final MTN-003B study visit – her ETV. If she agrees and the visit is conducted before the 6-months post-PUEV visit window opens, assign the visit interim visit code 91.1. Complete an MTN003B V2 Termination CRF to indicate that the participant has terminated the study.
- If less than 30 days have passed since her last semi-annual MTN-003B visit, ask the participant if she is willing and able to complete one final study visit (ETV) once at least 30 days have passed since her last semi-annual MTN-003B visit. If she agrees and the visit is conducted before the 6-months post-PUEV visit window opens, assign the visit interim visit code 91.1. Complete an MTN003B V2 Termination CRF to indicate that the participant has terminated the study.
- If the participant is unwilling or unable to complete one final study visit once 30 days have passed since her last completed MTN-003B semi-annual visit, then no further MTN-003B procedures are conducted. Her last MTN-003B semi-annual visit (around the time of the PUEV) will count as her ETV and final study visit. Complete an MTN003B V2 Termination CRF to indicate that the participant has terminated from the study.

18.6.2 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Section 7.3. Each visit includes administrative and regulatory procedures, anthropometric and clinical procedures, and laboratory and DXA procedures. Given that both VOICE and MTN-003B require semi-annual measurement of height and weight, measurements completed and documented for VOICE within 14 days (inclusive) of an MTN-003B follow-up visit may be used for MTN-003B. All MTN-003B visits may be conducted as split visits, with visit procedures conducted on multiple days within the same visit window.

Note that under Protocol Version 2.0, collection of medical history and contraceptive use are required procedures at MTN-003B follow-up visits, if these procedures are not done as part of a VOICE or other study visit. It is not necessary to collect information on all of the concomitant medications a participant is using. Rather, the protocol-required collection of concomitant medications should be limited to collection of contraceptive use data for recording on the MTN003B Version 2.0 Contraceptives Log CRF.

18.6.3 Modified Follow-up Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product in VOICE

Participants who temporarily hold or permanently discontinue use of study product in VOICE will not routinely be withdrawn from MTN-003B. Rather, every effort should be made to complete all protocol-specified MTN-003B procedures with these participants except that, for participants who become pregnant, the following procedures will not be performed:

- DXA scan
- Collection and storage of urine and serum

These procedures may be resumed according to the participant's original follow-up schedule after completion of the pregnancy.

18.7 Visit Checklists

Section Appendix 18-6 contains examples of checklists detailing the protocol-specified procedures that must be completed at MTN-003B study visits. The checklists also specify the data collection forms that must be completed at each visit. See Section 7.1 of this manual for detailed guidance on proper use of visit checklists.

18.8 Participant Retention

Please refer to Section 8 of this manual. All information contained in that section applies to MTN-003B. After VOICE PUEV, sites may have to adapt retention efforts as participants will only have visits every 6 months versus monthly. For example, interim phone contacts (e.g., every other month) may be implemented to maintain connections to participants between visits.

18.9 Study Product Considerations

Please refer to Section 9 of this manual. There are no additional study product considerations for MTN-003B.

18.10 DXA Scanning Procedures and Other Clinical Considerations

Each site will perform DXA scans using the Hologic Explorer instrument. It is expected that the same instrument and the same version of the system software will be used throughout the duration of MTN-003B. Site staff should immediately notify the MTN 003B study management team (mtn003b-mgmt@mtnstopshiv.org) if any instrument or software changes are anticipated and/or if any technical difficulties are encountered when performing DXA scans.

All scans will be performed according to manufacturer instructions and site SOPs, with appropriate protections for participant and operator exposure to radiation. Considerations that should be addressed in site SOPs include but are not limited to the following:

- Start up and shut down of the instrument
- Scheduled maintenance
- Calibration and quality control
- Entering participant information
- Preparation of the participant
- Positioning of the participant
- Choosing the correct scan types
- Performing scans
- Analyzing scans
- Generating and printing reports
- Backing up data
- Exporting data
- Radiation safety for the participant and the operator

Only trained technicians may perform DXA scans. Trained technicians should be designated on study staff rosters and training documentation should be available for inspection at any time. Prior to study initiation, experienced CORE (PITT) staff will assess technician competency by reviewing scans performed by each technician.

During the study, all scans will be reviewed by experienced CORE (PITT) staff. Reviews will take place at least monthly after study initiation. Study staff will upload all scans to an FTP server on a weekly basis. In addition, study staff will create and upload a summary report of their daily calibration and quality control data on a monthly basis. CORE (PITT) staff will provide feedback to site staff based on each review of the submitted scans and will correct the scans directly in the scan's electronic file. CORE (PITT) may also recommend other actions that may be needed throughout the duration of the study. The CORE (PITT) staff will provide corrected scans to each of the sites. For corrected scans, it is the site's responsibility to re-upload these scans onto the DXA computer and complete the DXA Scan CRFs within 10 working days of the scan date. For each scan, sites should wait until the CORE (PITT) confirms that the scan is correct as is, or sends a corrected scan file, before completing the DXA Scan CRF. All DXA Scan CRFs faxed to SCHARP should reflect any and all corrections to the scan data files that were made by the CORE (PITT).

The MTN-003B management team will conduct periodic reviews in which they compare the corrected scan data images/results from CORE (PITT) to the DXA Scan CRF data in the SCHARP database. If discrepancies are noted between the source scan data and the CRF data, SCHARP will place data QCs as appropriate. These QCs will appear on the monthly QC reports sent to the MTN-003B sites by SCHARP.

