

**MTN-042B**

**Assessing Baseline Pregnancy Outcomes in Sub-Saharan Africa**

**Microbicide Trials Network**

**Funding Agencies:**

**Division of AIDS, US National Institute of Allergy and Infectious Diseases  
US National Institutes of Health**

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**A Non-IND Study**

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# MTN-042B

## Assessing Baseline Pregnancy Outcomes in Sub-Saharan Africa

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## **MTN-042B**

### **Assessing Baseline Pregnancy Outcomes in Sub-Saharan Africa**

#### **LIST OF ABBREVIATIONS AND ACRONYMS**

CRS	clinical research site
CTU	clinical trials unit
DAIDS	Division of Acquired Immunodeficiency Syndrome
EC	Ethics Committee
EMA	European Medicines Agency
FDA	Food & Drug Administration (U.S.)
FHCRC	Fred Hutchinson Cancer Research Center
HIV	human immunodeficiency virus
ICH	International Council on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
LOC	Leadership and Operations Center
MTN	Microbicide Trials Network
MU-JHU	Makerere University – John Hopkins University Research Collaboration
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
PSP	Prevention Sciences Program
SAHPRA	South African Health Products Regulatory Authority
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDMC	Statistical Data Management Center
SOP	standard operating procedure
UPMC	University of Pittsburgh Medical Center
USA	United States of America

**MTN-042B**

**Assessing Baseline Pregnancy Outcomes in Sub-Saharan Africa**

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**MTN-042B**

**Assessing Baseline Pregnancy Outcomes in Sub-Saharan Africa**

**INVESTIGATOR SIGNATURE FORM**

Version 1.0; January 16, 2019

A Study of the Microbicide Trials Network

**Funded by:**

Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases  
US National Institutes of Health (NIH)

**IND Sponsor:**

A Non-IND Study (DAIDS Protocol ID: 38607)

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); standards of the International Council on Harmonisation (ICH) Guideline for Good Clinical Practice (E6); Institutional Review Board/Independent Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., NIH, DAIDS) and institutional policies.

I agree to maintain MTN study records in accordance with protocol-specified protections of participants' confidentiality and with site IRB/IEC policies and procedures. Study records must be maintained on-site for the entire implementation period of the study and a minimum of at least three years after completion of research as per 45 CFR 46.115 (b). DAIDS/designee will inform the investigator/institution as to when these documents no longer need to be retained.

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 (print)

\_\_\_\_\_  
Signature of Investigator of Record

\_\_\_\_\_  
Date

## MTN-042B

### Assessing Baseline Pregnancy Outcomes in Sub-Saharan Africa

#### PROTOCOL SUMMARY

- Short Title:** Assessing Baseline Pregnancy Outcomes in Sub-Saharan Africa
- Funders:** Division of AIDS, US NIH
- Protocol Chairs:** Katherine Bunge, MD, MPH  
Bonus Makanani, MBBS, FCOG(SA)  
Lee Fairlie, MBChB, FCPaedS
- Sample Size:** Approximately 11,000 (8 weeks of deliveries at 4 sites)
- Study Population:** All women delivering or receiving immediate postpartum care (within one week of delivery) at one or two facilities affiliated with each of the 4 sites, a primary care facility and a referral facility
- Study Sites:**
- Blantyre Clinical Research Site (CRS)
  - The University of Zimbabwe College of Health Sciences Clinical Trials Research Centre, Zengeza CRS
  - Makerere University - Johns Hopkins University (MU-JHU) Research Collaboration CRS
  - Wits RHI Shandukani Research Centre CRS
- Study Design:** Multi-site, chart review, cross sectional study
- Study Duration:** Approximately 8 weeks
- Primary Objective:** **Pregnancy Outcomes**
- To determine the frequency of the following pregnancy outcomes:
    - Full term live birth ( $\geq 37$  weeks)
    - Premature live birth ( $< 37$  weeks)
    - Stillbirth/intrauterine fetal demise ( $\geq 20$  weeks)
- Primary Endpoints:** **Pregnancy Outcomes**
- Full term live birth ( $\geq 37$  weeks)
  - Premature live birth ( $< 37$  weeks)
  - Stillbirth/intrauterine fetal demise ( $\geq 20$  weeks)
- Secondary Objectives** **Pregnancy Complications**
- To determine the frequency of the following pregnancy complications:
    - Fever of unclear etiology
    - Chorioamnionitis
    - Postpartum endometritis

- Postpartum hemorrhage
- Gestational hypertensive disorder
  - Gestational hypertension
  - Pre-eclampsia
  - Eclampsia

