

MTN-016

**HIV Prevention Agent Pregnancy Exposure Registry:
EMBRACE Study**

Microbicide Trials Network

**Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US *Eunice Kennedy Shriver* National Institute of Child Health and Human
Development
US National Institutes of Health**

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HIV Prevention Agent Pregnancy Exposure Registry:
EMBRACE Study

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LIST OF ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immunodeficiency Syndrome
AP	anterior-posterior
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
BMD	bone mineral density
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
DAIDS	Division of AIDS
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EAE	expedited adverse event
EC	Ethics Committee
EMBRACE	Evaluation of Maternal and Baby outcome Registry After Chemoprophylactic Exposure
FDA	Food and Drug Administration
GCLP	Good Clinical Laboratory Practices
GCP	Good Clinical Practices
GEE	generalized estimating equation
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
IoR	Investigator of Record
IRB	Institutional Review Board
ISR	Interim Study Review
LDMS	Laboratory Data Management System
mL	milliliter
MTN	Microbicide Trials Network
NIAID	National Institute of Allergy and Infectious Disease
NICHD	<i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
PMTCT	prevention of mother-to-child transmission
PPD	Pharmaceutical Product Development, LLC
PrEP	pre-exposure prophylaxis
PTID	participant identification number
RSC	Regulatory Support Center
RNA	ribonucleic acid
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	Statistical Data Management Center
SOP	standard operating procedure(s)
SSP	Study-specific Procedures
UNAIDS	United Nations Joint Programme on HIV/AIDS
VOICE	Vaginal and Oral Interventions to Control the Epidemic (MTN-003)

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MTN-016

**HIV Prevention Agent Pregnancy Exposure Registry:
EMBRACE Study**

INVESTIGATOR SIGNATURE FORM

**Version 2.0
11 February 2014**

A Study of the Microbicide Trials Network (MTN)

Sponsored by:

Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Child Health and Human Development
US National Institutes of Health

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Investigator of Record Agreement, which I have also signed. I agree to maintain all study documentation for a minimum of three years after the study is closed, unless otherwise specified by the Division of AIDS (DAIDS) or the Microbicide Trials Network (MTN) Coordinating and Operations Center. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee for review prior to submission and made available to DAIDS.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Investigator of Record

Signature of Investigator of Record

Date

MTN-016

HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study

PROTOCOL SUMMARY

Short Title: EMBRACE (Evaluation of Maternal and Baby Outcome Registry After Chemoprophylactic Exposure)

Protocol Co-Chairs: Richard Beigi, MD, Samuel Kabwigu, MBChB, MMed

Sample Size: Approximately 550 pregnant women and approximately 400 live infants

Study Population:

1. Current or recent participants who became pregnant during HIV prevention trials, or who have or had planned exposures in pregnancy safety studies, provided pregnancy outcome was less than 1 year from the date of the EMBRACE Screening/Enrollment Visit
2. The infants resulting from those pregnancies, provided infants have not yet reached their 1-year birth date.

Study Sites: As determined by the MTN Executive Committee

Study Design: Prospective observational cohort

Study Duration: Until all enrolled participants have completed study participation, or as otherwise determined by the study sponsor

Primary Objectives

1. To compare adverse pregnancy and delivery outcomes between participant mothers assigned to an active agent with those of mothers assigned to placebo/control.
2. To compare the prevalence of major malformations identified in the first year of life between infants of mothers assigned to an active agent with those of infants of mothers assigned to placebo/control.

Primary Endpoints

1. Pregnancy and delivery outcomes:
 - delivery prior to 37 completed weeks of gestation
 - stillbirth or intrauterine fetal demise (≥ 20 weeks)
 - spontaneous abortion (< 20 weeks)
 - ectopic pregnancy
 - intrapartum hemorrhage
 - postpartum hemorrhage
 - non-reassuring fetal status
 - chorioamnionitis
 - hypertensive disorders of pregnancy
 - gestational diabetes
 - intrauterine growth restriction

2. Major malformations, defined as structural abnormalities with surgical, medical, or cosmetic importance.¹

Secondary Objectives

1. To compare growth parameters in the first year of life between infants of mothers assigned to an active agent with those of mothers assigned to placebo/control.
2. To evaluate the prevalence and persistence of HIV drug resistance mutations in plasma among HIV-infected infants.

Secondary Endpoints

1. Weight, length, and head circumference at birth, one month, six months and 12 months.
2. HIV-1 drug resistance mutations among infants who acquire HIV-1 infection

1 KEY ROLES

1.1 Protocol Identification

Protocol Title: HIV Prevention Agent Pregnancy Exposure Registry
MTN Protocol Number: MTN-016
Short Title: EMBRACE
Date: 11 February 2014

1.2 Funding Agencies, Sponsor and Monitor Identification

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2 INTRODUCTION

2.1 HIV/AIDS Prevention

According to the United Nations Joint Programme on HIV/AIDS (UNAIDS), approximately 34 million people worldwide were living with HIV in 2011². Widespread implementation of HIV-1 prevention services, including behavioral strategies, has had only modest impact on the rate of new HIV-1 infections in most populations, thus continued efforts to identify effective preventative modalities are needed. Many different approaches are being evaluated in clinical trials including HIV treatment as prevention³, combination HIV prevention⁴, behavioral interventions⁵, vaccines⁶, chemoprophylaxis⁷ and topical microbicides in various delivery systems.⁸ Clinical trials conducted by the Microbicide Trials Network (MTN) include Phase 1 and 2 safety trials of new compounds as well as larger, Phase 2B and 3 product efficacy trials.

2.2 Background

While pregnancy is a common exclusion criterion in trials of candidate HIV prevention agents, it does occur among participants even when contraception is provided by the trial. Additionally, some trials (e.g., MTN-002, MTN-008) have been designed to evaluate the safety and pharmacokinetics of microbicide use at term and late preterm gestation.^{9,10,11,12} Thus, several opportunities exist to gather and analyze pregnancy

exposure data, which can inform safety profiles for candidate HIV prevention product use among reproductive age women. The need for data on exposures and infant outcomes of all candidate HIV prevention agents during pregnancy makes this registry an essential component of ongoing efforts to investigate the safety of these products. Since opening for enrollment, the MTN-016 study has collected data on exposure to drugs in pregnancy, potential confounding and/or relevant factors (such as maternal age, disease status during pregnancy, and gestational age at exposure, etc.), and pregnancy and infant outcomes. To date, the MTN-016 study has encountered no major obstacles to implementation. It is anticipated that new parent trials will open and operate under Version 2.0 of the MTN-016 protocol, e.g., excluding participants from MTN-003 (Vaginal and Oral Interventions to Control the Epidemic [VOICE]) and MTN-008.

2.3 Study Hypotheses and Rationale

2.3.1 Study Hypotheses

We hypothesize the following:

- Exposures to prevention agents during pregnancy will not be associated with an increased risk of adverse pregnancy or delivery outcomes.
- Exposures to prevention agents during pregnancy will not be associated with an increased risk of major malformations among infants exposed *in utero*.

2.3.2 Rationale

Pregnancy safety data is an essential component of the evaluation of all candidate HIV prevention agents intended for use by reproductive age women. In addition to the inevitable early pregnancy exposures that will occur, there are many other compelling reasons for continuing microbicide-specific investigations of safety in pregnancy:

1. Among pregnant and post-partum women, sexual activity, including sexual activity with multiple partners, is common. Therefore, women who may become pregnant and post-partum women may be suitable target populations for HIV prevention agent use.
2. Data suggest that pregnancy represents a time of heightened risk for the sexual acquisition of HIV.¹³
3. If microbicides and/or PrEP become widely available, pregnant women will likely use them with or without evidence of safety. In the absence of safety data, possible recommendations to perform a pregnancy test prior to each use would create a logistical barrier to widespread uptake.

This registry study will be unique, in that it will also capture infant outcomes, including growth, as defined by birth weight and serial measures of length, weight, head circumference, and abdominal circumference in the first year of life. Including these endpoints among the registry data will provide a richer picture of the potential impact of study product exposure on pregnancy and infant outcomes. Potential differences in infant growth patterns between those exposed and unexposed to active study agents are readily measurable and accounted for by secondary objectives in this study. Another unique feature of this protocol is its inclusion of data collected on pregnancy and infant outcomes for participants using placebo study agents. The prospective collection of these outcome data prior to the unblinding of study treatment assignment will build a natural comparison group into the study database. The impact of study product exposure during pregnancy in the presence of HIV-infection is also unknown. While this is likely to be a rare occurrence, it is prudent to measure the potential impact on the prevalence of HIV drug resistance mutations in the plasma of HIV-infected infants.

Notably, we do not include bone mineral density (BMD) and/or bone metabolism evaluations on enrolled infants for several reasons. First, we do not believe there are sufficient data to suggest that very early gestational exposures (e.g., the 1st trimester exposures likely to be a large majority in our registry) would be associated with a detectable change in infant BMD and/or bone metabolism. Secondly, we believe that requiring routine blood draws and/or technically challenging bone imaging procedures for infants would significantly deter enrollment. This registry, in its current form, is already more involved than most pregnancy exposure registries; expanding it will require greater and unwarranted investment on the part of the participants. Further, as there are very limited data among infants to support standards for BMD and/or bone metabolism evaluations via blood work or imaging studies, the data generated would be of uncertain value.

2.4 Study Agents

Currently, MTN HIV prevention trials are focusing on antiretroviral drug-based study products. Data on these agents may be found in the Background section of parent study protocols, as well as the relevant Investigator Brochures and product package inserts.

3 OBJECTIVES

3.1 Primary Objectives

1. To compare adverse pregnancy and delivery outcomes between participant mothers assigned to an active agent with those of mothers assigned to placebo/control.

2. To compare the prevalence of major malformations identified in the first year of life between infants of mothers assigned to an active agent with those of infants of mothers assigned to placebo/control.

3.2 Secondary Objectives

1. To compare growth parameters in the first year of life between infants of mothers assigned to an active agent with those of mothers assigned to placebo/control.
2. To evaluate the prevalence and persistence of HIV drug resistance mutations in plasma among HIV-infected infants.

4 STUDY DESIGN

4.1 Identification of Study Design

The HIV Prevention Agent Pregnancy Exposure Registry will be a prospective observational cohort investigation of women with exposures to active and non-active study agents in trials investigating candidate HIV prevention agents and the infants resulting from those pregnancies. Parent trial participants should be offered enrollment in the Registry whenever it is determined that there has been an exposure to a study agent during pregnancy.

Optimally, participant mothers will be enrolled in MTN-016 prospectively (prior to the outcome of pregnancy being known). Participant mothers may also be enrolled in the registry after the pregnancy outcome is known, but only up until one year following the date of pregnancy outcome. Sites are encouraged to enroll participants as early in pregnancy as possible to maximize the validity of the data. Further information on planned analyses is available in Section 10.

4.2 Summary of Major Endpoints

1. Pregnancy and delivery outcomes:
 - delivery prior to 37 completed weeks of gestation
 - stillbirth or intrauterine fetal demise (≥ 20 weeks)
 - spontaneous abortion (< 20 weeks)
 - ectopic pregnancy
 - intrapartum hemorrhage
 - postpartum hemorrhage
 - non-reassuring fetal status
 - chorioamnionitis
 - hypertensive disorders of pregnancy
 - gestational diabetes

- intrauterine growth restriction
2. Major malformations, defined as structural abnormalities with surgical, medical, or cosmetic importance.¹

Where pregnancy and delivery outcomes are included both in parent protocols and MTN-016, these outcomes will be assessed primarily in the parent protocol. Inclusion and exclusion criteria to be applied for the identification of major malformations will be consistent with those outlined in Holmes, 2001, except that abnormalities may be ascertained up to one year of age.¹ In summary, major malformations will include structural abnormalities meeting the following criteria:

1. Having surgical, medical, or cosmetic importance
2. Ascertained up to one year of age
3. Independently confirmed according to criteria outlined in the MTN-016 SSP Manual

The following will be excluded as major malformations:

1. Minor physical features
2. Deformities that represent the normal response of fetal tissue to mechanical forces, i.e., atypical body part growth and/or appearance attributable to fetal position and/or pressure of surrounding maternal tissue(s). For example, molding of the skull, also known as positional plagiocephaly, would not be considered a major malformation
3. Physical features at birth that are normally present before 37 weeks of gestation
4. Findings on prenatal ultrasonography but not on physical examination
5. Genetic disorders

These inclusion/exclusion criteria will be applied to reported major malformations to determine their eligibility for inclusion as primary endpoints.