Additional tips and guidance for performing DXA scans for MTN-003B are as follows:

- Routine calibration and quality control procedures must be performed on each day the instrument is used. Quality control results must be acceptable before scanning participants.

- It is recommended, but not required, that routine calibration and quality control procedures be performed three times weekly when the instrument is not in use.

- Data back-ups must be performed each day the instrument is used.

- When programming scans, participant ethnicity should not be specified.

- Pregnancy testing must be performed prior to DXA scanning at each MTN-003B visit; scans should only be performed for participants who are not pregnant. See Section 18.6.3 above.

- Prior to scanning, participants should be asked about and examined for metal objects that could be in the scan path, such as eyeglasses, earrings, wristwatches, coins, rings, buttons, buckles, and zippers. Any such objects should be removed prior to scanning. The participant should remove her shoes and may change from her clothes to an examination gown if needed.

- At each MTN-003B visit, four DXA scans are required per protocol: two scans of the lumbar spine and two scans of the left hip. The participant should first be positioned and then one scan of the spine and one scan of the hip should be performed. These scans are referred to as "Scan #1" on the DXA Scan case report form. The participant should then get up off the instrument. She should then be re-positioned and a second scan of the spine and hip should be performed. These scans are referred to as "Scan #2" on the DXA Scan case report form.

- At each MTN-003B follow-up visit, the participant's current BMD must be compared to her baseline BMD. The first scan of the spine and hip done at the MTN-003B screening and enrollment visit will be designated at the baseline scans for all comparisons. If the participant's follow-up BMD is more than one standard deviation lower than her baseline BMD, all four DXA scans should be repeated as soon as possible. If a decrease of more than one standard deviation is confirmed on repeat scans done while the participant is still in VOICE follow-up, the IoR or designee should consult the VOICE Protocol Safety Review Team (PSRT) on whether the participant should continue use of oral study product in VOICE.

    - The Z and T scores are already calculated as standard deviations. In order to calculate one standard deviation, take the baseline score and subtract the current scan score. If the number is more than 1.0, it indicates a greater than 1 standard deviation loss.

Further clinical considerations related to DXA scan results are as follows:

- For participants with BMD Z-scores (ages 18-29) or T-scores (ages 30 and older) less than -2.0 at their MTN-003B screening and enrollment visit, the IoR or designee should discuss options for treatment or prevention of osteoporosis with the participant and provide calcium supplements if clinically indicated.

- For participants with BMD Z-scores (ages 18-29) or T-scores (ages 30 and older) less than -2.0 during follow-up, the IoR or designee should:

  - Discuss options for treatment or prevention of osteoporosis with the participant and provide calcium supplements if clinically indicated

    and, if the participant is still in VOICE follow-up,

  - Consult the VOICE PSRT regarding possible temporary hold or permanent discontinuation of oral study product use in VOICE.
    Assessment of Breastfeeding: At each visit, the participant will be asked if she has breastfed since her last study visit, and/or is currently breastfeeding. For post-PUEV visits, a member of site staff may ask this question directly of the participant and source document the information on the MTN003B V2 Visit Procedures CRF (items 1-1a).

    Assessment of Malnutrition: At each visit, the participant is assessed for physical signs of malnutrition. At MTN-003B visits that occur during VOICE follow-up, this information is typically obtained in the context of the VOICE physical exams. For MTN-003B post-PUEV visits, a site clinician should complete this assessment based on a review of the participant's medical history and weight at the time of the visit.

18.11 Adverse Event Reporting and Safety Monitoring

All of the safety monitoring, review, and oversight procedures described in Section 8 of the VOICE protocol and Section 11.8 of this manual apply to MTN-003B for visits conducted while the participant is still participating in VOICE. All AEs reported for MTN-003B will be included in safety monitoring reports prepared for review by the VOICE PSRT and the NIAID Vaccine and Prevention Data Safety Monitoring Board (DSMB). Following the completion of VOICE, AE reporting will cease in MTN-003B, and no DSMB or SMC reviews are planned for MTN-003B. As such, site IoRs should notify the MTN-003B management team of any unexpected safety concerns.

Requirements for AE identification, documentation, and reporting begin at the MTN-003B screening and enrollment visit, even if the participant has not taken any study product at the time when her first scans are done. All adverse events (AEs) identified in MTN-003B must be documented in source documents, regardless of severity and presumed relationship to study product.

- For scans done on or prior to the VOICE PUEV, all new BMD losses of severity grade 2 and higher must be reported on VOICE AE Log case report forms.

- For scans done after the VOICE PUEV, gradable BMD losses and any other AEs identified should be chart-noted only (unless the participant is co-enrolled in another MTN trial, in which case the other trial's AE reporting guidelines apply). All AEs should still be source documented, clinically managed, and followed to resolution or stabilization. However, they will NOT be reported on AE Log CRFs.
- If a women reconsents to continue in the study after the VOICE PUEV and has an ongoing AE sites should mark the AE as "continuing at end of the study" on the CRF that was completed during her VOICE participation. Sites should then document the continuing AE in chart-notes for documentation under Version 2.0.

Severity should be graded according to the protocol-specific grading table shown in Figure 18-5.