**Birth Weight**

- To determine the mean birth weight
- To determine proportion low birth weight (<2500g)

**Newborn Complications**

- To determine the frequency of the following newborn complications:
  - Neonatal death (after delivery, before mother is discharged)
  - Neonatal ICU admission
  - Congenital malformations

**Method of Delivery**

- To determine the method of delivery:
  - Cesarean section
  - Vaginal delivery
    - Spontaneous/Unassisted
    - Assisted

**Secondary Endpoints: Pregnancy Complications**

- Fever of unclear etiology
- Chorioamnionitis
- Postpartum endometritis
- Postpartum hemorrhage
- Gestational hypertensive disorder
  - Gestational hypertension
  - Pre-eclampsia
  - Eclampsia

**Birth Weight**

- Mean birth weights of infants
- Low birth weight (<2500g)

**Newborn Complications within 7 days of life**

- Neonatal death (after delivery, before mother is discharged)
- Neonatal ICU admission
- Congenital malformations

**Method of Delivery**

- Cesarean section
- Vaginal delivery
  - Spontaneous/Unassisted
  - Assisted

# **1 KEY ROLES**

## **1.1 Protocol Identification**

Protocol Title: Assessing Baseline Pregnancy Outcomes in Sub-Saharan Africa

Protocol Number: MTN-042B

Date: January 16, 2019

## **1.2 Sponsor and Monitor Identification**

Funding Agencies: US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID)  
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## **2 INTRODUCTION**

### **2.1 Exclusion of pregnant women in drug studies**

The introduction of a new drug to market requires a carefully coordinated stepwise approach. First the drug is determined to be safe in pre-clinical trials involving animals and then in humans. Finally, the drug's efficacy is confirmed in larger clinical trials before the manufacturers seek regulatory approval. Most studies of investigational drugs intentionally exclude pregnant women and require that female participants of reproductive age use an effective method of contraception while using the investigational drug.

Without clear safety data in pregnancy derived from clinical trials, most drugs are released onto the market without an indication for use in pregnancy. Although medication use (and fetal exposure) during pregnancy is common, the current regulatory approach continues to limit research efforts during pregnancy.<sup>1</sup> The burden of whether to prescribe a new drug to a pregnant woman then falls to the health care provider who has to speculate about the potential risks to the fetus as well as possible dose adjustments due to physiologic changes associated with pregnancy.

### **2.2 Intentional research in a pregnant cohort and the need for a comparator**

The ethical imperative to investigate medication during pregnancy is a well-recognized concept with documented justification. Informed use of medical therapies during pregnancy is necessary to optimize care (principle of beneficence) and there is a large societal cost from the lack of safety data and the resulting reticence to use indicated therapies during pregnancy.<sup>1</sup> The FDA<sup>2</sup>, EMA<sup>3</sup>, and SAHPRA<sup>4</sup>, among other organizations, consider inclusion of pregnant women in clinical trials ethically justifiable when the trial holds the prospect of direct benefit to the mother and/or fetus, and adequate nonclinical studies have been completed on the investigational products. There is a growing movement to encourage the inclusion of pregnant women in clinical trials in order to obtain important safety data in a controlled, highly monitored setting.<sup>5</sup> The ideal time to conduct such trials would be immediately after the drug has been proven to be effective in a non-pregnant cohort. At that juncture, the benefit of the drug could be balanced against the risk of exposure to the mother and developing fetus; however, in such a scenario, conducting a placebo-controlled trial would be ethically challenging. A preferred model would be to provide the drug to all participants and follow pregnant women through to pregnancy outcome and infants through the first year of life. Pregnancy outcomes and adverse events would then be compared to the background rates. Background rates likely vary between different locations and clinical settings; thus, these rates should be assessed in the same populations included in the research in order to be a valid comparator. One way to obtain the needed background data is to conduct contemporaneous data collection in delivery facilities serving the same populations targeted for enrollment within the research study. MTN-042B is designed to serve this purpose for the MTN-042 study.

## 2.3 MTN-042

The U.S. National Institutes of Health-funded Microbicide Trials Network (MTN) is planning a Phase IIIb study called MTN-042 that will help answer key questions about the safety of oral PrEP and the dapivirine ring for HIV prevention when used during pregnancy. The study will be conducted at four trial sites in Malawi, Uganda, South Africa, and Zimbabwe, and enroll 750 women at different stages of pregnancy who would be randomly assigned to use either oral PrEP or the dapivirine ring until the time they deliver.