4.3 Description of Study Population

The study population will consist of current or recent participants who became pregnant during HIV prevention trials, or who have/had planned exposures in pregnancy safety studies (provided pregnancy outcome was less than one year from date of Screening/Enrollment Visit), and the infants resulting from those pregnancies (provided infants have not yet reached their 1 year birth date).

HIV-infected participants and their infants will not be excluded from this registry. This registry may be open to participants from other HIV prevention trials not part of the MTN as approved by the MTN Executive Committee.

4.4 Time to Complete Enrollment

The time to complete enrollment will be dependent upon the number of pregnancies occurring within parent trials. Accrual will remain open for the duration of MTN funding with the possibility of extension.

4.5 Expected Duration of Participation

The expected duration of participation is from the Mother's Screening and Enrollment Visit (optimally as close as possible to the onset of exposure during pregnancy) until follow-up is completed on the pregnancy outcome and/or infant (if the pregnancy results in a birth). If the pregnancy results or resulted in a live birth, the upper limit of scheduled participation may be one year of follow-up for the infant. If a pregnancy does not result in a live birth, participation would end after follow-up is completed on the pregnancy outcome, typically following the Pregnancy Outcome Visit.

4.6 Sites

The study is open to sites as determined by the MTN Executive Committee.

5 STUDY POPULATION

The study population will consist of female participants who became pregnant during HIV prevention agent trials, or who have or had planned exposures in pregnancy safety studies, and the infants resulting from those pregnancies. Mother participants must still be pregnant, or have had a pregnancy outcome diagnosis less than one year before screening/enrollment, and infant participants must be less than one year old. The study may include HIV-uninfected and -infected participants.

Mothers may participate in EMBRACE without participation of their infants; however, infants whose mothers have not enrolled in EMBRACE will not participate.

5.1 Selection of the Study Population: Mother

Recruitment

Potential participants will be recruited for EMBRACE as soon as possible after identification of pregnancy. Participants and their infants can be enrolled for subsequent pregnancies; subsequent pregnancies of an EMBRACE participant will require a separate informed consent process to be initiated. With assistance from the SDMC, the Site Investigator of Record (IoR) or designee will identify participants who become pregnant during participation in parent microbicide trials.

Retention

Each site will establish participant retention procedures. Study site staff members at each site are responsible for developing and implementing site-specific standard operating procedures (SOPs) to target high rates of retention.

Co-Enrollment Guidelines

Co-enrollment in other trials not involving investigational agents is permitted by this protocol. Co-enrollment in EMBRACE and studies of investigational agents (other than the parent protocol) will be considered on a case-by-case basis and must be approved by the Protocol Chair(s). However, it is expected that the Protocol Chair will permit co-enrollment in studies of potential benefit to the mother or baby including prevention of mother-to-child transmission (PMTCT) and/or adult or infant treatment of HIV infection.

5.2 Inclusion Criteria: Mother

Individuals who meet the following criteria are eligible for inclusion in the study:

1. Able and willing to provide written informed consent to take part in the study
2. During participation in a parent protocol, has/had a known confirmed pregnancy, meeting at least one of the following sets of criteria in A or B:
 - A: Two consecutive monthly study visits, at least 14 days apart, with positive pregnancy tests, in the absence of signs/symptoms of miscarriage or participant report of pregnancy termination.
 - B: One or more of the following assessments:
 - Auscultation of fetal heart tones
 - Positive pregnancy test confirmed by clinic staff in the presence of clinically confirmed enlarged uterus
 - Positive pregnancy test confirmed by clinic staff in the presence of missed menses (no menses occurring at least 60 days from the first day of the last menses) by participant report Clinical assessment of fetal movement
 - Demonstration of pregnancy by ultrasound
3. Able and willing to provide adequate locator information, as defined in site SOPs

Note: Participants do not have to be currently enrolled or engaged in follow-up in a parent protocol to participate in EMBRACE.

5.3 Exclusion Criteria: Mother

Individuals who meet the following criteria at screening will be excluded from the study:

1. Has any condition that in the opinion of the investigator or designee, would complicate interpretation of study outcome data, make participation in the study unsafe, or otherwise interfere with achieving the study objectives

2. Pregnancy outcome occurred greater than one year ago

5.4 Inclusion Criteria: Infant

Individuals who meet the following criteria are eligible for inclusion in the study:

1. Has written informed consent provided by parent(s)/guardian to take part in the study in a manner consistent with local standards, site Institutional Review Board (IRB) guidance and the US Code of Federal Regulations (CFR)
2. Born to EMBRACE participant mother from pregnancy concurrent with participation in parent study

5.5 Exclusion Criteria: Infant

Individuals who meet the following criteria at screening will be excluded from the study:

1. Has any condition that, in the opinion of the investigator or designee, would complicate interpretation of study outcome data, make participation in the study unsafe, or otherwise interfere with achieving the study objectives
2. Has reached 1 year birth date

6 STUDY PRODUCT

EMBRACE will not include the administration of any study product.

7 STUDY PROCEDURES

An overview of the study visits and evaluations schedule is presented in Appendices I and II. Presented in this section is additional information on visit-specific study procedures. A detailed instruction guide including visit windows will be provided in the EMBRACE Study-Specific Procedures (SSP) Manual, which will be available at www.mtnstopshiv.org.

Depending on the timing of screening and enrollment for the mother-infant pair, which may occur up until the time the infant is one year old, the follow-up schedule for mother and infant participants may vary. In cases where protocol-defined visits were missed because the mother or infant had not yet enrolled, such missed visits will not be considered protocol deviations or violations. Study visits for mothers and infants may or may not occur on different days. For example, the Screening and Enrollment Visit for

the mother and the Newborn/Initial Visit for the infant could occur on the same day in cases where the infant is already born.

It is expected that, in most cases, all required visit procedures will be completed at one visit; however, more than one visit may be needed to complete all required procedures. If a participant is being followed in her parent trial, site staff may schedule and complete MTN-016 visits on the same day as parent protocol visits. MTN-016 study visits may be completed off-site with consent and an approved SOP for this purpose.

Because laboratory testing, ultrasound, or other testing procedures may be performed at study visits, a post-visit contact may be required after a study visit to provide participants with their test results, clinically relevant post-test counseling, and/or clinically indicated treatment. Study staff may complete these contacts at the study site or at community-based locations, depending on site capacities and participant preferences. All contacts will be documented in participant study records and written documentation of test results will be provided upon request to participants and/or their primary care providers.

Procedures and documented results from the parent MTN study may be utilized for MTN-016, if the procedure(s) was performed/sample(s) was collected in the visit window and within the past 30 days, provided that the test kit, laboratory and/or specified clinical assessments, and method of data collection are the same in both studies. See the EMBRACE SSP Manual at <http://www.mtnstopshiv.org> for additional information.

Scheduled visits for the mother include the following:

- Screening and Enrollment
- Quarterly
- Pregnancy Outcome

Scheduled visits for the infant include the following:

- Newborn/Initial Visit
- Month 1
- Month 6
- Month 12

7.1 Screening and Enrollment: Mother

Day 0 for the participant mother will be the day of the Screening and Enrollment Visit – Mother.

- Administrative
 - Obtain written informed consent for screening and enrollment of mother
 - Identification number assignment (PTID)

- Locator information
- Eligibility assessment
- Reimbursement
- Schedule next visit
- Clinical
 - Obtain medical history
 - Obtain medication history
 - Obtain pregnancy history
 - Obtain genetic screening history

7.2 Quarterly Visit: Mother

If the mother is still pregnant, a quarterly visit will occur with the following components:

- Administrative
 - Locator information
 - Reimbursement
 - Schedule next visit
- Clinical
 - Update medical history
 - Update medication history
 - Update pregnancy history, including but not limited to pregnancy-related morbidities such as hypertensive disorders of pregnancy, antenatal hemorrhage, and abnormal placentation
 - Update genetic screening history

7.3 Ultrasound Exam

If the mother is still pregnant, a minimum of one obstetrical ultrasound exam should be performed. In cases where the study site already has a copy of results for an ultrasound meeting gestational age and measurement criteria recommended by the protocol, and allowing for complete documentation of the Ultrasound Results Form, the protocol-defined ultrasound may be omitted.

When deemed necessary by the Investigator of Record (IoR) or designee, additional ultrasounds may be ordered to confirm gestational age or provide follow-up information on potentially abnormal findings.

- For each ultrasound exam
 - Perform or refer for performance of obstetrical ultrasound
 - Complete ultrasound results form, including dating and anatomical survey data (as appropriate by gestational age).

Note: When possible, site staff should attempt to facilitate the performance of at least one obstetrical ultrasound for anatomical survey during the time period corresponding with 20 and 28 weeks gestation.

Note: Ultrasound exams should include, at a minimum, the following measurements:

- *If estimated gestational age is <14 0/7 weeks, a crown-rump length*
- *If estimated gestational age is 14 0/7 weeks or greater, a biparietal diameter (a femur length is useful but not required)*

7.4 Pregnancy Outcome Visit: Mother

- Administrative
 - Locator information
 - Reimbursement
 - Schedule next visit if indicated
- Clinical
 - Update medical history
 - Update medication history
 - Update pregnancy history, including but not limited to pregnancy-related morbidities such as hypertensive disorders of pregnancy, antenatal hemorrhage, and abnormal placentation, if applicable
 - Obtain pregnancy outcome
 - Type and number of pregnancy outcome(s)
 - Gestational age at pregnancy outcome
 - Method of calculation for gestational age at pregnancy outcome
 - If delivery, type of delivery (e.g., vaginal, vaginal forceps-assisted, vaginal vacuum-assisted, cesarean section)
 - Complications related to pregnancy outcome
 - Delivery complications (e.g., intrapartum and/or postpartum hemorrhage, non-reassuring fetal status, chorioamnionitis)
 - Other complications not related to a delivery
 - Baseline infant information (as available and per infant)
 - Number (e.g., singleton, twin, etc.)
 - Sex
 - Weight
 - Length
 - Head circumference
 - Apgar scores
 - Medical history (e.g., sepsis, respiratory distress, any abnormalities noted on infant exam)
 - Medication history

7.5 Interim Visit: Mother

- Administrative
 - Locator information
 - Schedule next visit if indicated
- Clinical
 - Update medical history if indicated
 - Update medication history if indicated
 - Update pregnancy history if applicable

7.6 Newborn/Initial Visit:

If the pregnancy results or resulted in a live-born infant, a Newborn/Initial Visit for the infant should occur during the first ten days of life when possible. If local custom, medical status, or other reason deemed acceptable by the IoR/designee, prohibits a study visit during this time period, the infant's first visit may be delayed, or the visit may occur off-site, if possible. If the timing of the Newborn/Initial Visit corresponds to the visit window for a scheduled 1-, 6-, or 12-month follow-up visit, procedures need not be duplicated within that particular visit window.