Figure 18-5
Protocol-Specific Severity Grading for Loss of Bone Mineral Density

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
BMD loss Age ≥ 30 years	BMD T-score -2.5 to -1.0	BMD T-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
BMD loss Age < 30 years	BMD Z-score -2.0 to -1.0	BMD Z-score < -2.0	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences

When grading the severity of BMD loss, either the T-score or the Z-score should be used consistently for each participant throughout her study participation, based on her age at enrollment into MTN-003B. In particular, for participants whose age increases from less than 30 years at enrollment to 30 or more years during follow-up, Z-scores should always be used. DXA scan print-outs will include both T-scores and Z-scores, and both sets of scores should be recorded on the MTN-003B DXA Scan case report form for all participants. However, only one set of scores should be used for purposes of severity grading for each participant.

Additional guidance for **reporting** BMD loss as an AE is as follows:

- Requirements for AE identification, documentation, and reporting begin at the MTN-003B screening and enrollment visit.

- AEs with an onset date after the VOICE PUEV will **not** be reported on AE Log CRFs.

- Use the term "bone mineral density loss" to report the AE. It is not necessary to include the anatomical location in the AE term.

- If grade 2 (or more severe) BMD loss is identified in more than one anatomical location at any given visit, do not report more than one AE. Complete one AE Log case report form for "bone mineral density loss" and assign the highest severity grade identified from all DXA scans completed at the visit.

- If a participant has an ongoing AE for BMD loss from a previous visit, do not complete another AE Log form for "bone mineral density loss" for subsequent BMD results, unless the severity increases.

- Pay careful attention to T-scores and Z-scores that are negative numbers. For example, remember that -2.3 is lower than -2.0. Therefore, a score of -2.3 is "worse" or "more severe" than a score of -2.0.

- Also pay careful attention to whether T-scores or Z-scores should be used for severity grading for each participant (based on participant age at enrollment into MTN-003B). The grading scales are different based on whether T-scores or Z-scores are used.

Figure 18-6 below presents examples illustrating the above-listed AE reporting guidance.

Figure 18-6
Examples of AE Reporting for Loss of Bone Mineral Density On or Prior to VOICE PUEV

Example 1: A 32 year-old participant has the following DXA scan results at her screening and enrollment visit:

Scan #1 T-scores	Scan #2 T-scores
Spine: -1.2 (grade 1)	Spine: -1.3 (grade 1)
Hip: -1.6 (grade 1)	Hip: -1.5 (grade 1)
Femoral neck of hip: -1.3 (grade 1)	Femoral neck of hip: -1.4 (grade 1)

At this visit, grade 1 "bone mineral density loss" would be source documented as an AE, but would not be not be reported on an AE Log case report form.

Example 2: A 32 year-old participant has the following DXA scan results at her screening and enrollment visit:

Scan #1 T-scores	Scan #2 T-scores
Spine: -1.7 (grade 1)	Spine: -1.6 (grade 1)
Hip: -2.5 (grade 1)	Hip: -2.6 (grade 2)
Femoral neck of hip: -2.4 (grade 1)	Femoral neck of hip: -2.4 (grade 1)

At this visit, grade 2 "bone mineral density loss" would be source documented and reported as an AE on an AE Log form, based on the highest severity grade identified (on scan #2 of the hip). Although not required, it is helpful if the anatomical location of the bone mineral density loss is recorded in the comments section of the AE Log form.

At this participant's Month 6 visit, the following DXA scan results are obtained:

Scan #1 T-scores	Scan #2 T-scores
Spine: -1.7 (grade 1)	Spine: -1.6 (grade 1)
Hip: -2.5 (grade 1)	Hip: -2.7 (grade 2)
Femoral neck of hip: -2.6 (grade 2)	Femoral neck of hip: -2.6 (grade 2)

At this visit, the participant's AE for grade 2 bone mineral density loss, which was identified at her screening and enrollment visit, is ongoing. Do not complete another AE Log form at this visit, even though grade 2 bone mineral density loss has now been identified in more than one anatomical location. Although not required, it is helpful to record in the comments section of the original AE Log form (completed at the screening and enrollment visit) that grade 2 bone mineral density loss has now been identified at the hip and the femoral neck of the hip.

Example 3: A 27 year-old participant has the following DXA scan results at her Month 18 visit:

Scan #1 Z-scores	Scan #2 Z-scores
Spine: -1.0 (grade 1)	Spine: -1.1 (grade 1)
Hip: -2.3 (grade 2)	Hip: -2.2 (grade 2)
Femoral neck of hip: -2.0 (grade 1)	Femoral neck of hip: -2.1 (grade 2)

At this visit, grade 2 "bone mineral density loss" would be source documented and reported as an AE on an AE Log form, based on the highest severity grade identified. Even though grade 2 bone mineral density loss has been identified in more than one anatomical location, only one AE Log form should be completed. Although not required, it is helpful if both anatomical locations are recorded in the comments section of the AE Log form.

18.12 Counseling Considerations

Although counseling is not specified as a study procedure in Section 7 of the MTN-003B protocol, study staff may be required to counsel MTN-003B participants as follows:

- Participants should be reminded of the rationale for pregnancy testing for both VOICE and MTN-003B and counseled to inform study staff of any suspected pregnancy.

- Participants identified as malnourished according to the clinical judgment of the IoR or designee should be counseled on locally available treatment options and sources of nutrition support.

- Participants with T-scores (age 30+) or Z-scores (age 18-29) less than -2.0 should be counseled on options for prevention or treatment of osteoporosis, including calcium supplementation if recommended by the IoR or designee.

