

# **MTN-003 Study-Specific Procedures Manual**

## **Table of Contents**

---

### **Section 1. Introduction**

|     |  |     |
|-----|--|-----|
| 1.1 | Sources of Procedural Information..... | 1-1 |
| 1.2 | Investigator Responsibilities .....    | 1-1 |
| 1.3 | Study Activation Process.....          | 1-2 |

### **Section 2. Protocol**

### **Section 3. Documentation Requirements**

|       |  |     |
|-------|--|-----|
| 3.1   | Essential Documents .....  | 3-1 |
| 3.2   | Participant Case History Documentation .....                                       | 3-2 |
| 3.2.1 | Case History Contents .....  | 3-2 |
| 3.2.2 | Concept of Source Data and Source Documentation .....                              | 3-3 |
| 3.2.3 | Document Organization .....  | 3-5 |
| 3.3   | Study Product Accountability, Chain of Custody, and Dispensing Documentation ..... | 3-6 |
| 3.4   | Record Retention Requirements.....   | 3-8 |

### **Section 4. Participant Accrual**

|          |   |      |
|----------|---|------|
| 4.1      | Study Accrual Plan and Site-Specific Accrual Targets .....                  | 4-1  |
| 4.2      | Screening and Enrollment .....  | 4-2  |
| 4.2.1    | Definition of Screening .....   | 4-2  |
| 4.2.1.1  | Assessment of Acute HIV Infection Prior to Enrollment .....                 | 4-7  |
| 4.2.2    | Screening Visit Locations .....   | 4.7  |
| 4.2.3    | Definition of Enrollment .....  | 4-7  |
| 4.2.4    | Screening and Enrollment Timeframe.....                                     | 4-8  |
| 4.2.5    | Enrollment Split Visits .....   | 4-9  |
| 4.2.6    | Screening and Enrollment Logs .....   | 4-9  |
| 4.2.7    | Assignment of Participant ID Numbers .....                                  | 4-10 |
| 4.2.8    | Screening HIV Testing.....  | 4-10 |
| 4.2.9    | Eligibility Screening Scenarios .....                                       | 4-11 |
| 4.2.10   | Random Assignment .....   | 4-11 |
| 4.2.10.1 | Overview .....  | 4-11 |
| 4.2.10.2 | Participant-Specific Procedures.....  | 4-17 |
| 4.3      | Product Use Instructions, First Product Use, and Adherence Counseling ..... | 4-18 |

### **Section 5. Informed Consent**

|       |  |     |
|-------|--|-----|
| 5.1   | Overview of Informed Consent Requirements and Procedures .....   | 5-1 |
| 5.2   | Informed Consent for Screening .....   | 5-3 |
| 5.3   | Informed Consent for Enrollment .....  | 5-3 |
| 5.3.1 | Informed Consent Process for Participants who Resume Study Participation After Voluntary Withdrawal..... | 5-4 |

|       |   |      |
|-------|---|------|
| 5.3.2 | Informed Consent Support Materials .....  | 5-4  |
| 5.3.3 | Comprehension Assessment.....   | 5-8  |
| 5.4   | Informed Consent for Specimen Storage and Possible Future Research Testing .....            | 5-10 |
| 5.5   | Documenting the Informed Consent Process .....  | 5-10 |
| 5.6   | Ongoing Assessment of Participant Comprehension .....                                       | 5-11 |
| 5.6.1 | Frequency of Ongoing Assessment .....   | 5-11 |
| 5.6.2 | Administering the Ongoing Assessment .....  | 5-12 |
| 5.6.3 | Responding to Participant Information Needs After Administering the Ongoing Assessment..... | 5-12 |
| 5.6.4 | Documenting the Ongoing Assessment .....  | 5-12 |