- Administrative
 - Written informed consent for screening and enrollment of infant, or verbal confirmation of previous consent, if already obtained
 - Eligibility assessment
 - Identification number assignment (if not already assigned)
 - Locator information
 - Reimbursement
 - Schedule next visit
- Clinical
 - Medical history
 - Medication history
 - Weight
 - Length
 - Head circumference
 - Abdominal circumference (preferably within 10 days, but no later than Month 1 Visit)
 - Physical exam
 - Photographic documentation of suspected or confirmed anomalies as clinically indicated (to be sent to MTN Statistical Data Management Center (SDMC))

- Laboratory
 - If clinically indicated according to the IoR/designee, US Food and Drug Administration (FDA)-approved HIV test with confirmatory tests as indicated

7.7 Months 1, 6, and 12: Infant

The first visit for an infant may also occur after the first ten days of life in cases where the mother-infant pair is not yet enrolled, provided that this first visit for the infant occurs before the infant has reached their 1-year birth date. Day 0 for the infant is on the first day of life.

Months 1, 6, and 12

- Administrative
 - Locator information
 - Reimbursement
 - Schedule next visit (1 and 6 months only; if indicated for month 12)
- Clinical
 - Update medical history
 - Update medication history
 - Weight
 - Length
 - Head circumference
 - Physical exam (see Appendix III)
 - If specific consent for this has been obtained, photographic documentation of suspected or confirmed anomalies as clinically indicated. **Photographs should include at least the following images: Anterior-posterior (AP) and lateral of face/head, neck and upper third of thorax, standing up picture of child (front and back), hands, feet, as well as AP and lateral images of any suspected abnormal finding. Photographs should NOT be restricted to the suspected abnormal finding.**
- Laboratory
 - As clinically indicated to follow a previous abnormal finding at the Newborn/Initial Visit

7.8 Interim Visit: Infant

- Administrative
 - Locator information
 - Schedule next visit if indicated
- Clinical
 - Update medical history

- Update medication history
 - If specific consent for this has been obtained, photographic documentation of suspected or confirmed anomalies as clinically indicated. Photographs should include at least the following images: AP and lateral of face/head, neck and upper third of thorax, standing up picture of child (front and back), hands, feet, as well as AP and lateral images of any suspected abnormal finding.
- Laboratory
 - As indicated to follow a previous abnormal finding
 - As indicated for confirmatory testing
 - As indicated for infants identified as HIV-infected (see Section 7.9)

7.9 Procedures for Infants of HIV-infected Mothers

Mothers who are diagnosed with HIV infection according to criteria in the EMBRACE SSP Manual may elect to have their infants tested for HIV infection. Infants diagnosed with HIV infection according to criteria in the EMBRACE SSP Manual will be tested for HIV-1 drug resistance mutations as soon as possible after diagnosis of HIV infection.

Infant testing may occur at a scheduled visit or an Interim Visit.

Testing during follow-up may include the following assays performed by the Site and/or Network Laboratory according to capacity:

- HIV-1 testing (ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), as indicated)
- Standard genotypic resistance testing
- Additional resistance testing may include allele-specific polymerase chain reaction (PCR) for relevant drug resistant codons and single genome sequencing

7.10 Procedures for Infants with Suspected or Confirmed Major Malformation

If, at any point in the study participation, a major malformation is suspected in an infant or other pregnancy outcome, a Major Malformation Assessment Worksheet, and, if needed, a Major Malformation Assessment Form should be completed. These forms will be included in the EMBRACE SSP Manual at <http://www.mtnstopshiv.org>.

7.11 Specimen Collection

Each study site will adhere to the standards of good clinical laboratory practices (GCLP), current DAIDS Good Clinical Laboratory Practice Standards, the EMBRACE SSP Manual (www.mtnstopshiv.org), and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS).

In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-collect specimens.

7.12 Specimen Handling

Specimens will be handled in accordance with Requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials (<http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/laboratorypolicy1.pdf>).

7.13 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the US Centers for Disease Control and Prevention (CDC) and NIH. All biological specimens will be transported using packaging mandated by CFR 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association Dangerous Goods Regulations. This applies to both US and international sites. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

7.14 Study Staff Performing Infant Procedures

Pediatric exams will be performed by an experienced clinician.

8 ASSESSMENT OF SAFETY

EMBRACE is an observational study involving no investigational products or procedures associated with significant risk to participants. Therefore, few safety concerns are expected as a result of study participation. The study site IoR is responsible for continuous close safety monitoring of all study participants and for alerting the protocol team if unexpected concerns arise. Study sites will have written procedures for ensuring prompt reporting to the IRB/Ethics Committees (ECs), of any unanticipated problem involving risks to subjects or others.

The Manual for Expedited Reporting of Adverse Events to DAIDS will not be used for this study for the following reasons: 1) this study is observational in nature; and, 2) this study does not involve a study drug or intervention.

The study team will monitor for and track unanticipated problems related to study procedures and/or to participation in the study, until participants' time of termination

from the study. Study staff will provide clinically appropriate treatment and/or referrals should any such problems occur.

For EMBRACE participants who are or were enrolled in a parent study, any unanticipated problems will be reported to the DAIDS Medical Officer concurrent with problem reporting to the responsible site IRB/ECs overseeing the research according to pre-established procedures as required by 45 CFR 46. Participants co-enrolled in EMBRACE and a parent study will have serious adverse events (SAEs) and Expedited Adverse Events (EAEs) considered reportable in the parent study reported via the safety reporting system utilized by the parent study. Once a participant is no longer enrolled in the parent study, any unanticipated study-related injury will be reported to the site IRB/EC according to individual IRB requirements and DAIDS Medical Officer.

Participants may experience social harms—non-medical adverse consequences as a result of their participation in the study. All reports of social harm, regardless of severity, will be collected for data purposes. Social harms that are judged by the IoR to be serious or unexpected will be reported to responsible site IRB/ECs at least annually, or according to their individual requirements. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed.

Relationship to study participation or procedures will be assessed based on the following definitions:

- Related: There is a reasonable possibility that the problem may be related to study participation
- Not Related: There is not a reasonable possibility that the problem is related to study participation

9 CLINICAL MANAGEMENT

9.1 Criteria for Early Termination

Participants may voluntarily withdraw from the study for any reason at any time. The site investigators may withdraw participants to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the Office of Human Research Protection (OHRP)), or site IRBs/ECs terminate the study prior to its planned end date. Study staff will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may resume study procedures and follow-up. Participants will be asked to complete a final/early termination study visit.

9.2 Findings Identified During Follow-up

Any infant noted to have abnormal or clinically suspicious findings on physical exam, growth monitoring and/or testing will be provided with or referred to local providers of pediatric care. Note, all women, upon enrolling in the study, will receive referrals for prenatal care if they are still pregnant. In the case of HIV drug resistance mutation testing, the IoR/designee will make reasonable efforts to furnish a written copy of the results to the infant's care provider, with permission of the parent(s) or guardian, as applicable. In the case of identified structural anomalies and/or potential deviations from normal health, the IoR/designee will make every effort to communicate directly with the referral entity, provided that consent has been obtained for this purpose.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

This is a prospective observational cohort study of pregnant women and their infants identified in microbicide trials conducted by the MTN. Infants will be followed for 12 months. Infants from multiple-birth pregnancies are eligible for enrollment. Participants and their infants can be enrolled for subsequent pregnancies and will need to be re-enrolled into EMBRACE.

10.2 Study Endpoints

A pregnant woman is defined as a woman meeting the criteria outlined in Section 5.2. Data for the primary and secondary study endpoints will be collected from the pregnant women and the infants born from these women.

10.2.1 Primary Endpoints: Pregnant Women

Consistent with the primary study objectives, the following endpoints will be assessed for pregnant women:

- delivery prior to 37 completed weeks of gestation
- stillbirth or intrauterine fetal demise (≥ 20 weeks)
- spontaneous abortion (< 20 weeks)
- ectopic pregnancy
- intrapartum hemorrhage
- postpartum hemorrhage
- non-reassuring fetal status
- chorioamnionitis
- hypertensive disorders of pregnancy
- gestational diabetes

- intrauterine growth restriction

10.2.2 Primary Endpoints: Infants

Consistent with the primary study objectives, the following primary endpoint will be assessed for infants:

- Major malformations, defined as structural abnormalities with surgical, medical, or cosmetic importance.

10.2.3 Secondary Endpoint: Infants

Consistent with the secondary objectives, the following endpoints will be assessed for infants:

- Weight, length, and head circumference at birth, one month, six months and 12 months.
- HIV-1 drug resistance mutations among infants who acquire HIV-1 infection

10.3 Sample Size

The overall number of participants to be enrolled in this protocol depends on pregnancy rates in the parent studies. At the time Version 2.0 of this protocol was approved, information was available on the number of pregnant women enrolled into MTN-016 from parent protocol MTN-003 (VOICE). Below we summarize the number of MTN-003 participants who were eligible and enrolled in MTN-016. Among 5,029 participants enrolled into MTN-003, 428 (9%) participants reported a pregnancy. Among these, 243 (57%) were eligible for MTN-016 based on two consecutive monthly visits with a positive pregnancy test (Criteria A from Section 5.2). Of these, 195 (80%) were enrolled in MTN-016 based on this eligibility criterion. An additional 17 women were enrolled based on Criteria B, resulting in a total of 212 pregnant women enrolled in MTN-016 from parent protocol MTN-003. A total of 201 infants were eligible for enrollment from MTN-003. Of these, 185 (92%) infants were enrolled into MTN-016.

Sample size estimates for the number of pregnant women and infants expected from future safety and effectiveness studies, such as MTN-020 (ASPIRE), are based on data from MTN-003, since future trial populations are likely to be similar to the MTN-003 trial population. For example, assuming 3,476 women are enrolled into MTN-020, we estimate that there will be approximately 313 (9% of 3,476) pregnant women and 147 (47% of 313) infants eligible for enrollment into MTN-016. This is a conservative estimate as it is difficult to anticipate the number of pregnant women generated by future and other MTN trials. Both MTN-003 and MTN-020 required use of a highly effective method of contraception as a criterion for enrollment. Future trials that do not have this eligibility requirement may have a higher pregnancy rate.

Pregnant women may elect to terminate participation in the parent study, not meet all eligibility criteria, and/or not wish to enroll in this study, or become lost to follow-up in the parent study. Of the 313 women that we estimate will become pregnant during MTN-020, we estimate that approximately 50% of the women will not enroll due to one of the above reasons. This estimate is also based on the enrollment trends for MTN-003. Thus, we estimate that 158 (50% of 313) pregnant women and 136 (92% of 147) infants will enroll into MTN-016 from MTN-020. We will target no more than 5% lost to follow-up of pregnant women and of mother/infant pairs.

In the absence of a contraceptive effect for the active agent or the placebo, we expect the number of enrolled pregnant women to be essentially balanced, resulting in 79 pregnant women per study arm (total n=158). Similarly, the number of enrolled infants should be approximately balanced, producing about 68 infants per study arm (total n=136). The primary objective involves a comparison of the endpoint by parent protocol study arm. Pregnant women are not randomized to study arms, thus it is anticipated that a certain level of imbalance will be present that may decrease power. However, study power estimates were generated assuming an equal number of participants in both study arms.

The overall proportion of pregnancy loss in MTN-003 among women enrolled in MTN-016 was approximately 6%. Since it is anticipated that the additional primary outcomes for pregnant women will range in frequency from 1%-10% in the placebo arm, a plot showing minimum absolute differences of 5%-20% for a sample size of 158 (79 in each arm) with 80% and 90% power is shown below (Figure 1). For example, if a primary outcome were observed in 5% of pregnant women in the placebo arm, then the study would have at least 80% power to detect a minimum absolute difference of 16%.

