

MTN-024/IPM 031 Study-Specific Procedures Manual

Table of Contents

Section 1. Introduction

1.1	Procedural Specifications	1-1
1.2	Sources of Procedural Information	1-1
1.3	Investigator Responsibilities.....	1-2
1.4	Study Activation Process	1-2
1.5	IRB/EC Submission	1-3

Section 2. Documentation Requirements

2.1	Essential Documents	2-1
2.2	Participant Research Records	2-1
2.2.1	Concept of Source Data and Source Documentation	2-2
2.2.2	Required Source Documentation	2-2
2.2.2.1	Chart Notes	2-3
2.2.2.2	Visit Checklists	2-3
2.2.2.3	Laboratory	2-4
2.2.2.4	Case Report Forms (CRFs)	2-5
2.2.3	Protocol Deviations	2-5
2.2.4	Document Organization and Participant Confidentiality	2-6
2.3	Study Product Accountability, Chain of Custody, and Dispensing Documentation in the Pharmacy.....	2-6
2.4	Record Retention Requirements.....	2-7
2.5	Appendices	2-8
	Section Appendix 2-1- Source Documentation of Study Procedures.....	2-8
	Section Appendix 2-2 - CRFs Used as Source Documents.....	2-11
	Section Appendix 2-3 - CRFs Not Used as Source Documents	2-12

Section 3. Participant Accrual, Screening and Enrollment

3.1	Pre-Screening Procedures	3-1
3.2	Study Accrual Plan and Site-Specific Accrual Targets.....	3-1
3.3	Participant Accrual SOP	3-2
3.4	Screening and Enrollment.....	3-2
3.4.1	Screening and Enrollment Timeframe.....	3-2
3.4.2	Screening and Enrollment Logs	3-2
3.4.3	Definition of Screening	3-3
3.4.4	Eligibility Determination SOP	3-3
3.4.5	Screening Procedures.....	3-3
3.4.6	Assignment of Participant ID Numbers	3-4
3.4.7	Participants Found to be Ineligible (Screen Failures)	3-5
3.5	Enrollment.....	3-5
3.5.1	Definition of Enrollment	3-5
3.5.2	Enrollment Procedures.....	3-5
3.5.3	Random Assignment/Prescription Assignment	3-7

Section 4. Informed Consent

4.1	Overview of Informed Consent Requirements and Procedures	4-1
4.2	Site-Specific Informed Consent Forms	4-1
4.3	SOP for Obtaining Informed Consent.....	4-2
4.4	Informed Consent for Screening and Enrollment	4-2
4.4.1	Informed Consent for Specimen Storage and Possible Future Research Testing.....	4-2
4.4.2	Informed Consent for PK and Intensive PK Subset	4-3
4.5	Informed Consent Support Materials	4-5
4.6	Comprehension Assessment.....	4-5
4.6.1	Administration of Comprehension Assessment	4-6
4.7	Documenting the Informed Consent Process	4-7
4.8	Ongoing Assessment of Participant Comprehension	4-7

Section 5. Study Procedures

5.1	Study Follow-up Plan and Participant Retention Targets	5-1
5.2	Types of Follow-up Visits	5-1
5.3	Follow-up Visit Procedures	5-1
5.3.1	1-Week and 13-Week Follow-Up Phone Calls	5-1
5.3.2	Split Visit Procedures	5-2
5.3.3	Missed Visits	5-2
5.4	Modified Procedures for Participants Who Become HIV-infected (Per Appendix II)	5-2
5.5	Modified Procedures for Participants Who Become Pregnant	5-2
5.6	Modified Procedures for Visits When Product Is Not Dispensed (Participant is on a Clinical Hold/Discontinuation or Refuses to Accept Study Product).....	5-3
5.7	Participant Transfers	5-3
5.8	Voluntary Withdrawal/Early Termination	5-4
5.9	12-Week Final Clinic Visit/Early Termination.....	5-4
5.9.1	Participant Locator Information	5-5
5.9.2	AE Management and Documentation	5-5
5.9.3	Referral to Non-Study Service Providers	5-5
5.9.4	Post-Study Contact	5-5
5.10	Participant Retention	5-6
5.10.1	Retention Definitions	5-6
5.10.2	Retention Requirements	5-6
5.10.3	Retention SOP	5-6
5.10.4	Obtaining and Updating Locator Information	5-7
5.10.5	Retention Tips	5-7