## **Section 6. Participant Follow-up**

|         |   |      |
|---------|---|------|
| 6.1     | Study Follow-up Plan and Participant Retention Targets .....                      | 6-1  |
| 6.2     | Types of Follow-up Visits .....   | 6-2  |
| 6.3     | Follow-up Visit Scheduling.....   | 6-2  |
| 6.3.1   | Target Visit Dates.....   | 6-2  |
| 6.3.2   | Visit Windows.....  | 6-2  |
| 6.3.3   | Visits Conducted Over Multiple Days: “Split Visits” .....                         | 6-4  |
| 6.3.3.1 | Study Product Considerations During Split Visits .....                            | 6-5  |
| 6.3.4   | Missed Visits .....   | 6-6  |
| 6.4     | Follow-up Visit Locations.....  | 6-6  |
| 6.5     | Follow-up Visit Procedures.....   | 6-10 |
| 6.6     | HIV Testing During Follow-Up .....  | 6-13 |
| 6.7     | Study Product Return, Re-Supply, and Re-Issue During Follow-up.....               | 6-15 |
| 6.7.1   | Study Product Return .....  | 6-16 |
| 6.7.2   | Study Product Re-Supply .....   | 6-19 |
| 6.7.3   | Study Product Re-Issue .....  | 6-23 |
| 6.8     | Modified Follow-up Procedures for Participants Who Become Pregnant .....          | 6-25 |
| 6.9     | Modified Follow-up Procedures for Participants Infected with Hepatitis B .....    | 6-26 |
| 6.10    | Modified Follow-up Procedures for Participants Who Become Infected with HIV ..... | 6-27 |
| 6.11    | Participant Transfers.....  | 6-32 |
| 6.12    | Early Terminations Prior to the Expected PUEV .....                               | 6-33 |
| 6.12.1  | Early Terminations After the PUEV .....   | 6-33 |
| 6.13    | Resumption of Study Participation After Voluntary Withdrawal .....                | 6-34 |

## **Section 7. Visit Checklists**

|     |                               |     |
|-----|-------------------------------|-----|
| 7.1 | Use of Visit Checklists ..... | 7-1 |
| 7.2 | Sequence of Procedures.....   | 7-2 |

## **Section 8. Participant Retention**

|     |   |     |
|-----|---|-----|
| 8.1 | Retention Definitions .....                     | 8-1 |
| 8.2 | Retention Requirements .....                    | 8-2 |
| 8.3 | Retention SOPs.....                             | 8-3 |
| 8.4 | Obtaining and Updating Locator Information..... | 8-3 |
| 8.5 | Retention Tips .....                            | 8-4 |

## **Section 9. Study Product Considerations for Non-Pharmacy Staff**

|       |  |      |
|-------|--|------|
| 9.1   | Responsibilities and Obligations with Regard to Blinding .....                                     | 9-1  |
| 9.2   | Study Product Identification and Terminology .....   | 9-3  |
| 9.3   | Study Product Regimens .....   | 9-3  |
| 9.4   | Instructions for Inserting Study Gel and Taking Study Tablets .....                                | 9-4  |
| 9.5   | Dispensing Study Products During On-Site Visits.....   | 9-5  |
| 9.5.1 | Dispensing from the Pharmacy Directly to Participants .....  | 9-6  |
| 9.5.2 | Dispensing from the Pharmacy to Clinic Staff.....  | 9-6  |
| 9.5.3 | Dispensing from the Pharmacy to Runners for Transfer to Clinic Staff .....                         | 9-7  |
| 9.6   | Dispensing Study Products and Collecting Unused Study Products at In-Home Follow-Up Visits.....    | 9-7  |
| 9.6.1 | Delivering Study Products During an In-Home Visit for a Participant Who Left the Clinic Early..... | 9-9  |
| 9.7   | Dispensing More Than a 60-Day Supply of Study Product .....  | 9-10 |
| 9.8   | Study Product Returns.....   | 9-11 |
| 9.9   | Study Product Retrieval.....   | 9-12 |