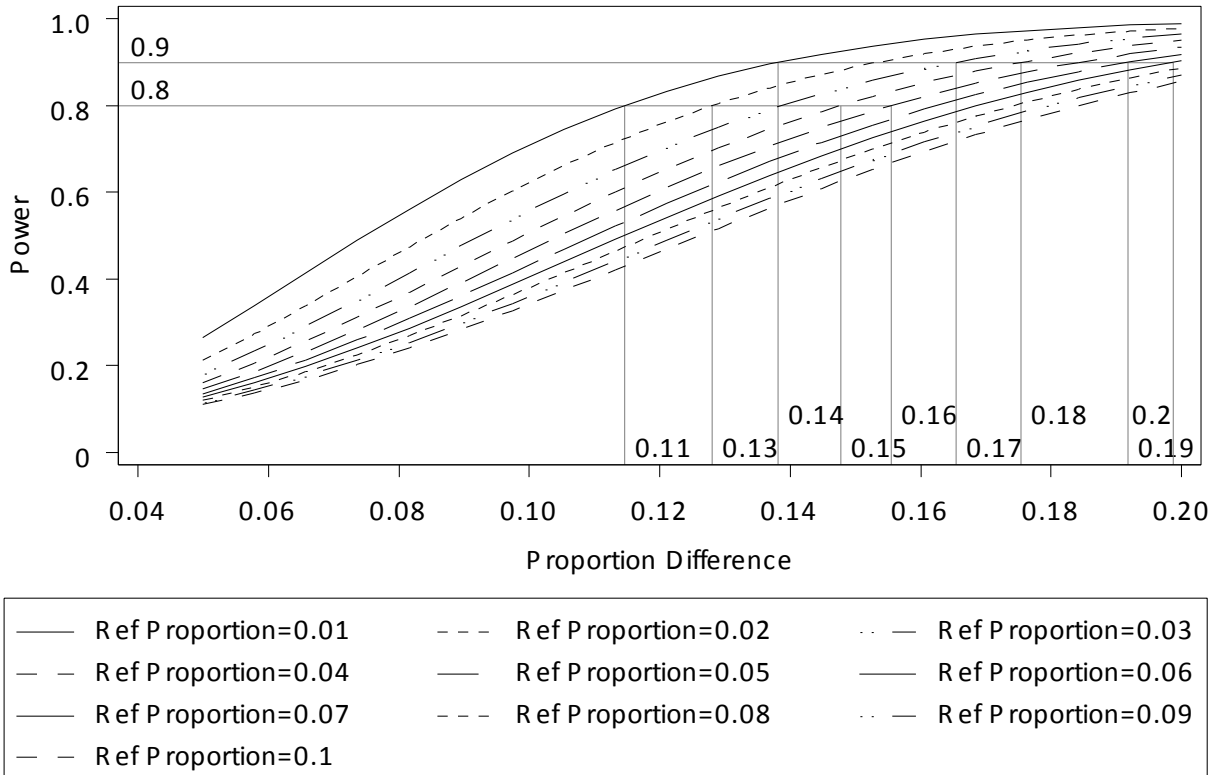


Figure 1: Power estimates for maternal outcomes

Similarly, since major malformations in infants are relatively rare, for the purpose of power calculations, we will conservatively assume that the proportion of major malformations will range in frequency in the placebo arm from 1% to 5%. A plot showing minimum absolute differences of 2% - 15% for a sample size of 136 (68 in each arm) with 80% and 90% power is shown below (Figure 2). For example, if a major malformation were observed in 1% of infants in the placebo arm, then the study would have at least 80% power to detect a minimum absolute difference of 13%.

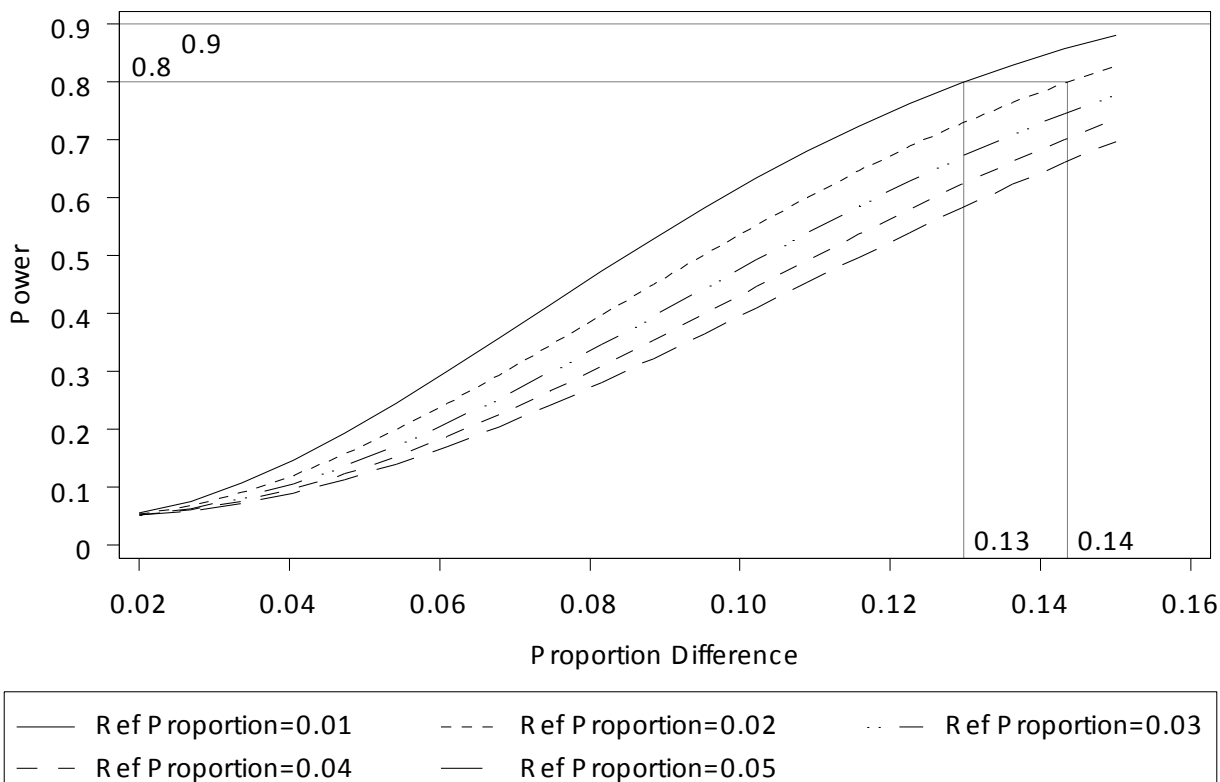


Figure 2. Power estimates for infant outcomes.

10.4 Blinding

Blinding/unblinding processes will be dictated by the parent study protocols. In the event that an Investigator feels that specific product knowledge is necessary to protect participant safety while the parent protocol is still blinded, they should follow the processes outlined in the parent protocol for early unblinding.

10.5 Participant Accrual and Retention

All women meeting criteria outlined in Section 5, including those identified as both pregnant and HIV-infected, will be recruited into this study. Once a participant has enrolled in the study, the study site will make every reasonable effort to retain her for the entire study period. A maximum of 5% loss-to-follow-up of enrolled pregnant women and infants will be targeted.

10.6 Data and Safety Monitoring Analysis

10.6.1 Interim Study Review (ISR) Committee

No Data and Safety Monitoring Board (DSMB) oversight is planned for this observational study, since pregnancy outcome data are assessed by the DSMB in their

review of the parent protocol. If treatment assignment is blinded in the parent protocol, the MTN ISR Committee will conduct interim reviews of study progress (pooled data only), including rates of participant accrual, retention, and assessment of the primary outcomes while the parent protocol is blinded. Additional reviews are anticipated to occur approximately annually following the initial review. At the time of these reviews, or at any other time, the protocol chair in combination with an external MTN reviewer may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. The protocol chair or external MTN reviewer may consider recommending termination of this study if recruitment and retention are lower than targeted, or if study data quality is poor. The MTN-016 protocol leadership team will routinely monitor study conduct and progress (including participant accrual, retention and data quality); see the MTN-016 SSP for additional details. Once results from a parent protocol are unblinded and analyzed, analysis of the primary and secondary outcomes by study arm can be conducted.

10.7 Data Analysis

In most cases, the analyses will be stratified by parent protocol. However, when appropriate, analyses combining data from multiple protocols may be conducted. When the use of descriptive statistics to assess group or site characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Typically, within-arm assessment of the change from the baseline measurement to a follow-up measurement will be analyzed using McNemar's test (for categorical response variables) or the paired *t*-test or Wilcoxon signed-ranks test (for continuous variables). In general, when use of formal testing to assess differences between study arms is required, the following methods will be used: for binomial response variables, chi-square tests (or Fisher's exact test, if appropriate) and logistic regression; for continuous variables, *t*-tests and linear regression, or nonparametric methods if data are non-Normal. To assess baseline differences between study arms, participants will be compared for baseline characteristics including demographics and laboratory measurements using descriptive statistics.

The proportion of participants with adverse pregnancy and delivery outcomes (as specified in Section 10.2.1) will be compared by study arm using a Fisher exact test or chi-square test, depending on the prevalence, with a two-sided level of significance. The proportions of major malformations observed in infants will be compared using the same methods.

For each of the growth parameters (i.e., birth weight, serial length, weight, and head circumference), the mean observed in the active agent and non-active agent groups will be compared using a Student's *t*-test at selected time points: birth, one, six, and 12 months. More generally, GEE (generalized estimating equation) methods and robust variance estimates will be used to evaluate group differences over the first year. Incomplete data from infants that are lost to follow-up or terminate early in the study

(including from death) will be included in these analyses if a growth parameter is available at one of the selected time points.

Among infants who acquire HIV-1 infection, the proportion of infants with HIV-1 drug resistance mutations will be compared by study arm using Fisher's exact test with a two-sided level of significance.

Note that caution must be exercised in the interpretation of any difference (or lack of difference) found. Although characteristics of the women in the active arm and placebo/control arm should be similar at baseline (in the parent studies) due to randomization, women who become pregnant in the active agent group may not be similar to women who become pregnant in the non-active agent group (possibly due to a potential contraceptive effect of the active intervention).

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study case report forms will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site must identify all case report forms to be used as source documents. Data are transferred to the MTN SDMC, entered, and cleaned using the DataFax data management system.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with current DAIDS policies. Each investigator will maintain, and store securely, complete, accurate, and current study records throughout the study. Study records must be maintained on site for the entire period of study implementation. Thereafter, instructions for record storage will be provided by DAIDS. No study records may be moved to an off-site location or destroyed prior to receiving approval from DAIDS.

11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures for EMBRACE in accordance with current DAIDS policies.

11.4 Study Activation

All study sites will complete DAIDS Protocol Registration procedures in accordance with the current DAIDS Protocol Registration Policy (<http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/pr>

[otocolregpolicy.pdf](#)). Pending successful protocol registration, submission of all other required study activation documents to the MTN CORE, and DAIDS approval, MTN CORE staff will “activate” the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site by the MTN CORE.

11.5 Study Coordination

Study implementation will be directed by this protocol and further guided by the SSP Manual provided by FHI 360, SCHARP, and the MTN NL.

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by PPD, LLC. (Wilmington, NC) in accordance with Requirements for On-Site Monitoring of DAIDS Funded and/or Sponsored Clinical Trials (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/on_sitemonitor_reqs.pdf). Study monitors will visit the site to do the following:

- Review procedures and documentation
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including CFR Title 45 Part 46, and Title 21 Parts 50, 56, and 312.
- Perform source document verification to ensure the accuracy and completeness of study data
- Assess implementation and documentation of internal site quality management procedures
- Assess site staff training needs

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the MTN CORE, SDMC, and NL, NIAID, and local and US regulatory authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

The investigators will make efforts to minimize risks to participants. Before beginning the study, the investigators will have obtained IRB/EC approval. The investigators will permit audits by the NIH, MTN CORE, applicable US/local government and regulatory authorities, IRBs/ECs, or any of their appointed agents.