18.13 Laboratory Considerations

Urine and blood will be collected for storage at each scheduled MTN-003B visit. Per protocol, testing of these specimens will be determined at a later date. The MTN Network Laboratory (NL) will instruct study sites to ship stored specimens for testing as needed throughout the study.

18.13.1 Urine Collection and Storage

Collect urine as described in Section 12.5.1 of this manual. If other urine tests for a given participant are required to be performed for VOICE or another trial on the same day as an MTN-003B visit, specimens for these tests may be aliquoted from the same urine sample or a separate sample may be collected. Freeze 10 mL of urine at -70º C within 8 hours of collection (sites may choose aliquot size). Enter all aliquots in LDMS. If less than 10 mL is available for storage, store all available urine and notify the MTN NL via an e-mail to mtn003mgmt@mtnstopshiv.org.

18.13.2 Blood Collection and Serum Storage

Collect approximately 15 mL of blood in plain (no additive) tubes as described in Section 12.6.1 of this manual. Centrifuge specimens and freeze all available serum at -70º C within 8 hours of collection (sites may choose aliquot size). Enter all aliquots in LDMS. If less than 7 mL is available for storage, store all available serum and notify the MTN NL via an e-mail to mtn003mgmt@mtnstopshiv.org.

18.13.3 Guide to Logging in MTN-003B Specimens in LDMS

Test	Primary	Primary Additive	Primary Volume	Primary Units	Aliquot Derivative	Aliquot Sub Add/Derv	Aliquot Volume	Aliquot Units
Serum for storage	BLD	NON	15	mL	SER	N/A	Variable	mL
Urine for storage	URN	NON	15-60	mL	URN	N/A	Variable	mL

Note: MTN-003B appears in LDMS as MTN 003.1.

18.14 Data Collection

Only data collection issues unique to MTN-003B are covered in this section. For more information on VOICE data collection procedures, see Section 14 of this manual. All information contained in that section applies to MTN-003B.

For questions about this section or about general data collection policies, procedures, or materials for MTN-003B, please contact Karen Patterson (karen@scharp.org or karenp@scharp.org).

18.14.1 PTIDs

PTIDs will not be assigned for MTN-003B. The same PTIDs assigned for VOICE will be used for MTN-003B. For more information on assigning PTIDs for VOICE, please refer to Section 14.3.1 of this manual.

18.14.2 Visit Codes

Visit codes are used to identify the visit at which a case report form is completed. Most DataFax forms include boxes in the upper right-hand corner for a visit code. However, if a form is only completed once during a study, the visit code will be automatically assigned in DataFax and, therefore, site staff will not be required to record the visit code on the form. For MTN-003B, the Eligibility form and Lactation and Contraceptive History form are completed only at the screening and enrollment visit and do not require a visit code.

Through the VOICE PUEV, MTN-003B uses the same visit codes as VOICE (Figure 18-7). In general, MTN-003B visit codes are associated with the month of the visit. However, the MTN-003B screening and enrollment visit is assigned the same visit code as the VOICE enrollment visit (03.0). See Section 14.3.3 of this manual for detailed information on VOICE visit codes.

Note: All visit codes assigned to MTN-003B visits should end with a zero (e.g., 09.0, 15.0) regardless of when the MTN-003B visit occurs in relation to the corresponding VOICE visit.

Figure 18-7a
VOICE and MTN-003B Visit Codes Through VOICE PUEV

Visit	Visit Code
VOICE Screening Part 1	01.0
VOICE Screening Part 2	02.0
VOICE Enrollment and MTN-003B Screening and Enrollment	03.0

Month 1	04.0
Month 2	05.0
Month 3	06.0
Month 4	07.0
Month 5	08.0
VOICE and MTN-003B Month 6 (MTN-003B Semi-Annual Visit)	09.0
Month 7	10.0
Month 8	11.0
Month 9	12.0
Month 10	13.0
Month 11	14.0
VOICE and MTN-003B Month 12 (MTN-003B Semi-Annual Visit)	15.0
Month 13	16.0
Month 14	17.0
Month 15	18.0
Month 16	19.0
Month 17	20.0
VOICE and MTN-003B Month 18 (MTN-003B Semi-Annual Visit)	21.0
Month 19	22.0
Month 20	23.0
Month 21	24.0
Month 22	25.0
Month 23	26.0
VOICE and MTN-003B Month 24 (MTN-003B Semi-Annual Visit)	27.0
Month 25	28.0
Month 26	29.0
Month 27	30.0
Month 28	31.0
Month 29	32.0
VOICE and MTN-003B Month 30 (MTN-003B Semi-Annual Visit)	33.0
Month 31	34.0
Month 32	35.0
Month 33	36.0
Month 34	37.0
Month 35	38.0
Month 36	39.0

Figure 18-7b
MTN-003B Visit Codes After VOICE PUEV

Visit	Visit Code
Post PUEV Month 6	92.0
Post PUEV Month 12	93.0

Figure 18-8a
Follow-up Visit Coding Examples for MTN-003B During VOICE Follow-up

Example 1: A participant completes her Month 12 visit for VOICE and her Month 12 visit for MTN-003B on the Month 12 target date. The Month 12 visit code (15.0) is assigned to all case report forms completed for both the VOICE visit and the MTN-003B visit.

Example 2: A participant completes her Month 12 visit for VOICE on the Month 12 target date. She then completes her Month 12 visit for MTN-003B three days later (still within the Month 12 visit window). The Month 12 visit code (15.0) is assigned to all case report forms completed for both the VOICE visit and the MTN-003B visit.