## **Section 10. Clinical Considerations**

|        |  |       |
|--------|--|-------|
| 10.1   | Baseline Medical/Menstrual History and Ascertainment of Concomitant Medications 10-1 |       |
| 10.1.1 | Baseline Medical/Menstrual History .....   | 10-1  |
| 10.1.2 | Initial Ascertainment of Concomitant Medications.....                                | 10-4  |
| 10.1.3 | Pre-Existing Conditions.....   | 10-5  |
| 10.2   | Interval Medical/Menstrual History and Updating of Concomitant Medications .....     | 10-6  |
| 10.2.1 | Interval Medical/Menstrual History .....   | 10-6  |
| 10.2.2 | Updating Concomitant Medications Information.....                                    | 10-7  |
| 10.3   | Hepatitis B Vaccination.....   | 10-7  |
| 10.4   | Physical Exams.....  | 10-8  |
| 10.4.1 | Weight .....   | 10-8  |
| 10.4.2 | Height .....   | 10-9  |
| 10.4.3 | Blood Pressure.....  | 10-10 |
| 10.5   | Pelvic Exams .....   | 10-11 |
| 10.5.1 | Overview .....   | 10-11 |
| 10.5.2 | Detailed Procedural Instructions .....   | 10-12 |
| 10.5.3 | Documentation of Findings .....  | 10-14 |
| 10.6   | Genital Bleeding Assessment.....   | 10-18 |
| 10.6.1 | Genital Bleeding Assessment for Pregnant Participants .....                          | 10-18 |
| 10.6.2 | Participant Reports of Genital Bleeding.....   | 10-20 |
| 10.6.3 | Clinician Assessment of Genital Bleeding .....                                       | 10-20 |
| 10.6.4 | Documentation of Genital Bleeding .....  | 10-24 |
| 10.7   | STI/RTI Management.....  | 10-27 |
| 10.7.1 | STI/RTI Treatment .....  | 10-27 |
| 10.7.2 | Screening and Enrollment Considerations .....  | 10-30 |
| 10.7.3 | Adverse Event Reporting Considerations .....   | 10-31 |
| 10.8   | Pap Smear Management.....  | 10-32 |
| 10.9   | Urinary Tract Infections .....   | 10-33 |
| 10.10  | Contraception Considerations .....   | 10-34 |
| 10.11  | Pregnancy and Breastfeeding Considerations .....                                     | 10-35 |

|       |  |       |
|-------|--|-------|
| 10.12 | Care and Support for Seroconverters .....    | 10-36 |
| 10.13 | Calculating Creatinine Clearance Rates ..... | 10-36 |
| 10.14 | Management of Laboratory Test Results .....  | 10-37 |
| 10.15 | Clinical and Product Use Management .....    | 10-37 |

## **Section 11. Adverse Event Reporting and Safety Monitoring**

|        |  |       |
|--------|--|-------|
| 11.1   | Definitions and General Reporting Guidance .....                     | 11-1  |
| 11.1.1 | Adverse Event (AE) .....   | 11-1  |
| 11.1.2 | Reportable Adverse Events .....                                      | 11-2  |
| 11.1.3 | Serious Adverse Events (SAEs)/ Expedited Adverse Events (EAEs) ..... | 11-7  |
| 11.1.4 | Reporting EAES.....  | 11-8  |
| 11.2   | Adverse Event Terminology .....                                      | 11-10 |
| 11.3   | Adverse Event Severity .....   | 11-13 |
| 11.4   | Adverse Event Relationship to Study Product .....                    | 11-18 |
| 11.5   | Adverse Event Outcomes and Follow-Up Information .....               | 11-19 |
| 11.6   | Reporting Recurrent Adverse Events .....                             | 11-22 |
| 11.7   | Social Harms .....   | 11-23 |
| 11.8   | MTN-003 Safety Monitoring, Review, and Oversight.....                | 11-24 |
| 11.9   | Safety Distributions from DAIDS .....                                | 11-25 |

## **Section 12. Counseling Considerations**

|        |   |       |
|--------|---|-------|
| 12.1   | HIV Counseling.....                                   | 12-1  |
| 12.1.1 | Risk Reduction Counseling .....                       | 12-4  |
| 12.1.2 | HIV Sexual Risk and Risk Reduction .....              | 12-5  |
| 12.2   | Contraception Counseling .....                        | 12-7  |
| 12.3   | Study Product Adherence Counseling — Enrollment ..... | 12-8  |
| 12.3.1 | Product Use Instructions .....                        | 12-8  |
| 12.3.2 | First Product Use .....                               | 12-9  |
| 12.3.3 | Study Product Adherence Counseling - Enrollment ..... | 12-10 |
| 12.4   | Study Product Adherence Counseling — Follow-up .....  | 12-12 |
| 12.5   | Product Use Instructions — Follow-up .....            | 12-12 |