13.1 Institutional Review Boards/Ethics Committees

Each participating study site is responsible for assuring that this protocol and the associated site-specific informed consent documents and study-related documents (such as participation education and recruitment materials) are reviewed by its responsible IRB/EC prior to implementation of the protocol. Any amendments to the protocol, informed consent forms, or other study-related documents must be approved by the responsible IRB/EC, MTN CORE and DAIDS prior to implementation.

13.2 Protocol Registration and Study Activation

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

MTN CORE (FHI 360) staff will notify each study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued.

13.3 Risk Benefit Statement

13.3.1 Risks

General

Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions. Participants may also feel worried while waiting for their ultrasound results. Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

Risks for Infants

For the infant, phlebotomy may lead to bruising, swelling, or infection (rare) at the site of the blood draw. These are considered very rare risks and occur in less than 5% of people undergoing phlebotomy.

13.3.2 Benefits

Participants in this study may experience no direct benefit. Participants may benefit from referral to early prenatal care and/or PMTCT services. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may help prevent adverse pregnancy outcomes in the future. In addition to the benefits listed, infant participants may also have abnormalities detected as part of the evaluations in this investigation that may not have otherwise been detected. The IoR/designee will initiate referrals to local providers for ongoing evaluation and care of such infants. Infant participants may have the opportunity to access earlier care for certain abnormalities, which could improve prognosis depending on the condition.

13.4 Informed Consent Process

Written informed consent will be obtained from all potential study participants and from the parent(s)/guardian for infant participants, prior to the initiation of any study-related procedures. Sites may elect to use the combined mother and infant Sample Informed Consent documents (Appendix IV) or the separate mother (Appendix V) and infant (Appendix VI) Sample Informed Consent documents as applicable. Study staff will administer a comprehension checklist to potential participants and the

parent(s)/guardian for infant participants, prior to obtaining written informed consent to ensure that participants and the parent(s)/guardian for infant participants, fully comprehend the nature of the study. The comprehension checklist will be included in the MTN-016 SSP Manual. In obtaining and documenting informed consent, the investigators and their designees will comply with applicable local and domestic regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. Participants are provided with copies of the informed consent forms if they are willing to receive them. Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendices IV, V, VI, and VII that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template form into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

13.5 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Each study site will implement confidentiality protections that reflect the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by any of the following:

- DAIDS and/or its contractors, including study monitors
- Representatives of the MTN CORE, SDMC, and/or NL
- Other government and regulatory authorities
- Site IRBs/ECs

The MTN has obtained a Certificate of Confidentiality from the US Department of Health and Human Services that is applicable for this study. This Certificate protects study staff from being compelled to disclose study-related information by any US Federal, State or local civil, criminal, administrative, legislative or other proceedings. It thus serves to protect the identity and privacy of study participants. Since the Certificate cannot be enforced outside of the US, however, it will apply only to US site staff and participants.

13.6 Special Populations

This section outlines considerations made for the inclusion or exclusion of special populations in this study.

13.6.1 Pregnant Women

Pregnant women will be offered enrollment in this study in accordance with guidelines set forth in the US 45 CFR 46.

13.6.2 Children

Infants born to women participating in EMBRACE will be offered enrollment in this study in accordance with guidelines set forth in the US 45 CFR 46 and DAIDS policy (<http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/enrollingchildrenrequirements.pdf>).

13.6.3 Prisoners

MTN-016 does not meet the criteria for prisoner participation per US 45 Code of Federal Regulations (CFR) 46.306 (a)(2)(D). MTN-016 is not suitable for further reviews by local IRBs/ECs for the inclusion of prisoners.

13.7 Compensation

Compensation will be provided to participants according to guidelines established by local IRBs/ECs.

13.8 Access to HIV-related Care

13.8.1 HIV Counseling and Testing

HIV testing for participant infants will be offered, as clinically indicated, including relevant pre-test and post-test counseling, by the study. Infants who have positive or indeterminate results will have limited follow-up confirmatory testing provided by the study. Referral for additional counseling related to testing or diagnosis will occur if needed or requested by the mother or guardian.

13.8.2 Care for Participants Identified as HIV-Infected

Parents or guardians (as applicable) will be provided with HIV test results for their infant in the context of post-test counseling. Parents/guardians of infants who are identified as

HIV-infected during the study will be referred to available sources of medical and psychosocial care and support, and local research studies for HIV-infected infants.

13.9 Study Discontinuation

The NIAID, MTN, OHRP, other applicable government or regulatory authorities, or site IRBs/ECs may discontinue this study at any time.

14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies will govern publication of the results of this study.

15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS (Mother)

	Screening/ Enrollment	Ultrasound	Quarterly	Pregnancy Outcome	Interim
Informed Consent	X				
PTID	X				
Locator	X		X	X	X
Eligibility Assessment	X				
Reimbursement	X		X	X	
Schedule Study Visit	X		X	*	*
Medical History	X		X	X	*
Medication History	X		X	X	*
Pregnancy History	X		X	*	*
Genetic Screening History	X		X		
Ultrasound (with follow-up as clinically indicated)		*			
Pregnancy Outcome				X	

* if indicated

APPENDIX II: SCHEDULE OF STUDY VISITS AND EVALUATIONS (Infant)

	Newborn/ Initial Visit	Month 1 Visit	Month 6 Visit	Month 12 Visit	Interim Visit
Informed Consent	***				
PTID	****				
Locator	X	X	X	X	X
Eligibility Assessment	X				
Reimbursement	X	X	X	X	
Schedule Study Visit	X	X	X	*	*
Medical History	X	X	X	X	X
Medication History	X	X	X	X	X
Weight	X	X	X	X	*
Length	X	X	X	X	*
Head Circumference	X	X	X	X	
Abdominal Circumference	**				
Physical Exam	X	X	X	X	*
Photographic Documentation	*	*	*	*	*
HIV Test with Confirmatory Test	*	*	*	*	*
Procedures for HIV-infected infants <ul style="list-style-type: none"> • HIV-1 testing • Standard genotypic resistance testing • Plasma for storage • Additional resistance testing per Section 7 	*	*	*	*	*

* if indicated

** preferably within 10 days, but no longer than 1 month after birth

*** if consent has not been obtained during the mother's screening/enrollment visit

**** if not already assigned

APPENDIX III: COMPONENTS OF EXAMINATIONS

Neonatal Physical Exam (see MTN-016 SSP Manual for details)

Growth parameters

- Length, weight and head circumference
- Assessment of proportionality and symmetry
- Specific measurements where indicated by observation

General appearance

- Tone, posture, positioning, alertness, vigor, color, respiratory effort and other observations

Detailed examination

- Skin - pigmentation pattern (areas of increased or decreased pigmentation), dimples, vascular or other lesions, or excessive peeling
- Head - shape, symmetry, fontanelles
- Scalp - hair patterning and location of hair whorls
- Facial features
 - Eyes - pupils, orbits (hyper or hypotelorism) including palpebral fissure inclination and length
 - Ears - location, rotation, configuration and size, patency
 - Nose - appearance and patency of nares
 - Appearance of nasal bridge and columella
 - Mouth - appearance of upper lip, philtrum and vermilion border
 - Intra-oral examination of palate, alveolar ridges and tongue
 - Mandible - shape and symmetry
- Neck - posterior hairline, presence of sinus tracts, torticollis, redundant skin or webbing
- Chest - shape, symmetry, circumference, location of nipples, accessory nipples
- Cardiovascular - heart murmurs, pulses
- Lungs - symmetry of breath sounds
- Abdomen - appearance of umbilicus, muscle tone, integrity of wall, enlarged organs or masses
- Genitalia - size, appearance, palpation of testes (in males), presence of ambiguity
- Anus - location and patency
- Back - symmetry, spine, presence of sinuses or hair tufts in inter-gluteal cleft
- Extremities - proportions, appearance, range of motion (including hips), pulses, presence of reduction or duplication of segments
- Hands and feet - nails; creases (palmar, phalangeal, and flexion); joints
- Neurological - tone, response, alertness, reflexes

**APPENDIX IV: SAMPLE INFORMED CONSENT– MOTHER AND INFANT
(Screening and Enrollment)**

**MTN-016
HIV Prevention Agent Pregnancy Exposure Registry:
EMBRACE Study**

Version 2.0

**PRINCIPAL INVESTIGATOR: TBD
PHONE: TBD
Short Title for the Study: EMBRACE**

Introduction

MTN-016, or EMBRACE (Evaluation of Maternal and Baby outcome Registry After Chemoprophylactic Exposure) is a research study that is designed to include certain women, and, possibly their babies. Even though you may be pregnant with more than one baby, we will be using the term “baby” throughout this consent. This consent applies to you and to the offspring from this pregnancy.

You, and possibly your baby, may participate if the following are true.

1. You became pregnant while taking part in a human immunodeficiency virus (HIV) prevention study.

OR

2. You have or had planned exposure to any study agent, either active or non-active, while taking part in a pregnancy safety study.

AND

3. The pregnancy outcome is less than 1 year from the date of the Screening/Enrollment Visit for this study (live-born babies would be less than 1 year of age).

You can include your baby in this study, if you wish, as long as you meet the criteria above. You are being asked to take part in this study so that we can look at how HIV prevention medications might affect pregnancy and baby outcomes. HIV is the virus that causes AIDS.

This study is being paid for by the United States National Institutes of Health. The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR].

Before you decide whether to take part in this study, we want to explain the purpose of the study, the risks and benefits, and what is expected of you. This consent form gives information that the study staff will discuss with you. You are free to ask questions at any time. If you agree to take part in this study, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

Why Is This Study Being Done?

The main purpose of this study is to see if using a medication to prevent HIV affects the health of pregnant women and their babies.

What Do I Have To Do If I Am In This Study?

You will stay in the study until the outcome of your pregnancy is known. Because examination results (outlined below) may help other doctors make the best medical choices for you and your baby, study staff may give the results of your study tests to your other doctors, but they will only do this if you permit them to.

Also, if you are taking part in another study, please tell the study staff, and they will talk to you about the cases where you may and may not be permitted to be in more than one study.

Clinic Visits

This study will require some visits to the clinic. Visits will be broken up into different categories. Following the short description are more details about each visit to help you decide about participation.

Mother Visits

1. Mother's Screening and Enrollment (to see if you can and want to participate)
2. Ultrasound Visit (to check on your baby if needed)
3. Mother's Quarterly Visit (to see how you are doing and ask if there are any changes)
4. Mother's Pregnancy Outcome Visit (to give us information about you and your pregnancy)

Baby Visits

1. Newborn/Initial Visit (to allow you to enroll your baby if you like, and to allow us to get some basic information about your baby's health)
2. Baby Follow-Up Visits (to allow us to follow the health of your baby)

Mother's Screening and Enrollment Visit

This visit will continue today after you read, discuss and sign or make your mark on this form. It will take about [insert amount of time]. The study clinician will review the records from your HIV prevention study to make sure you meet the requirements for this study. Then you will be asked some questions. The questions will be about you, where you live, and medicines you take. You also will be asked to do the following:

- Tell study staff about any health problems you might have had
- Tell the study staff about other times that you were pregnant

Ultrasound Visit

Have an ultrasound to check the growth of your baby if this applies to you and if you do not have complete results from an ultrasound taken by another doctor. An ultrasound is a test that uses sound waves to check on the growth of your baby. It is done by placing a device on your belly. It does not involve any procedures or examinations inside of you.

Mother's Quarterly Visits (every 3 months)

These visits will take place every 3 months. You may have fewer visits depending on how far along in your pregnancy you are when you join the study. These visits will take about [insert amount of time]. You will be asked questions about where you live and how to keep in touch with you. At these visits you will also be asked to do the following:

- Tell the study staff about any changes in your health.
- Tell the study staff about any changes in the medicines you are taking.
- Answer questions about your pregnancy.
- Have an ultrasound if you have never had one before or if the study doctor thinks you may need to have one done.