Example 3: A participant completes her Month 12 visit for VOICE and most of her Month 12 visit for MTN-003B on the Month 12 target date. She is not able to complete her DXA scans on this day but returns two days later (still within the Month 12 visit window) to complete the scans. The Month 12 visit code (15.0) is assigned to all case report forms completed for the VOICE visit and the split MTN-003B visit.

Example 4: A participant completes most of her Month 12 visit for VOICE and all of her Month 12 visit for MTN-003B on the Month 12 target date. She does not complete the pelvic exam required for VOICE at the Month 12 visit because she is menstruating but returns five days later to complete the exam. The Month 12 visit code (15.0) is assigned to all case report forms completed for the split VOICE visit and the MTN-003B visit.

Example 5: A participant completes her Month 12 visit for VOICE on the Month 12 target date. The Month 12 visit code (15.0) is assigned to all case report forms completed for this VOICE visit. She is scheduled to return two days later (still within the Month 12 visit window) to complete her Month 12 MTN-003B visit, but is not able to return that day. Instead, she travels to her home village to care for a sick relative. She is away for three weeks and the Month 12 visit window closes before she can return to complete her Month 12 MTN-003B visit. When she does return, she presents to the study site during her Month 13 visit window and completes her MTN-003B procedures then. In this case, the Month 13 visit code (16.0) is assigned to all case report forms completed for the MTN-003B visit (because the visit was conducted within the Month 13 visit window). Also in this case, an MTN-003B Missed Visit form must be completed for the Month 12 MTN-003B visit (visit code 15.0), because the visit was not completed within the Month 12 visit window.

Example 6: A participant completes her Month 12 visit for VOICE on the Month 12 target date (02 DEC 10). She is scheduled to return two days later (still within the Month 12 visit window) to complete her Month 12 MTN-003B visit. She returns as scheduled (on 04 DEC 10) but is complaining of fever and body aches that day. She is attended to by a study clinician who documents the visit per site SOPs. Due to her illness, the participant requests to return to the study site on a different day to complete her Month 12 visit for MTN-003B. She returns four days later (on 08 DEC 10) and completes her Month 12 visit for MTN-003B that day. In this case, the Month 12 visit code (15.0) is assigned to all case report forms completed for VOICE on 02 DEC 10 and all case report forms completed for MTN-003B on 08 DEC 10. The visit on 04 DEC 10 is considered a VOICE interim visit (visit code = 15.1) because all of the Month 12 procedures required for VOICE had already been completed on 02 DEC 10.

Figure 18-8b
Follow-up Visit Coding Examples for MTN-003B After VOICE Follow-up

Example 1: A participant presents for her 6 Months Post-PUEV visit on the target date, 12-JAN-12. The participant completes all MTN-003B visit procedures that day except for the blood draw, which she wants to defer as she is feeling tired that day. She returns to the site a week later, 19-JAN-12, to complete the blood draw. Since all 6 months post-PUEV procedures are conducted within the allowable visit window, all CRFs completed for the visit should be assigned the 6 months post-PUEV visit code of 92.0.

Example 2: A participant completes most of her 6 Months Post-PUEV visit procedures on the target date of 09-JAN-12, then has to leave the visit early before she can complete the DXA scan. She is unable to return to the site until 2 months later to complete the DXA scan. Since the participant is still within the allowable visit window for the 6 months post-PUEV visit, the site conducts the scan and assigns all CRFs, including the DXA Scan CRF, visit code 92.0. Since the scan is being performed on a different day than the initial pregnancy test, a repeat pregnancy test is required on the day of the scan to confirm that the participant is not pregnant before the scan is performed.

Example 3: A participant completes most of her 6 Months Post-PUEV visit procedures on the target date of 05-JAN-12, then has to leave the visit early before she can complete the DXA scan. Despite repeated site efforts to contact the participant, site staff are unable to schedule the participant to return to the site until her 12 months post-PUEV visit. Once the 6-Months Post-PUEV visit window closed, any required 6 Months Post-PUEV visit procedures that were not conducted on 05-JAN-12 are considered missing. Complete all required MTN003B V2 CRFs for the 6 Months Post-PUEV visit. Assign them the date of 05-JAN-12 and visit code 92.0. On the DXA Scan CRF, record "05-JAN-12" as the Scan Date; indicate in the item 1 response that a scan was not performed and the reason why.

Example 4: A participant completes most of her 12 Months Post-PUEV visit on 12-JAN-12 and tests positive for pregnancy. Thus, a DXA scan is not performed. The participant returns to the site a month later stating that she is no longer pregnant. Site staff conduct a pregnancy test and confirm that the participant is no longer pregnant. They then conduct the DXA scan at that time. Since the participant is still within the allowable 12 Months Post-PUEV visit window, they are able to complete the 12 Months Post-PUEV visit procedures by conducting the DXA scan at that time. Assign all CRFs completed for the 12 Months Post-PUEV visit, including the DXA Scan CRF, visit code 93.0.

18.14.3 Case Report Form Completion Schedule

Some MTN-003B case report forms are required to be completed at each study visit, while other forms are required only at one visit or only when specifically indicated. Figures 18-9a and 18-9b list the case report forms that are required to be completed at MTN-003B visits.

Note: Data from MTN003B visits conducted on or prior to the PUEV are housed in a separate DataFax study database from MTN003B post-PUEV visit data. Thus, there are two separate sets of CRFs for MTN003B, as noted in Figures 18-9a and 18-9b below. CRFs used to document post-PUEV visit data have the title "MTN003B V2" in the CRF name. MTN003B V2 CRFs must be used exclusively to document post-PUEV visit data.