## **Section 13. Laboratory Considerations**

|        |  |      |
|--------|--|------|
| 13.1   | Overview and General Guidance.....                     | 13-1 |
| 13.2   | Specimen Labeling .....                                | 13-2 |
| 13.3   | Procedures for Specimens That Cannot be Evaluated..... | 13-2 |
| 13.4   | Use of LDMS .....                                      | 13-2 |
| 13.5   | Urine Testing.....                                     | 13-4 |
| 13.5.1 | Specimen Collection .....                              | 13-4 |
| 13.5.2 | Pregnancy Testing .....                                | 13-4 |
| 13.5.3 | Dipstick Urinalysis .....                              | 13-5 |
| 13.5.4 | Chlamydia and Gonorrhea Testing.....                   | 13-5 |
| 13.6   | Blood Testing .....                                    | 13-6 |
| 13.6.1 | Specimen Collection and Initial Processing .....       | 13-6 |
| 13.6.2 | HIV Testing.....                                       | 13-6 |
| 13.6.3 | Syphilis Testing.....                                  | 13-8 |
| 13.6.4 | Hepatitis B Surface Antigen and Surface Antibody.....  | 13-8 |

|         |   |       |
|---------|---|-------|
| 13.6.5  | Hematology Testing .....  | 13-8  |
| 13.6.6  | Serum Chemistries .....   | 13-9  |
| 13.6.7  | Plasma Archive .....  | 13-9  |
| 13.6.8  | CD4+ T Cell Count .....   | 13-10 |
| 13.6.9  | HIV RNA PCR.....  | 13-10 |
| 13.6.10 | HSV-1 and HSV-2 Testing.....                                    | 13-11 |
| 13.6.11 | Peripheral Blood Mononuclear Cells (PBMC) for Drug Levels ..... | 13-11 |
| 13.7    | Testing of Vaginal and Cervical Specimens .....                 | 13-12 |
| 13.7.1  | Vaginal pH .....  | 13-12 |
| 13.7.2  | Wet Mount for Candidiasis .....                                 | 13-13 |
| 13.7.3  | Rapid Test for Bacterial Vaginosis (BV) .....                   | 13-13 |
| 13.7.4  | Rapid Test for Trichomoniasis.....                              | 13-13 |
| 13.7.5  | Vaginal Gram Stain.....   | 13-14 |
| 13.7.6  | Papanicolaou (Pap) Test.....                                    | 13-15 |
| 13.7.7  | Vaginal Swabs for Biomarker Analysis .....                      | 13-15 |
| 13.7.8  | Endocervical Swabs for Biomarker Analysis.....                  | 13-15 |

## **Section 14. Data Collection**

|        |   |       |
|--------|---|-------|
| 14.1   | DataFax Overview.....                                   | 14-1  |
| 14.2   | DataFax Form Completion.....                            | 14-2  |
| 14.2.1 | General Guidelines.....                                 | 14-2  |
| 14.2.2 | How to Mark Response Boxes.....                         | 14-3  |
| 14.2.3 | How to Record Numbers .....                             | 14-3  |
| 14.2.4 | How to Record Dates .....                               | 14-4  |
| 14.2.5 | How to Record Time .....                                | 14-5  |
| 14.2.6 | Data Corrections and Additions .....                    | 14-6  |
| 14.2.7 | How to Handle Missing and Unknown Data.....             | 14-7  |
| 14.3   | MTN-003 Study-Specific Data Collection Information..... | 14-7  |
| 14.3.1 | Participant ID numbers (PTIDs).....                     | 14-8  |
| 14.3.2 | Study Visit Timing .....                                | 14-8  |
| 14.3.3 | Visit Codes and Page Numbers .....                      | 14-13 |
| 14.3.4 | Staff Initials/Date .....                               | 14-16 |
| 14.3.5 | Case Report Form Completion Schedule .....              | 14-16 |
| 14.3.6 | Site Review of DataFax Forms .....                      | 14-22 |
| 14.3.7 | Faxing DataFax Forms .....                              | 14-22 |
| 14.3.8 | Non-DataFax Forms .....                                 | 14-23 |
| 14.4   | Form Supply and Storage .....                           | 14-23 |
| 14.4.1 | Form and Specimen Label Supply .....                    | 14-23 |
| 14.4.2 | Form Storage .....                                      | 14-23 |
| 14.5   | Completing Interviewer-administered Forms.....          | 14-24 |
| 14.6   | Form Completion Instructions.....                       | 14-27 |
| 14.7   | Case Report Forms .....                                 | 14-30 |