Mother's Pregnancy Outcome Visit

This will be your last visit and it will take [insert amount of time]. Any babies born will be assigned an identification number and enrolled in the study at this point, and your baby will keep coming back for your baby's visits. You will be asked questions about where you live and how to keep in touch with you. At this visit you will be asked to do the following:

- Tell the study staff about any changes in your health.
- Tell the study staff about any changes in the medicines you are taking.
- Answer questions about your pregnancy.
- Tell us about the outcome of your pregnancy.

We also ask for permission to look at your medical records, particularly the records of your labor and delivery, for medical information about you and your baby.

Newborn/Initial Visit

If your pregnancy results in a live birth, this visit should take place after the birth of your baby, but ideally before your baby is 10 days old. This visit should take about xx hours. You will be asked questions about where you live, how to keep in touch with you and your baby, about the health of your baby and any medicines your baby might be taking. At this visit, the study staff may also do the following to make sure your baby is healthy:

- Measure the weight, length, head size, and belly size of your baby
- Perform a physical exam
- If it looks like something might be wrong with your baby, the study doctor might take pictures of your baby and share the pictures with experts who

may be able to see what the problem might be. If you agree to have pictures taken of your baby, you will be asked to mark your permission at the end of this consent. We can give you a copy of any of the photographs. If you do not wish to have photographs taken of your baby, you will be able to mark at the end of this consent that no photographs may be taken of your baby.

Baby Follow-Up Visits (1, 6, and 12 months)

We will ask you to bring your baby in for follow-up visits to make sure your baby is healthy. You will be asked questions about where you live, how to keep in touch with you and your infant about the health of your baby and any medicines your baby might be taking. These visits could take about xx hours. At this visit, the study staff will also do the following to make sure your baby is healthy:

- Measure the weight, length, and head size of your baby
- Perform a physical exam
- If it looks like something might be wrong with your baby, the study doctor might take pictures of your baby and share those pictures with experts who may be able to see what the problem might be. If you agree to have pictures taken of your baby, you will be asked to mark your permission at the end of this consent. We can give you a copy of any of the photographs. If you do not wish to have photographs taken of your baby, you will be able to mark at the end of this consent that no photographs may be taken of your baby.

Any Time During The Study:

Please tell the study staff about any medical problems you or your baby have during the study. You can contact the study staff between regular visits to report these problems. The study staff will check you or your baby as needed and will refer you or your baby for medical care. At each study visit, the study staff will update your medical history and the medical history of your baby as well as information on where you live and how to keep in touch with you.

How Many Women and Babies Will Be In This Study?

Women who became pregnant during HIV prevention trials or women who enroll or enrolled in an HIV prevention trial while pregnant (as long as their pregnancy outcome was less than 1 year ago), and babies born to these women (as long as the baby has not reached its one year birth date) can be in this study. This number is expected to be about 550 women, and about 400 babies.

How Long Will My Baby and I Be In This Study?

You will be in this study until the outcome of your pregnancy is known. If you have or had a live birth, your baby will be in this study until about the time that they turn one year old. If you have more than one baby in this pregnancy (such as twins), each baby may participate in this study.

Can the Doctor Take Me or My Baby Off This Study Early?

The study doctor may take you or your baby off the study early without your permission for any of the following reasons:

- The study is stopped or canceled.
- Staying in the study would be harmful to you or your baby.
- Other reasons that may prevent you or your baby from completing the study successfully

What Are The Risks Of This Study?

You may feel worried while waiting for your ultrasound results. Trained staff members are available to help you deal with any feelings or questions you have. You may also be uncomfortable with the personal types of questions asked.

Possible Risks to Your Privacy or Your Baby's Privacy

We will make every effort to protect your privacy and the privacy of your baby while you are in this study. All study visits – for your baby – will take place in private. However, it is possible that others may learn of your participation or the participation of your baby and, because of this, may treat you unfairly. For example, you could have problems getting or keeping a job or being accepted by your family or community. There also is a risk to your privacy or the privacy of your baby if someone else taking part in this study knows you. Efforts to protect your privacy and the privacy of your baby include only allowing medical staff to see any photographs that might be taken of your baby. If you do not feel comfortable about having any photographs taken of your baby, a doctor may write a detailed description instead, and you will still be allowed to stay in the study, and your baby, if enrolled, will also still be allowed to stay in the study.

What are the Benefits of This Study?

You may experience no direct benefit from being in this study. You or others may benefit in the future from information learned in this study. Knowledge gained from this study may help in the development of medications for the prevention of HIV infection. You may also get some personal satisfaction from being part of research on preventing HIV. You or your baby may also benefit from clinical information gained from the exams performed as part of the study.

New Information

You will be told any new information learned during this study that might affect your willingness to stay in the study.

What Other Choices Do I Have Besides This Study?

You and your baby do not have to participate in this study. The decision to not be in this study will not affect your regular care the regular care of your baby in any way.

What About Confidentiality?

We will do everything we can to protect your privacy the privacy of your baby Also, any scientific publication about this study will not use your name the name of your baby or identify you or your baby personally.

[Insert the following paragraph for US sites only] In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study to anyone you choose. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

People who may review your records include the following: (insert Name of Site) Institutional Review Board (IRB), Ethics Committees (EC), National Institutes of Health (NIH), study staff, study monitors, and other government and regulatory authorities.

What Are The Costs To Me?

There is no cost to you for study visits, exams, or ultrasounds performed on you or your baby as a part of the study. This study will not provide or pay for others to provide routine prenatal care, delivery, postpartum, or routine baby care.

Will I Receive Any Payment?

You will receive payment for your time and effort in this study. You may also receive payment for activities [such as child care, travel cost, loss of work time - local sites to list particulars] that are affected by your participation or the participation of your baby in this study.

What Happens If I Am Injured?

If you are injured, or if your baby is injured as a result of being in this study, you will be given immediate treatment for your injuries. If your baby is injured as a result of being in this study, he/she will be given immediate treatment for injuries as well. However, you [insert if applicable: or your insurance company (or the infant's insurance company)] may have to pay for this care. This institution or the United States National Institutes of Health does not have a program to provide money for your or your infant's injuries. You will not be giving up any of your legal rights by signing this consent form.

What Will Happen If I Become Infected With HIV While In This Study?

If either you or your baby becomes infected with HIV while participating in the study, we would like you continue to come in for your study visits. We will also provide counseling and referrals to available care and support for you and/or your baby. If you become infected with HIV, it is possible that your baby will also be at risk of becoming infected with HIV. Because of this, we will ask you to complete a separate consent form to have your infant tested for HIV.

What Are My Rights?

Being in this study is completely voluntary. You may choose not to be in or to leave the study at any time, or to remove your baby from the study at any time. You and your baby will be treated the same no matter what you decide. If you choose not to be in or to leave the study, or if you choose to remove your baby from the study, neither you nor your baby will lose the benefit of services to which either of you would otherwise be entitled at this clinic. Study staff will tell you about any new information from this or other studies that may affect your or the health and welfare of your baby. At the end of the study, you will be told when study results may be available and how to learn about them.

What Do I Do If I Have Problems or Questions?

For questions about this study or a research-related injury, contact: [insert contact information]. For questions about your rights as a research participant, contact: [insert contact information]

SIGNATURES

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

If you have read the informed consent, or had it read and explained to you, and all your questions have been answered, and you agree to be in this study, please sign your name or make your mark below.

Please mark one of the following boxes to show whether you agree/ do not agree to have photograph(s) of your baby taken as may be requested by study staff:

- The study staff may take photograph(s) of my baby
- The study staff may **NOT** take photograph(s) of my baby

Mother/Guardian Name (print)

Mother/Guardian Signature/Mark and Date

Father's Name (print)

Father's Signature/Mark and Date
(If Reasonably Available)

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness' Signature and Date

**APPENDIX V: SAMPLE INFORMED CONSENT – MOTHER
(Screening and Enrollment)**

**MTN-016
HIV Prevention Agent Pregnancy Exposure Registry:
EMBRACE Study**

Version 2.0

**PRINCIPAL INVESTIGATOR: TBD
PHONE: TBD
Short Title for the Study: EMBRACE**

Introduction

MTN-016, or EMBRACE (Evaluation of Maternal and Baby outcome Registry After Chemoprophylactic Exposure) is a research study that is designed to include certain women, and, possibly their babies. Even though you may be pregnant or may have delivered more than one baby, we will be using the term “baby” throughout this consent.

You, and possibly your baby, may participate if the following are true.

1. You became pregnant while taking part in a human immunodeficiency virus (HIV) prevention study.

OR

2. You have or had planned exposure to any study agent, either active or non-active, while taking part in a pregnancy safety study.

AND

3. The pregnancy outcome is less than 1 year from the date of the Screening/Enrollment Visit for this study (live-born babies would be less than 1 year of age).

You may participate in this study even if you have miscarried. You are being asked to take part in this study so that we can look at how HIV prevention medications might affect pregnancy and baby outcomes. HIV is the virus that causes AIDS.

This study is being paid for by the United States National Institutes of Health. The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR].

Before you decide whether to take part in this study, we want to explain the purpose of the study, the risks and benefits, and what is expected of you. This consent form gives information that the study staff will discuss with you. You are free to ask questions at any time. If you agree to take part in this study, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

Why Is This Study Being Done?

The main purpose of this study is to see if using a medication to prevent HIV affects the health of pregnant women and their babies.

What Do I Have To Do If I Am In This Study?

You will stay in the study until the outcome of your pregnancy is known.

Because examination results (outlined below) may help other doctors make the best medical choices for you, study staff may give the results of your study tests to your other doctors, but they will only do this if you permit them to.

Also, if you are taking part in another study, please tell the study staff, and they will talk to you about the cases where you may and may not be permitted to be in more than one study.

If you agree to participate in this study, and your pregnancy results in, or has already resulted in, a live birth, you will be asked to sign another consent form for your baby that will allow the health of your baby to be followed for the first year of life to see if your use of a medication to prevent HIV affected the health of your baby. More information about this can be found on the infant consent form.

Clinic Visits

This study will require some visits to the clinic. Visits will be broken up into different categories. Following the short description are more details about each visit to help you decide about participation.

1. Screening and Enrollment (to see if you can and want to participate)
2. Ultrasound Visit (to check on your baby if needed)
3. Quarterly Visit (to see how you are doing and ask if there are any changes)
4. Pregnancy Outcome Visit (to give us information about you and the outcome of your pregnancy, whether it resulted in a live birth or not)

Screening and Enrollment Visit

This visit will continue today after you read, discuss and sign or make your mark on this form. It will take about [insert amount of time]. The study clinician will review the records from your HIV prevention study to make sure you meet the requirements for this study. Then you will be asked some questions. The questions will be about you, where you live, and medicines you take. You also will do the following:

- Tell study staff about any health problems you might have had

- Tell the study staff about other times that you were pregnant

Ultrasound Visit

Have an ultrasound to check the growth of your baby if this applies to you and if you do not have complete results from an ultrasound taken by another doctor. **An ultrasound is a test that uses sound waves to check on the growth of your baby. It is done by placing a device on your belly. It does not involve any procedures or examinations inside of you.**

Quarterly Visits (every 3 months)

These visits will take place every 3 months. You may have fewer visits depending on how far along in your pregnancy you are when you join the study. These visits will take about [insert amount of time]. You will be asked questions about where you live and how to keep in touch with you. At these visits you will also be asked to do the following:

- Tell the study staff about any changes in your health
- Tell the study staff about any changes in the medicines you are taking
- Answer questions about your pregnancy
- Have an ultrasound if you have never had one before or if the study doctor thinks you may need to have one done

Pregnancy Outcome Visit

This will be your last visit and it will take [insert amount of time]. If you consent to enroll your baby, a second form is required. You will be asked questions about where you live and how to keep in touch with you. At this visit you will be asked to do the following:

- Tell the study staff about any changes in your health.
- Tell the study staff about any changes in the medicines you are taking.
- Answer questions about your pregnancy.
- Tell us about the outcome of your pregnancy.