Figure 18-9a
MTN-003B Case Report Form Completion Schedule for Visits *Prior to* PUEV

MTN-003B Screening and Enrollment Visit		VISIT CODE: 03.0
Form Acronym	Form Name	Plate #
ELB	MTN 003B Eligibility*	360
LCH	MTN 003B Lactation and Contraceptive History	365
VP	MTN 003B Visit Procedures	363
DXA	MTN 003B DXA Scan	364
PAQ	MTN 003B Physical Activity Questionnaire	361-362
FFQ	MTN 003B Food Frequency Questionnaire	370-371
Non-DataFax	MTN 003B LDMS Specimen Tracking Sheet	N/A
MTN-003B Semi-Annual and Final Follow-Up Visits		VISIT CODES: 09.0, 15.0, 21.0, 27.0, 33.0
Form Acronym	Form Name	Plate #
VP	MTN 003B Visit Procedures	363
DXA	MTN 003B DXA Scan	364
PAQ	MTN 003B Physical Activity Questionnaire	361-362
FFQ	MTN 003B Food Frequency Questionnaire	370-371
Non-DataFax	MTN 003B LDMS Specimen Tracking Sheet	N/A
MTN-003B Missed Visits or Early Termination Prior to Expected PUEV		VISIT CODE: will vary
Form Acronym	Form Name	Plate #
MVB	MTN 003B Missed Visit	464
ETB	MTN 003B Early Termination	390

*An MTN-003B Eligibility form should be completed for each VOICE participant assigned to oral study product until the MTN-003B accrual target is met, regardless of whether the participant enrolls in MTN-003B. For VOICE participants assigned to oral study product who do not enroll in MTN-003B, only the MTN-003B Eligibility form will be completed. Otherwise, all forms listed above for the screening and enrollment visit will be completed.

Figure 18-9b
MTN-003B V2 Case Report Form Completion Schedule for Visits *After* PUEV

MTN-003B 6 Months Post-PUEV Visit		VISIT CODE: 92.0
Form Acronym	Form Name	Plate #
REC	MTN 003B V2 Reconsent*	008
VP	MTN 003B V2 Visit Procedures	363
DXA	MTN 003B V2 DXA Scan	364
PAQ	MTN 003B V2 Physical Activity Questionnaire	361-362
FFQ	MTN 003B V2 Food Frequency Questionnaire	370-371

CLB	MTN003B V2 Contraceptives Log**	435
Non-DataFax	MTN 003B V2 Participant-reported Follow-up Medical and Menstrual History	N/A
Non-DataFax	MTN 003B LDMS Specimen Tracking Sheet	N/A
MTN-003B 12 Months Post-PUEV Visit		VISIT CODE: 93.0
Form Acronym	Form Name	Plate #
VP	MTN 003B V2 Visit Procedures	363
DXA	MTN 003B V2 DXA Scan	364
PAQ	MTN 003B V2 Physical Activity Questionnaire	361-362
FFQ	MTN 003B V2 Food Frequency Questionnaire	370-371
TMB	MTN 003B V2 Termination	495
Non-DataFax	MTN 003B V2 Participant-reported Follow-up Medical and Menstrual History	N/A
Non-DataFax	MTN 003B LDMS Specimen Tracking Sheet	N/A
MTN-003B Missed Visits or Early Termination Prior to 12 Months Post-PUEV Visit		VISIT CODE: will vary
Form Acronym	Form Name	Plate #
MVB	MTN 003B V2 Missed Visit	464
TMB	MTN 003B V2 Termination	495

*An MTN-003B V2 Reconsent form should be completed for each MTN003B participant who remained in study follow-up through the VOICE PUEV (i.e., did not terminate early from VOICE or MTN-003B prior to the VOICE PUEV). For participants who are asked and do not reconsent to extended MTN003B follow-up under Protocol Version 2.0, the REC form is the only MTN003B V2 form that will be completed. Otherwise, if the participant did consent to extended follow-up post-PUEV, all forms listed above for the 6 Months Post-PUEV Visit will be completed.
** Any time a change in a participant's contraceptive use is noted, it should be documented on the Contraceptives Log CRF, and the CRF should be refaxed to SCHARP.

18.14.4 Form and Specimen Label Supply

All case report forms needed for MTN-003B will be supplied in visit packets. Each packet will contain all of the required forms for a designated study visit:

- The MTN-003B Screening and Enrollment Visit packet will include all of the forms listed for this visit in Figure 18-9a.

- The MTN-003B Follow-up Visit packets will include all of the forms listed for follow-up visits in Figures 18-9a and 18-9b.

An extra supply of MTN-003B Eligibility forms will be provided, as some women may screen for MTN-003B but not enroll in the study. For these women, only the MTN-003B Eligibility form will be completed.

An extra supply of MTN-003B V2 Reconsent forms also will be provided, as some women may refuse consent to Protocol Version 2.0. For these women, only the MTN-003B V2 Reconsent form will be completed.

The MTN SDMC will ensure that study sites have access to MTN-003B specimen labels (either printed on-site or printed by the SDMC). Specimen labels should be used for all primary specimen collection containers. For MTN-003B, primary specimens include blood and urine. The same labels should be used for MTN003B specimens collected pre- and post-PUEV. Please refer to Sections 13 and 18.13 of this manual for more information on specimen collection and labeling.