## **Section 15. Data Communiqués**

## **Section 16. ACASI Users Manual**

## **Section 17. Study Reporting Plan**

|      |                                |      |
|------|--------------------------------|------|
| 17.1 | Purpose of Reporting Plan..... | 17-1 |
|------|--------------------------------|------|

|         |   |      |
|---------|---|------|
| 17.2    | Study Reports .....                                   | 17-1 |
| 17.2.1  | Data Quality Control (QC) Report .....                | 17-3 |
| 17.2.2  | Clinical Data Quality Control (CQC) Queries .....     | 17-3 |
| 17.2.3  | Unresolved Adverse Experiences Listing .....          | 17-3 |
| 17.2.4  | Specimen Monitoring Report .....                      | 17-3 |
| 17.2.5  | Enrollment and Retention Report .....                 | 17-3 |
| 17.2.6  | Visit Adherence and Procedure Completion Report ..... | 17-4 |
| 17.2.7  | Product Adherence Report .....                        | 17-4 |
| 17.2.8  | Site Data Management Quality Report .....             | 17-4 |
| 17.2.9  | Safety (PSRT) Reports .....                           | 17-4 |
| 17.2.10 | Study Monitoring Committee (SMC) Report .....         | 17-4 |
| 17.2.11 | Data Safety Monitoring Board (DSMB) Report .....      | 17-5 |
| 17.2.12 | Network Lab Assay Results Report .....                | 17-5 |

## **Section 18. Bone Mineral Density Substudy**

|         |   |       |
|---------|---|-------|
| 18.1    | Introduction .....  | 18-2  |
| 18.2    | Protocol .....  | 18-2  |
| 18.3    | Documentation Requirements .....  | 18-2  |
| 18.3.1  | Essential Documents .....   | 18-2  |
| 18.3.2  | Participant Case History Documentation .....  | 18-2  |
| 18.3.3  | Study Product Accountability, Chain of Custody, Dispensing Documentation .....  | 18-3  |
| 18.3.4  | Record Retention Requirements .....   | 18-3  |
| 18.4    | Participant Accrual .....   | 18-3  |
| 18.4.1  | Study Accrual Plan and Site-Specific Accrual Targets .....  | 18-3  |
| 18.4.2  | Assignment of Participant ID Numbers .....  | 18-4  |
| 18.4.3  | Screening: Definition and Procedures .....  | 18-4  |
| 18.4.4  | Definition of Enrollment .....  | 18-6  |
| 18.4.5  | Screening and Enrollment Timeframe .....  | 18-6  |
| 18.4.6  | Screening and Enrollment Logs .....   | 18-6  |
| 18.5    | Informed Consent .....  | 18-7  |
| 18.6    | Participant Follow-up .....   | 18-7  |
| 18.6.1  | Follow-up Visit Scheduling .....  | 18-7  |
| 18.6.2  | Follow-up Visit Procedures .....  | 18-10 |
| 18.6.3  | Modified Follow-up Procedures for Participants Who Temporarily Hold or<br>Permanently Discontinue Study Product ..... | 18-10 |
| 18.7    | Visit Checklists .....  | 18-10 |
| 18.8    | Participant Retention .....   | 18-10 |
| 18.9    | Study Product Considerations .....  | 18-10 |
| 18.10   | DXA Scanning Procedures and Other Clinical Considerations .....   | 18-10 |
| 18.11   | Adverse Event Reporting and Safety Monitoring .....   | 18-13 |
| 18.12   | Counseling Considerations .....   | 18-14 |
| 18.13   | Laboratory Considerations .....   | 18-16 |
| 18.13.1 | Urine Collection and Storage .....  | 18-16 |
| 18.13.2 | Blood Collection and Serum Storage .....  | 18-16 |
| 18.13.3 | Guide to Logging in MTN-003B Specimens in LDMS .....  | 18-16 |
| 18.14   | Data Collection .....   | 18-16 |
| 18.14.1 | PTIDs .....   | 18-16 |
| 18.14.2 | Study Visit Timing .....  | 18-17 |
| 18.14.3 | Visit Codes .....   | 18-17 |