We also ask for permission to look at your medical records, particularly the records of your labor and delivery, for medical information about you and your baby.

Any Time During The Study:

Please tell the study staff about any medical problems you have during the study. You can contact the study staff between regular visits to report these problems. The study staff will check you as needed and will refer you for medical care. At each study visit, the study staff will update your medical history and information on where you live and how to keep in touch with you.

How Many Women Will Be In this Study?

Women who became pregnant during HIV prevention trials or women who enroll/enrolled in an HIV prevention trial while pregnant (as long as pregnancy outcome was less than 1 year ago) will be in this study. This number is expected to be about 550 women.

How Long Will I be In This Study?

You will be in this study until the outcome of your pregnancy is known.

Can the Doctor Take Me Off This Study Early?

The study doctor may take you off the study early without your permission for any of the following reasons:

- The study is stopped or canceled.
- Staying in the study would be harmful to you.
- Other reasons that may prevent you from completing the study successfully

What Are The Risks Of This Study?

You may feel worried while waiting for your ultrasound results. Trained staff members are available to help you deal with any feelings or questions you have. You may also be uncomfortable with the personal types of questions asked.

Possible Risks to Your Privacy

We will make every effort to protect your privacy while you are in this study. Your visits here will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly. For example, you could have problems getting or keeping a job or being accepted by your family or community. There also is a risk to your privacy if someone else taking part in this study knows you.

What are the Benefits of This Study?

Participants in this study may experience no direct benefit. You or others may benefit in the future from information learned in this study. Knowledge gained from this study may help in the development of medications for the prevention of HIV infection. You may also get some personal satisfaction from being part of research on preventing HIV.

New Information

You will be told any new information learned during this study that might affect your willingness to stay in the study.

What Other Choices Do I Have Besides This Study?

You do not have to participate in this study. The decision to not be in this study will not affect your regular care in any way.

What About Confidentiality?

We will do everything we can to protect your privacy. Also, any scientific publication about this study will not use your name or identify you personally.

[Insert the following paragraph for US sites only] In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study to anyone you choose. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

People who may review your records include the following: (insert Name of Site) Institutional Review Board (IRB), Ethics Committees (EC), National Institutes of Health (NIH), study staff, study monitors, and other government and regulatory authorities.

What Are The Costs To Me?

There is no cost to you for study visits, exams, or ultrasounds performed as a part of the study. This study will not provide or pay for others to provide routine prenatal care, delivery, postpartum, or routine baby care.

Will I Receive Any Payment?

You will receive payment for your time and effort in this study. You may also receive payment for activities [such as child care, travel cost, loss of work time - local sites to list particulars] that are affected by your participation in this study.

What Happens If I Am Injured?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. However, you [insert if applicable: or your insurance company] may have to pay for this care. This institution or the United States National Institutes of Health does not have a program to provide money for your injuries. You will not be giving up any of your legal rights by signing this consent form.

What Will Happen If I Become Infected With HIV While In This Study?

If you become infected with HIV while participating in the study, we would like you to continue to come in for your study visits. We will also provide counseling and referrals to available care and support. If you become infected with HIV, it is possible that your baby will also be at risk of becoming infected with HIV. Because of this, we will ask you to complete a separate consent form to have your baby tested for HIV.

What Are My Rights?

Being in this study is completely voluntary. You may choose not to be in or to leave the study at any time. You will be treated the same no matter what you decide. If you choose not to be in or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic. Study staff will tell you about any new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. At the end of the study, you will be told when study results may be available and how to learn about them.

What Do I Do If I Have Problems or Questions?

For questions about this study or a research-related injury, contact: [insert contact information]

For questions about your rights as a research participant, contact: [insert contact information]

SIGNATURES

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

If you have read the informed consent, or had it read and explained to you, and all your questions have been answered, and you agree to be in this study, please sign your name or make your mark below.

Participant's Name (print)

Participant's Signature/Mark and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness' Signature and Date

**APPENDIX VI: SAMPLE INFORMED CONSENT – INFANT
(Screening and Enrollment)**

**MTN-016
HIV Prevention Agent Pregnancy Exposure Registry:
EMBRACE Study**

Version 2.0

PRINCIPAL INVESTIGATOR: TBD
PHONE: TBD
Short Title for the Study: EMBRACE

Introduction

MTN-016, or EMBRACE (Evaluation of Maternal and Baby outcome Registry After Chemoprophylactic Exposure) is a research study of women who became pregnant while taking part in human immunodeficiency virus (HIV) prevention research studies, or who had planned exposures to any study agent (active or non-active) in pregnancy safety studies as long as the pregnancy outcome was less than 1 year from the date of the EMBRACE Screening/Enrollment Visit. This study includes the babies of these women, if the parent consents and each baby is less than 1 year old. Even though you may be pregnant or may have delivered more than one baby, we will be using the term “baby” throughout this consent. You are being asked to agree to have your baby take part in this study because you have been pregnant during an HIV prevention study. HIV is the virus that causes AIDS.

This study is being paid for by the United States National Institutes of Health. The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR].

Before you decide whether you would like your baby to take part in this study, we want to explain the purpose of the study, the risks and benefits, and what is expected of you and your baby. This consent form gives information that the study staff will discuss with you. You are free to ask questions at anytime. If you agree to have your baby take part in this study, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

Why Is This Study Being Done?

The main purpose of this study is to see if using a medication to prevent HIV affects the health of pregnant women and their babies.

What Do I Have To Do If I Am In This Study?

Your baby will only stay in the study until he or she turns one year old. If you decide to let your baby take part in this study, you will be asked to bring your baby back for visits for as long as the baby is in the study. At study visits you will answer questions about

your baby's health and the study doctor will check your baby's growth. Because the examination results (outlined below) may help other doctors make the best medical choices for you and your baby, study staff will give the results of your study tests to your other doctors, if you wish and with your permission.

The visits your baby will have in this study are described in detail below.

Newborn/Initial Visit

If your pregnancy results in a live birth, this visit should take place after the birth of your baby, but when your baby is 10 days old or younger. You will be asked questions about where you live, how to keep in touch with you and your baby, about the health of your baby and any medicines your baby might be taking. At this visit, the study staff may also do the following to make sure your baby is healthy:

- Measure the weight, length, head size, and belly size of your baby
- Perform a physical exam
- If it looks like something might be wrong with your baby, the study doctor might take a picture of your baby and share that picture with experts who may be able to see what the problem might be. If you agree to have pictures taken of your baby you will be asked to mark your permission at the end of this consent. We can give you a copy of any of the photographs. If you do not wish to have photographs taken of your baby, you will be able to mark at the end of this consent that no photographs may be taken of your baby.

Follow-Up Visits (Infant) (1, 6, and 12 months)

We will ask you to bring your baby in for follow-up visits to make sure your infant(s) is/are healthy. You will be asked questions about where you live, how to keep in touch with you and your baby, about the health of your baby, and any medicines your baby might be taking. At this visit, the study staff will also do the following to make sure your baby is healthy:

- Measure the weight, length, and head size of your baby
- Perform a physical exam
- If it looks like something might be wrong with your baby, the study doctor might take a picture of your baby and share that picture with experts who may be able to see what the problem might be. If you agree to have pictures taken of your baby, you will be asked to mark your permission at the end of this consent. We can give you a copy of any of the photographs. If you do not wish to have photographs taken of your baby, you will be able to mark at the end of this consent that no photographs may be taken of your baby.

Any Time During The Study:

Please tell the study staff about any medical problems you might have with your baby during the study. You can contact the study staff between regular visits to report these problems. The study staff will check your baby as needed and will refer you for medical care. At each study visit, the study staff will update the medical history of your baby as well as information on where you and your baby live and how to keep in touch with you.

How Many Babies Will Be In this Study?

Babies who are born to women who became pregnant during HIV prevention trials or to women who enroll or enrolled in an HIV prevention trial while pregnant (as long as the baby has not reached its one year birth date) will be in this study. This number is expected to be about 400 babies.

How Long Will My Baby Be In This Study?

Your baby will be in this study until about the time he or she turns one year old. If you have more than one baby in this pregnancy (such as twins), each of those babies may participate in this study.

Can the Doctor Take My Baby Off This Study Early?

The study doctor may take your baby off the study early without your permission for any of the following reasons:

- The study is stopped or canceled.
- Staying in the study would be harmful to your baby.
- Other reasons that may prevent your baby from completing the study successfully

What Are The Risks Of This Study?

You may be uncomfortable with the personal types of questions asked.

Possible Risks to Your Baby's Privacy

We will make every effort to protect the privacy of your baby while you are in this study. Visits here will take place in private. However, it is possible that others may learn of the participation of your baby here and, because of this, may treat you unfairly. For example, you could have problems getting or keeping a job or being accepted by your family or community. There also is a risk to the privacy of your baby if someone else taking part in this study knows you. Efforts to protect you and the privacy of your baby include only allowing medical staff to see any photographs that might be taken of your baby. If you do not feel comfortable about having any photographs taken of your baby, a doctor may write a detailed description instead, and your baby will still be allowed to stay in the study.

What are the Benefits of This Study?

Participants in this study may experience no direct benefit. You or others may benefit in the future from information learned in this study. Knowledge gained from this study may help in the development of medications that are safe for use in pregnant women, for the prevention of HIV infection. You may also get some personal satisfaction from being part of research on preventing HIV.

New Information

You will be told any new information learned during this study that might affect your willingness to let your baby stay in the study.

What Other Choices Does My Baby Have Besides This Study?

You do not have to have your baby participate in this study. The decision to not have your baby participate in this study will not affect the regular care of your baby in any way.

What About Confidentiality?

We will do everything we can to protect the privacy of your baby. Also, any scientific publication about this study will not use the name of your baby or identify your baby personally.

[Insert the following paragraph for US sites only] In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study to anyone you choose. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

People who may review your records include the following: (insert Name of Site) Institutional Review Board (IRB), Ethics Committees (EC), National Institutes of Health (NIH), study staff, study monitors, and the government and other regulatory authorities.

What Are The Costs To Me?

There is no cost to you for study visits or exams of your baby. This study will not provide or pay for others to provide routine infant care.

Will I Receive Any Payment?

You will receive payment for your time and effort in this study. You may also receive payment for activities affected by the participation of your baby in this study, [such as child care, travel cost, loss of work time - local sites to list particulars].

What Happens If My Baby Is Injured?

If your baby is injured as a result of being in this study, your baby will be given immediate treatment for any injuries. However, you [insert if applicable: or your insurance company (or the baby's insurance company)] may have to pay for this care. This institution or the United States National Institutes of Health does not have a program to provide money for your or your baby's injuries. You will not be giving up any of your legal rights by signing this consent form.

What Will Happen If My Baby Becomes Infected With HIV While In This Study?

If your baby becomes infected with HIV while participating in the study, we would like you to continue to bring your baby in for study visits. We will also provide counseling and referrals to available care and support for your baby. We will ask you to complete a separate consent form to have your baby come to the clinic for HIV-related visits.

What Are My Rights?

Being in this study is completely voluntary. You may choose not to let your baby be in or to leave the study at any time. You and your baby will be treated the same no matter what you decide. If you choose not to let your baby be in or to leave the study, you and your baby will not lose the benefit of services to which you would otherwise be entitled at this clinic. Study staff will tell you about any new information from this or other studies that may affect your or the health or welfare of your baby. At the end of the study, you will be told when study results may be available and how to learn about them.

What Do I Do If I Have Problems or Questions?