18.14.5 Form Storage

Specifications for form storage will be detailed in each site's data management SOP. It is recommended that, for each participant, study forms be stored in a hard-cover notebook. MTN-003B forms may be stored in the same notebook as VOICE forms.

18.14.6 How to Complete Interviewer-Administered Forms

Please refer to Section 14.5 of this manual for information on completing interviewer-administered forms. For MTN-003B, the Physical Activity Questionnaire (PAQ) and the Food Frequency Questionnaire (FFQ) are interviewer-administered.

18.14.7 Form Completion Instructions

Detailed form completion instructions are provided on the back of each form page. These instructions include the purpose of each form as well as how each form should be completed. Some items on forms are straightforward and do not require specific instructions. Therefore, instructions for all form items are not listed on the back of each form; rather, instructions are provided only for those items needing a detailed explanation. For the MTN-003B interviewer-administered forms — the PAQ and the FFQ — instructions on how to probe for participant responses are included in the instructions on the back of each form.

18.14.8 Case Report Forms

See Section Appendix 18-7. This appendix contains each case report form developed for MTN-003B.

18.15 Data Communiqués

Please see Section 15 of this manual. All data communiqués issued for VOICE, when relevant, also apply to MTN-003B. In addition, any data communiqués specific to MTN-003B should be added to Section Appendix 18-8.

Section Appendix 18-1
MTN-003B Protocol

Section Appendix 18-2
Suggested Filing Structure for MTN-003B Essential Documents

File/Binder #1: Protocol and Current Informed Consent Forms 1. MTN-003B protocol (including signed and dated protocol signature page): Version 1.0, Clarification Memo #01, and any other Clarification Memos, Letters of Amendment, and Amendments issued after Version 1.0. 2. Currently-approved (blank) MTN-003B informed consent forms
File/Binder #2: Regulatory Authority Documentation (if applicable) 3. Regulatory authority correspondence/authorization/approval/notification of protocol
File/Binder #3A: IRB/EC Documentation for [IRB/EC A] 4. FWA documentation, roster, and relevant submission requirements/guidelines/SOPs for IRB/EC A (may cross-reference VOICE essential document files) 5. IRB correspondence for IRB/EC A: file complete copies of all correspondence to and from the IRB/EC; include all enclosures/attachments for all submissions, even if copies of the enclosures/attachments are filed elsewhere; include all approval documentation.
File/Binder #3A: IRB/EC Documentation for [IRB/EC B] 6. FWA documentation, roster, and relevant submission requirements/guidelines/SOPs for IRB/EC B (may cross-reference VOICE essential document files) 7. IRB correspondence for IRB/EC B: file complete copies of all correspondence to and from the IRB/EC; include all enclosures/attachments for all submissions, even if copies of the enclosures/attachments are filed elsewhere; include all approval documentation.
File/Binder #4: Product Safety Information 8. May cross-reference Investigator's Brochure for Tenofovir Gel, Package Insert for Viread, and Package Insert for Truvada in VOICE essential document files
File/Binder #5: Study-Specific Procedures (SSP) Manual 9. Cross-reference Section 18 of the VOICE SSP Manual in VOICE essential document files. Since some sections of the VOICE SSP Manual will apply to MTN 003 B after VOICE is completed, the sites should reference the location of the VOICE SSP Manual or keep a full copy of the final VOICE SSP Manual in their MTN 003 B files.
File/Binder #6: Study-Specific Standard Operating Procedures 10. Final approved version of each SOP, and any subsequent updates to each (cross reference VOICE SOPs as applicable)
File/Binder #7: Staffing Documentation (for all of the following, except the FDA Form 1572, may cross-reference VOICE essential document files when applicable) 11. FDA Form 1572 (copy of original form submitted to the DAIDS Protocol Registration Office (PRO), and any subsequent updates) 12. MTN-003B Investigator of Record CV 13. Financial disclosure forms 14. Study staff roster, identification and signature sheet, and delegation of duties 15. CVs for study staff other than the IoR 16. Study staff job descriptions 17. Documentation of study staff training
File/Binder #8: Local Laboratory Documentation 18. May cross-reference VOICE essential document files
File/Binder #9: Monitoring Visit Documentation 19. May cross-reference VOICE essential document files
File/Binder #10: Documentation of Other MTN Site Visits 20. May cross-reference VOICE essential document files
File/Binder #11: Study-Related Sponsor Communications 21. Study-Related Communications to and from DAIDS 22. Communications to and from DAIDS RCC (includes copies of all submissions to the DAIDS PRO) Notes: • Communications should be filed beginning from the date of the first MTN-003B study team conference call: 10 June 2009. • Communications related to individual MTN-003B participants will be filed in individual participant study records.

File/Binder #12: Other Study-Related Communications

23. Study-related communications to and from MTN CORE
24. Study-related communications to and from MTN SDMC
25. Study-related communications to and from MTN Network Lab
26. Other study-related communications

Notes:

- Communications should be filed beginning from the date of the first MTN-003B study team conference call: 10 June 2009.
- Communications related to individual MTN-003B participants will be filed in individual participant study records.

File/Binder #13: Study Site Staff Meeting Documentation

27. MTN-003B staff meeting agendas, participant lists/sign-in sheets, and summaries

Note:

- Meeting documentation should be filed beginning from the date of the first MTN-003B study team conference call: 10 June 2009.