Section 6. Study Product Considerations for Non-Pharmacy Staff

6.1	Responsibilities and Obligations with Regard to Blinding	6-1
6.1.1	Emergency Unblinding Process	6-1
6.2	Random Assignment.....	6-2
6.3	Dispensing Study Product.....	6-3
6.3.1	Chain of Custody.....	6-3
6.3.2	Initial Vaginal Ring Dispensing - Prescription Overview	6-3
6.4	Study Product Accountability	6-4
6.4.1	Documentation of Ring Provision and Ring Collection.....	6-4
6.5	Duration of Use of Each Vaginal Ring	6-5

6.6 Vaginal Ring Re-supply During Follow-up	6-5
6.6.1 Vaginal Ring Hold and Resumption	6-7
6.6.2 Permanent Discontinuation	6-7
6.7 Study Product Retrieval	6-7
6.8 Study Product Considerations During Split Visits	6-8
6.9 Study Product Considerations During Missed or Late Visits	6-8
6.10 Appendices	6-9
Section Appendix 6-1: MTN-024/IPM 031 PRESCRIPTION.....	6-9
Section Appendix 6-2: MTN-024/ IPM 031 VAGINAL RING REQUEST SLIP	6-10
Section Appendix 6-3: MTN-024/IPM 031Randomization Envelope Tracking Record	6-11

Section 7. Clinical Considerations

7.1 Baseline Medical Conditions [Pre-Existing Conditions] and Medications	7-1
7.1.1 Pre-existing Conditions Collection at the Screening Visit	7-1
7.1.2 Participant-Reported Conditions	7-1
7.1.3 Pre-existing Conditions Review and Updated at the Enrollment Visit.....	7-1
7.1.4 Baseline Medications	7-2
7.1.4.1 Study-approved Lubricant	7-2
7.2 Medical and Medication History Review at Follow Up	7-3
7.2.1 Participant-reported Follow-up Medical History	7-3
7.2.2 Review of Medications History	7-3
7.3 Physical Exams	7-4
7.3.1 Consideration at Screening and Enrollment.....	7-4
7.3.2 Physical Exams Conducted at Follow-up.....	7-4
7.3.3 Weight	7-4
7.3.4 Height.....	7-5
7.3.5 Blood Pressure.....	7-5
7.4 Pelvic Exam Overview	7-5
7.4.1 Pelvic Exam Technique.....	7-5
7.4.2 Detailed Procedural Instructions	7-5
7.4.3 PK Subset and Intensive PK Subset	7-7
7.4.3.1 Vaginal Fluid Collection (PK Subset)	7-7
7.4.3.2 Cervical Biopsies Collection (Intensive PK Subset)	7-7
7.4.4 Documentation Findings	7-8
7.5 Genital Bleeding Assessment	7-9
7.6 STI/RTI/UTI	7-9
7.6.1 Considerations at Screening/Enrollment.....	7-9
7.6.2 STI/RTI/UTI Diagnosis	7-10
7.6.3 STI/RTI/UTI Management.....	7-11
7.7 Vaginal Discharge	7-11
7.8 Management of Laboratory Test Results	7-11
7.9 Clinical and Product Use Management	7-12

Section 8. Adverse Event Reporting and Safety Monitoring

8.1 Definitions and General Reporting Guidance	8-1
8.1.1 Adverse Event (AE).....	8-1
8.1.2 Reporting Adverse Events	8-1
8.1.3 Serious Adverse Events (SAEs)	8-2
8.1.4 Reporting Adverse Events in an Expedited Manner (EAE Reporting)	8-2
8.2 Adverse Event Terminology	8-5
8.2.1 Reporting Genital, Genitourinary, and Reproductive System AEs.....	8-6

8.2.2 Reporting Abdominal Pain as an AE	8-8
8.2.3 Reporting Laboratory Abnormalities as AEs	8-8
8.2.4 Postmenopausal Considerations	8-9
8.3 Adverse Event Severity Grading.....	8-9
8.4 Adverse Event Relationship Assessment.....	8-10
8.5 Adverse Event Outcomes and Follow-Up Information: During Study Participation.....	8-11
8.6 Adverse Event Outcomes and Follow-Up Information: After Study Termination	8-11
8.6.1 Reporting Recurrent Adverse Events.....	8-12
8.7 Social Harms.....	8-12
8.8 Safety Distributions from DAIDS	8-13
8.9 Safety Monitoring, Review, and Oversight.....	8-13
8.10 Appendices	8-15
Section Appendix 8-1: Roles and Responsibilities of the PSRT	8-15