For questions about this study or a research-related injury, contact: [insert contact information]

For questions about your rights as a research participant, contact: [insert contact information]

SIGNATURES

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

If you have read the informed consent, or had it read and explained to you, and all your questions have been answered, and you agree to let your baby be in this study, please sign your name or make your mark below.

Please mark one of the following boxes to show whether you agree/ not agree to have photograph(s) of your baby taken as may be requested by study staff:

- The study staff may take photograph(s) of my baby
- The study staff may **NOT** take photograph(s) of my baby

Mother/Guardian Name (print)

Mother/Guardian Signature/Mark and Date

Father's Name (print)

Father's Signature/Mark and Date
(if reasonably available)

Baby's Name (print)

Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)

Witness' Signature and Date

APPENDIX VII: SAMPLE INFORMED CONSENT – INFANT TESTING

MTN-016 HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study

Version 2.0

PRINCIPAL INVESTIGATOR: TBD
PHONE: TBD
Short Title for the Study: EMBRACE

Introduction

With your permission, your baby is enrolled in the EMBRACE study, which is funded by the United States National Institutes of Health. A baby of an HIV-infected mother is at risk of getting the HIV infection through the womb, at the time of labor and delivery, or through breast milk. Because your baby is at risk for HIV infection, you are being asked to agree to additional testing for your baby.

The person in charge of this study at this site is [INSERT NAME OF PRINCIPAL INVESTIGATOR].

Before you decide whether to have additional testing for your baby, we want to explain the purpose of these tests, the risks and benefits, and what is expected of you. This consent form gives information that the study staff will discuss with you. You are free to ask questions at any time. If you agree to take part in this study, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

Laboratory Assessments for Babies

There are two kinds of HIV tests done as part of this study. You may choose to have these tests done for your baby as part of this study.

The first test is to find out (or confirm) if your infant has HIV infection. The test for HIV of your baby would mean that a small blood sample about XX drops [or mL] [SITES TO INSERT LOCAL EQUIVALENT] would be taken from your baby. It may be necessary to test again at other times depending on the results of the first tests and on whether the baby is being breastfed.

If your baby is HIV infected, another test of the HIV virus will be available for your baby, as well. This is a test to see whether the HIV virus in your baby has any resistance to the medications used to treat HIV. Today and at other study visits for your baby, we will need a blood sample of about XX mL [SITES TO INSERT LOCAL EQUIVALENT] for this test. Some samples will be collected and stored in your own country before being shipped to a central laboratory in the US for testing at a later date.

Depending on the type of test used, these test results may or may not be useful for your baby's healthcare provider to make decisions about your baby's medical care. With your permission, these results may be shared with your baby's healthcare provider.

What Are The Risks Of These Tests?

When blood is drawn, there may be bruising, swelling, or infection (rare) where the needle goes in to draw the blood. You may feel worried while waiting for test results for your baby.

What Will Happen If My Baby Is Infected With HIV?

If tests show that your baby is infected with HIV, we will make certain that your baby is receiving appropriate available medical care. Care and treatment of HIV is not provided through EMBRACE. The results of the HIV resistance tests may be made available to your baby's healthcare provider.

Possible Risks to Your Privacy or Your Baby's Privacy

We will make every effort to protect your privacy and the privacy of your baby while you are here for testing, and your baby's blood will be obtained in a private place. However, it is possible that others may learn that your baby is having blood drawn here and, because of this, may treat you unfairly. For example, you could have problems getting or keeping a job or being accepted by your family or community. There also is a risk to your privacy or the privacy of your baby if someone else taking part in this study knows you.

What are the Benefits of These Tests?

You may experience no direct benefit from these extra tests. The doctors who are taking care of your baby may be able to use this information to help choose the best treatment. You or others may benefit in the future from information learned in this study. Knowledge gained from this study may help in the development of medications for the prevention of HIV infection. You may also get some personal satisfaction from being part of research on preventing HIV.

New Information

You will be told any new information learned during this study that might affect your willingness to let your baby stay in the study.

What Other Choices Do I Have Besides This Study?

You and your baby do not have to participate in these extra tests. The decision to not have these extra tests will not affect your regular care or the regular care of your baby in any way.

What About Confidentiality?

We will do everything we can to protect your privacy and the privacy of your baby. Also, any scientific publication about this study will not use your name or the name of your infant or identify you or your baby personally.

[Insert the following paragraph for US sites only] In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study to anyone you choose. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

People who may review your records include the following: (insert Name of Site) Institutional Review Board (IRB), Ethics Committees (EC), National Institutes of Health (NIH), study staff, study monitors, and government and other regulatory authorities.

What Are The Costs To Me?

There is no cost to you for these extra tests. This study will not provide or pay for others to provide routine prenatal care, delivery, postpartum, or routine infant care.

Will I Receive Any Payment?

Because you and your baby are participants in EMBRACE, compensation is being provided through that study. [Sites to insert if applicable: You will be compensated for your time and effort in this study.]

What Happens If My Baby Is Injured?

If your baby is injured as a result of being in this study, they will be given immediate treatment for injuries as well. However, you [insert if applicable: or your insurance company (or the baby's insurance company)] may have to pay for this care. This institution or the United States National Institutes of Health does not have a program to provide money for your or your baby's injuries. You will not be giving up any of your legal rights by signing this consent form.

What Are My Rights?

Having these extra tests is completely voluntary. If you choose not to have these extra tests, neither you nor your baby will lose the benefit of services to which either of you would otherwise be entitled at this clinic.

What Do I Do If I Have Problems or Questions?

For questions about this study or a research-related injury, contact: [insert contact information]. For questions about your rights as a research participant, contact: [insert contact information]

SIGNATURES

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

If you have read the informed consent, or had it read and explained to you, and all your questions have been answered, and you agree to be in this study, please sign your name or make your mark below.

Mother/Guardian Name (print)

Mother/Guardian Signature/Mark and Date

Father's Name (print)

Father's Signature/Mark and Date
(If Reasonably Available)

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness' Signature and Date

**APPENDIX VIII: SAMPLE INFORMED CONSENT – OFF SITE VISIT
(MOTHER AND INFANT)**

**MTN-016
HIV Prevention Agent Pregnancy Exposure Registry:
EMBRACE Study**

Version [INSERT]

PRINCIPAL INVESTIGATOR:

PHONE:

Short Title for the Study: EMBRACE

Introduction

You have decided to take part in MTN-016 or EMBRACE (Evaluation of Maternal and Baby outcome Registry After Chemoprophylactic Exposure) study, which is funded by the United States National Institutes of Health. As part of the EMBRACE study, you have agreed to come to the study clinic for your scheduled study visits. If needed, some of the study visits for you and/or your baby may take place at your home or other location outside of the research clinic, if you agree. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the type of visit and the duration of it) and the procedures to maintain your information in a confidential manner. This consent form gives you information about off-site visits. The study staff will talk with you about this information. Please ask study staff any questions you may have. You will be asked to sign or make your mark on this form to indicate whether you agree to off-site visits. You will be offered a copy of this form to keep.

Participation in off-site visits is voluntary.

To conduct visits outside of the study clinic we will need you to authorize us to do so. Choosing not to be visited outside of the study clinic will not affect your participation in the MTN-016 study. You can withdraw your consent for off-site visits at any time. If you choose not to have off-site visits, it will not affect the care you would normally receive.

Are there benefits to agreeing to off-site visits?

It is generally expected that your study visits will occur at the study clinic. However, consenting to off-site visits may allow study staff to conduct visit procedures should there be occasions when you are unable to come to the study clinic.

Are there any possible risks?

It is important that you know that off site visits may eventually affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

Will I be paid for off-site visits?

You will be reimbursed for transportation and the time spent when off-site visits are conducted outside your home. The payment will be XX. When the off-site visit is conducted in your home, you will be reimbursed for time spent. The payment will be XX.

How will my privacy be protected?

Staff members conducting off-site visits will only do so at mutually agreed upon times and locations. No study records from previous visits will be taken off-site.

As with other study records, documentation from off-site visits may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- Institutional Review Board/Ethics Committees
- other local regulatory authorities
- study staff
- study monitors

We will do everything we can to protect your privacy and the privacy of your baby. Also, any scientific publication about this study will not use your name or the name of your infant or identify you or your baby personally.

[Insert the following paragraph for US sites only] In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study to anyone you choose. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

What Are My Rights?

Having off-site visits is completely voluntary. If you choose not to have off-site visits, neither you nor your baby will lose the benefit of services to which either of you would otherwise be entitled at this clinic.

What Do I Do If I Have Problems or Questions?

For questions about this study or a research-related injury, contact: [insert contact information]. For questions about your rights as a research participant, contact: [insert contact information]

SIGNATURES

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

If you have read the informed consent, or had it read and explained to you, and all your questions have been answered, and you agree to be in this study, please sign your name or make your mark below.

Mother/Guardian Name (print)

Mother/Guardian Signature/Mark and Date

Father's Name (print)

Father's Signature/Mark and Date
(If Reasonably Available)

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)
(As appropriate)

Witness' Signature and Date

REFERENCES

- 1 Holmes L, Harvey E, Coull B, Huntington K, Khoshbin S, Hayes A, Ryan L. The Teratogenicity of Anticonvulsant Drugs. *N Engl J Med* 2001; 344:1132-1138.
- 2 Global Fact Sheet. http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_FactSheet_Global_en.pdf. Accessed 19 July 2013.
- 3 HIV test and treat to prevent HIV Transmission among MSM and transgender women (SABES?). <http://clinicaltrials.gov/ct2/show/NCT01815580>. Accessed 14 August 2013.
- 4 Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART). <http://clinicaltrials.gov/ct2/show/NCT01900977>. Accessed 14 August 2013.
- 5 Primary HIV Prevention in Pregnant and Lactating Ugandan Women (PRIMAL). <http://clinicaltrials.gov/ct2/show/NCT01882998>. Accessed 14 August 2013.
- 6 Safety and Effectiveness of HIV-1 DNA Plasmid Vaccine and HIV-1 Recombinant Adenoviral Vector Vaccine in HIV-Uninfected, Circumcised Men and Male-to-Female (MTF) Transgender Persons Who Have Sex With Men. <http://clinicaltrials.gov/ct2/show/NCT00865566>. Accessed 14 August 2013.
- 7 On Demand Antiretroviral Pre-exposure Prophylaxis for HIV Infection in Men Who Have Sex With Men (IPERGAY). <http://clinicaltrials.gov/ct2/show/NCT01473472>. Accessed 14 August 2013.
- 8 Phase 3 Safety and Effectiveness Trial of Dapivirine Vaginal Ring for Prevention of HIV-1 in Women (ASPIRE). <http://clinicaltrials.gov/ct2/show/NCT01617096>. Accessed 14 August 2013.
- 9 Beigi R, Noguchi LM, Parsons T, Macio I, Kunjara R, Chen J, Hendrix C, Masse B, Valentine M, Piper J and Watts D. Pharmacokinetics and placental transfer of tenofovir 1% vaginal gel in term pregnancy. *Journal of Infectious Diseases* 2011; 204: 1527-1531.
- 10 Tenofovir Gel in Pregnancy and Lactation. <http://clinicaltrials.gov/ct2/show/NCT01136759>. Accessed 14 August 2013.
- 11 Beigi R, Noguchi LM, Parsons T, Macio I, Kunjara R, Chen J, Hendrix C, Masse B, Valentine M, Piper J and Watts D. Pharmacokinetics and placental transfer of

tenofovir 1% vaginal gel in term pregnancy. *Journal of Infectious Diseases* 2011; 204: 1527-1531.

- ¹² Tenofovir Gel in Pregnancy and Lactation.
<http://clinicaltrials.gov/ct2/show/NCT01136759>. Accessed 14 August 2013.
- ¹³ Gray, R. H. et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet* 357, 1149-53 (2001).