File/Binder #14: Conference Call Documentation

28. MTN-003B Protocol Team conference call summaries
29. Summaries of other MTN-003B conference calls

Note:

- Conference call summaries will be filed beginning from the date of the first MTN-003B study team conference call: 10 June 2009.

File/Binder #15: DAIDS and Other Reference Documentation

30. May cross-reference VOICE essential document files

File/Binder #16: Site-Specific Study Activation Documentation

31. Site-Specific Study Activation Notice and supporting documentation

Section Appendix 18-3
Guide to Required Case History Elements and Source Documents for MTN-003B

Required Case History Element	Source Documents*
Basic participant identifiers.	VOICE locator form, VOICE Demographics form.
Documentation that the participant provided written informed consent to screen for and participate in the study.	Signed and dated informed consent forms; signed and dated chart notes stating that informed consent was obtained prior to initiating study procedures; informed consent coversheet.
Documentation that the participant met the study selection (eligibility) criteria.	VOICE medical history, pregnancy testing, and randomization source documents; MTN-003B signed and dated chart notes.
A record of the participant's random assignment.	Not applicable for MTN-003B; cross reference VOICE randomization source documents.
A record of the participant's exposure to the investigational study products.	Not applicable for MTN-003B; cross reference VOICE source documents for study product dispensing and returns.
A record of all contacts, and all attempted contacts, with the participant.	Signed and dated chart notes and/or other worksheets or site-specific documents if designated in site SOPs.
A record of all procedures performed by study staff.	Completed visit checklists; signed and dated chart notes detailing (i) procedures performed in addition to those contained on the checklist and/or (ii) the reason why procedures contained on the checklist were not performed.
Information on the participant's condition before, during, and after the study.	All documents listed above; DXA scan source documents, all interviewer-administered case report forms, MTN-003B and MTN003B V2 Visit Procedures forms, MTN-003B Lactation and Contraceptive History form, MTN-003B and MTN003B V2 Missed Visit forms; MTN003B V2 Contraceptives Log; MTN003B V2 Participant-reported Follow-up Medical and Menstrual History form (non-DataFax); signed and dated chart notes; medical records and other documents bearing information pertinent to the study obtained from non-study sources; other designated site-specific source documents.

Section Appendix 18-4

Use of MTN-003B DataFax and Non-DataFax Forms as Source Documents

Note: rows in grey denote version 2 CRFs.

MTN-003B Forms	Source?	Comments
MTN-003B Eligibility	Mixed	Form may be source for items 6, 6a, 8, and 8a. All other should be completed based on source data recorded on other VOICE and MTN-003B source documents.
MTN003B V2 Reconsent	Mixed	The informed consent form for Protocol Version 2.0 is source for items 1 and 1a. The VOICE PUEV checklist and chart notes are source for item 1b. The form may be source for item 2.
MTN-003B Visit Procedures	Mixed	Form may be source for items 1, 1a, 5, and 6. All other items should be completed based on other VOICE and MTN-003B source documents.
MTN003B V2 Visit Procedures	Mixed	Form may be source for items 1, 1a, and 4-7. Item 2 should be completed based on source data recorded on the participant's medical history source document (e.g., MTN003B V2 Participant-reported Follow-up Medical and Menstrual History form (non-DataFax)). Item 3 should be based on the pregnancy test source document (e.g., pregnancy testing log or local lab report).
MTN-003B Lactation and Contraceptive History	Mixed	Form may be source for item 1 (including 1a and 1b). Item 2 should be completed based on source data recorded on the participant's VOICE medical history source documents.
MTN-003B Food Frequency Questionnaire	Mixed	Items 1-3b are interviewer-administered; participant responses must be recorded directly onto the form. Items 4-5 are completed based on source data recorded on VOICE source documents for concomitant medications.
MTN003B V2 Food Frequency Questionnaire	Yes	All items are interviewer-administered; participant responses must be recorded directly onto the form.
MTN-003B Physical Activity Questionnaire	Yes	All items are interviewer-administered; participant responses must be recorded directly onto the form.
MTN003B V2 Physical Activity Questionnaire	Yes	All items are interviewer-administered; participant responses must be recorded directly onto the form.
MTN-003B DXA Scan	No	All items should be completed based on source data recorded on other VOICE and MTN-003B source documents.
MTN003B V2 DXA Scan	Mixed	The DXA machine report is source for item 1, items 3-5 BMD, T-scores, and Z-scores, and item 6. The form may be source for items 3-5 Severity Grade. Item 2 source is the age source document specified in VOICE and the MTN-003B source document for enrollment.
MTN-003B Missed Visit	Yes	Form may be source for all items.
MTN003B V2 Missed Visit	Yes	Form may be source for all items.
MTN003B V2 Contraceptives Log	Yes	Form may be source for all items.
MTN-003B Early Termination	No	All items should be completed based on source data recorded on other MTN-003B source documents.

MTN-003B Forms	Source?	Comments
MTN003B V2 Termination	No	All items should be completed based on source data recorded on other MTN-003B source documents.
MTN003B V2 Participant-reported Follow-up Medical and Menstrual History	Yes	Form may be source for all items.
LDMS Specimen Tracking Sheet (non-DataFax)	No	All items should be completed based on source data recorded on other MTN-003B source documents.

Section Appendix 18-5
MTN-003B Informed Consent Comprehension Checklist

Section Appendix 18-6
MTN-003B Visit Checklists

Section Appendix 18-7
MTN-003B Case Report Forms

Section Appendix 18-8
MTN-003B Data Communiqués