Section 9. Counseling Considerations

9.1 HIV Pre and Post-Test Counseling	9-1
9.2 HIV/STI Risk Reduction and Male Condom Counseling	9-2
9.3 Ring Use Adherence Counseling.....	9-3
9.3.1 First Product Use	9-4
9.3.2 Clinician Instructions for Checking Ring Placement.....	9-4
9.4 Follow-up Study Product Use Adherence Counseling	9-5
9.5 Protocol Adherence Counseling.....	9-6
9.5.1 Biopsy Procedural Counseling	9-6

Section 10. Laboratory Considerations

10.1 Overview and General Guidance	10-2
Table 10-1: Overview of Laboratory Testing Locations, Specimens, and Methods	10-3
Table 10-2: Overview of Specimens for Storage and Shipment.....	10-4
Table 10-3: Overview of Laboratory Tests by visit	10-5
10.2 Specimen Labeling.....	10-6
10.3 Procedures for Specimens that cannot be evaluated.....	10-6
10.4 Use of LDMS	10-6
Figure 10-1: LDMS Entry Screen	10-7
10.4.1: Weight measurements in LDMS.....	10-8
Figure 10-2: LDMS Weight Entry Screen	10-8
Table 10-4 LDMS Specimen Management Guide.....	10-9
Table 10-5 LDMS Codes	10-10
10.4.2 Off-Hours Contact Information.....	10-11
10.5 Urine Testing for CT/GC (Chlamydia Trachomatis and Neisseria Gonorrhoea), Pregnancy, Urinary Tract Infection.	10-11
10.5.1 Specimen Collection	10-11
10.5.2 Testing for Chlamydia Trachomatis and Neisseria Gonorrhoeae by NAAT	10-11
10.5.3 Pregnancy Testing	10-12
10.5.4 Urinary Tract Infection.....	10-12
10.6 Blood Specimens for Chemistry, FSH, Hematology, HIV testing, Syphilis, Plasma Archive, Blood Dapivirine.....	10-12
10.6.1 Specimen Collection and Initial Processing	10-12
10.6.2 Chemistry (Alanine transaminase, Aspartate aminotransferase, and Creatinine), FSH (Follicle Stimulating Hormone), and Hematology (CBC with Platelets)	10-13
10.6.3 HIV Testing	10-13
10.6.4 Syphilis Testing	10-13

10.6.5 Plasma Archive	10-14
10.6.6 Blood for PK (Dapivirine).....	10-15
10.7 Cervicovaginal Lavage (CVL) for Biomarkers, Aliquot storage, and Cell Pellet.	10-16
10.7.1 Collection procedure for CVL	10-16
10.7.2 Processing of the CVL Cell Pellet and Supernatant for biomarker and storage	10-17
10.7.3 CVL Biomarkers	10-17
10.7.4 CVL Cell Pellet	10-18
10.8 Vaginal Specimens for Herpes Lesions, Gram Stain, Microbiology Culture, Vaginal Fluid pH, Vaginal Wet Mount, Trichomonas, Swab for Biomarkers, Vaginal Secretions for PK, and IVR for PK.....	10-18
10.8.1 Herpes Lesion Testing	10-18
10.8.2 Gram Stains on Vaginal Fluid	10-18
10.8.3 Microbiology: Vaginal Swab for Quantitative Culture	10-20
10.8.4 Vaginal Fluid pH.....	10-21
10.8.5 Vaginal Fluid Wet Mount Testing if indicated for BV and Yeast (KOH).....	10-21
Table 10-6 Summary of Wet Prep Assessments and Diagnostic Criteria	10-21
10.8.6 Rapid Test for Trichomonas.....	10-22
10.8.7 NAAT Chlamydia and Gonorrhea Testing.....	10-23
10.8.8 Vaginal Swab for Biomarkers.....	10-23
10.8.9 Vaginal Swab for PK.....	10-23
10.8.10 Testing of Intravaginal Ring (IVR)	10-25
Figure 10-3: 3"X5" amber Zippit pouch	10-25
10.9 Cervical Specimens for Biopsy PK, Cytobrush for Flow Cytometry, and Pap Test.....	10-26
10.9.1 Cervical Biopsy	10-26
10.9.2 Cytobrush for Flow Cytometry at Pittsburgh & Case Western sites	10-26
10.9.3 Papanicolaou (Pap) Test (*only if indicated)	10-28
10.10 Appendices	10-30
Section Appendix 10-1: HIV Antibody Testing Algorithm	10-30