|   |       |
|---|-------|
| 18.14.4 Case Report Form Completion Schedule .....          | 18-20 |
| 18.14.5 Form and Specimen Label Supply .....                | 18-20 |
| 18.14.6 Form Storage .....                                  | 18-21 |
| 18.14.7 How to Complete Interviewer-Administered Forms..... | 18-21 |
| 18.14.8 Form Completion Instructions.....                   | 18-21 |
| 18.14.9 Case Report Forms .....                             | 18-21 |
| 18.15 Data Communiqués .....                                | 18-21 |

## **Section 19: Household and Community Factors Associated with VOICE Product Adherence Substudy (VOICE-C)**

|   |       |
|---|-------|
| 19.1 Introduction .....   | 19-2  |
| 19.2 Protocol .....   | 19-3  |
| 19.3 Documentation Requirements .....   | 19-3  |
| 19.3.1 Essential Documents .....  | 19-3  |
| 19.3.2 Participant File Documentation.....  | 19-4  |
| 19.3.2.1 Participant File Contents .....  | 19-4  |
| 19.3.2.2 Concept of Source Data and Source Documentation .....                                | 19-5  |
| 19.3.2.3 Document Organization.....   | 19-6  |
| 19.3.3 Record Retention Requirements.....   | 19-8  |
| 19.4 Participant Accrual .....  | 19-8  |
| 19.4.1 Study Accrual Plan and Site-Specific Accrual Targets .....                             | 19-8  |
| 19.4.2 Assignment of Participant ID Numbers.....  | 19-11 |
| 19.4.3 Screening Definition and Eligibility Criteria.....                                     | 19-11 |
| 19.4.4 Definition of Enrollment .....   | 19-16 |
| 19.4.5 Screening and Enrollment Timeframe.....  | 19-17 |
| 19.4.6 Screening and Enrollment Logs .....  | 19-17 |
| 19.4.7 Weekly VOICE-C Progress Reports .....  | 19-18 |
| 19.5 Informed Consent .....   | 19-18 |
| 19.6 Visit Procedures .....   | 19-19 |
| 19.6.1 Visit Scheduling .....   | 19-19 |
| 19.6.2 Data Collection Procedures .....   | 19-21 |
| 19.6.3 Modified Procedures for Participants Who Miss Scheduled<br>Data Collection Visits..... | 19-24 |
| 19.7 Visit Checklists.....  | 19-24 |
| 19.8 Participant Retention .....  | 19-24 |
| 19.9 Reporting of Social Harms, Adverse Events and Adherence Issues .....                     | 19-24 |
| 19.10 Counseling Considerations.....  | 19-26 |
| 19.11 Data Collection.....  | 19-26 |
| 19.11.1 PTIDs.....  | 19-26 |
| 19.11.2 Study Visit Timing .....  | 19-26 |
| 19.11.3 Visit Codes .....   | 19-27 |
| 19.11.4 Case Report Form Completion Schedule .....  | 19-28 |
| 19.11.5 Form Supply .....   | 19-28 |
| 19.11.6 Form Storage .....  | 19-28 |
| 19.11.7 How to Complete Interviewer Administered Forms .....                                  | 19-28 |
| 19.11.8 Form Completion Instructions.....   | 19-29 |
| 19.11.9 Case Report Forms .....   | 19-29 |
| 19.11.10 Data Flow: Quantitative Data Management .....  | 19-29 |
| 19.11.11 Data Flow: Qualitative Data Management .....   | 19-30 |