Section 11. Data Collection

11.1 DataFax Overview	11-1
11.2 DataFax Form Completion.....	11-2
11.2.1 General Guidelines	11-2
11.2.2 How to Mark Response Boxes	11-3
11.2.3 How to Record Numbers	11-3
11.2.4 How to Record Dates	11-4
11.2.5 How to Record Time	11-5
11.2.6 Data Corrections and Additions	11-6
11.2.7 How to Handle Missing and Unknown Data	11-7
11.2.8 Non-DataFax Forms.....	11-7
11.2.9 Faxing Data Fax Forms.....	11-8
11.2.10 Form Storage	11-8
11.2.11 MTN Data Management SOP	11-8
11.3 Study-Specific Data Collection Information.....	11-9
11.3.1 Participant ID Numbers (PTIDs).....	11-9
11.3.2 Study Visit Timing	11-9
11.3.3 Visit Codes and Page Numbers	11-11
11.3.4 Staff Initials/Date	11-12
11.3.5 Form Supply.....	11-12
11.3.6 Case Report Form Completion Schedule	11-13
11.3.7 Completing Interviewer-administered Forms	11-14
11.3.8 Site Review (Quality Control) of DataFax Forms	11-14
11.3.9 MTN-024/IPM 031 QC Review Step #1	11-15
11.3.10 MTN-024/IPM 031 QC Review Step #2	11-15

11.4 Form-specific Completion Instructions.....	11-15
11.5 Case Report Forms	11-16

Section 12. Data Communiqués

Section 13. Study Reporting Plan

13.1 Study Reports	13-1
13.1.1 Data Quality Control (QC) Report	13-2
13.1.2 Clinical Data Quality Control (CQC) Report	13-3
13.1.3 Unresolved Adverse Experiences (AE) Listing	13-3
13.1.4 Unresolved Product Holds	13-3
13.1.5 LDMS Specimen Monitoring Report.....	13-3
13.1.6 Screen Out	13-3
13.1.7 Enrollment and Retention Report	13-3
13.1.8 Visit Adherence and Procedure Completion Report	13-4
13.1.9 Site Data Management Quality Report	13-4
13.1.10 Data Summary Report	13-4
13.1.11 Protocol Safety Review Team (PSRT) Report	13-4
13.1.12 Network Lab Assay Results Report	13-4
13.1.13 Study Monitoring Committee (SMC) Report	13-5
13.1.14 Protocol Deviations	13-5

Section 14. Behavioral Measures

14.1 Overview	14-1
14.2 Troubleshooting	14-1
14.3 Equipment Requirements and Set-up	14-2
14.3.1 Keyboard and Mouse Use	14-2
14.4 Data Collection Instruments.....	14-2
14.4.1 Computer Assisted Self-Interview (CASI) questionnaires	14-2
14.4.1.1 Baseline Questionnaire	14-2
14.4.1.2 Follow-up Questionnaire	14-3
14.4.1.3 Exit Questionnaire	14-3
14.4.1.4 CASI Question-by-Question Instructions.....	14-4
14.4.2 In Depth Interview (IDI)	14-4
14.4.2.1 Scheduling the Interview	14-4
14.4.2.2 Preparing for the IDI	14-5
14.4.2.3 Initiating and Conducting the Video Interview	14-6
14.4.2.4 Safety Reporting.....	14-6
14.5 Qualitative Data Management	14-7
14.5.1 Audio Files	14-7
14.5.2 Interview Notes	14-7
14.5.3 Debriefing Reports	14-7
14.5.4 Transcription	14-8
14.5.5 File Naming Conventions	14-8
14.5.6 Data Tracking.....	14-8
14.5.7 Special Cases and Technical Issues	14-9
14.5.7.1 Technical Problems Preventing CASI Completion	14-9
14.5.7.2 Interrupted Visits	14-9
14.5.7.3 Management of Errors on CASI	14-9
14.6 Staff Training	14-9

14.7 Appendices	14-11
Section Appendix 14-1 Quick Tips for Web-Based Behavioral Assessments.....	14-11
Section Appendix 14-2 Quick Tips for In-Depth Interview.....	14-12
Section Appendix 14-3 Contact Information for In-Depth Interview Scheduling and Adverse Event/Social Harm Reporting to Clinical Sites	14-14