The trial design involves a stepwise backwards approach with four cohorts. Only women late in pregnancy (about 36 weeks) will be enrolled into the first cohort (n=150). Participants will be carefully monitored during product use, and after each cohort has completed study product use, an interim safety review will be conducted. Rates of adverse pregnancy outcomes observed in the clinical trial cohort will be compared to the background rate at each institution determined in this study, MTN-042B. A significant discrepancy may result in halting the clinical trial. If no safety concerns are identified, the second cohort (30-35 weeks; n=150) will begin enrollment and a similar review be conducted after the second cohort has completed study product. This process will be repeated for the next cohort (20-29 weeks; n=150) such that by the time the last and largest cohort (12-20 weeks; n=300) is enrolled, researchers will be confident that adverse pregnancy outcomes observed in the clinical trial are comparable to background rates. In the later cohorts where gestational age will be recorded more accurately, including ultrasound, and women followed for longer periods of the pregnancy, it is expected that outcomes will be defined more precisely.

## 2.4 Rationale

This cross-sectional chart review study will provide important background pregnancy outcome data for MTN-042 and other clinical trials involving pregnant women in Sub-Saharan Africa.

## 3 OBJECTIVES

### 3.1 Primary Objective:

#### **Pregnancy Outcomes**

- To determine the frequency of the following pregnancy outcomes:
  - Full term live birth ( $\geq 37$  weeks)
  - Premature live birth ( $< 37$  weeks)
  - Stillbirth/intrauterine fetal demise ( $\geq 20$  weeks)



## 3.2 Secondary Objectives

### Pregnancy Complications

- To determine the rate of the following pregnancy complications:
  - Fever of unclear etiology
  - Chorioamnionitis
  - Postpartum endometritis
  - Postpartum hemorrhage
  - Gestational hypertensive disorder
    - Gestational hypertension
    - Pre-eclampsia
    - Eclampsia

### Birth Weight

- To determine the mean birth weight
- To determine proportion with low birth weight (<2500g)

### Newborn Complications within 7 days of life

- To determine the rate of the following newborn complications:
  - Neonatal death (after delivery, before mother is discharged)
  - Neonatal ICU admission
  - Congenital malformations

### Method of Delivery

- To determine the method of delivery:
  - Cesarean section
  - Vaginal delivery
    - Spontaneous/Unassisted
    - Assisted

## 4 STUDY DESIGN

### 4.1 Identification of Study Design

This is a multi-site, chart review, cross-sectional study.

### 4.2 Summary of Major Endpoints

#### Primary Endpoints:

#### Pregnancy Outcomes

- Full term live birth ( $\geq 37$  weeks)
- Premature live birth (<37 weeks)
- Stillbirth/intrauterine fetal demise ( $\geq 20$  weeks)

## Secondary Endpoints:

### **Pregnancy Complications**

- Fever of unclear etiology
- Chorioamnionitis
- Postpartum endometritis
- Postpartum hemorrhage
- Gestational hypertensive disorder
  - Gestational hypertension
  - Pre-eclampsia
  - Eclampsia

### **Birth Weight**

- Mean birth weights of infants
- Low birth weight (<2500g)

### **Newborn Complications within 7 days of life**

- Neonatal death (after delivery, before mother is discharged)
- Neonatal ICU admission
- Congenital malformations

### **Method of Delivery**

- Cesarean section
- Vaginal delivery
  - Spontaneous/Unassisted
  - Assisted

## **4.3 Description of Study Population**

The MTN-042B study population will consist of all women who deliver or receive immediate postpartum care (within one week of delivery) at the identified facilities

## **4.4 Data Collection Period**

Birth records from a period of 8 weeks at the identified facilities will be included in the abstraction. Data abstraction will be conducted in real time, but may extend beyond this period as needed.

## **4.5 Sites**

There are four proposed sites for data collection:

- Blantyre Clinical Research Site (CRS)
- The University of Zimbabwe College of Health Sciences Clinical Trials Research Centre; Zengeza CRS
- Makerere University - Johns Hopkins University (MU-JHU) Research Collaboration CRS
- Wits RHI Shandukani Research Centre CRS

## **5 STUDY POPULATION**

### **5.1 Identification of the Study Population**

Pregnant women who deliver or who are admitted to the facility within 7 days of delivery for postpartum care over the 8-week data collection period will be identified through birth registries, and/or delivery and admission logs.

### **5.2 Data Collection Process**

Monday through Friday, members of the research team will go to the participating facility and review birth registries, delivery and/or postpartum admission log entries since the last data abstraction. There will be no interaction with women who have given birth or their health care providers. Each patient identified will be assigned a participant number. A master log linking the participant ID to a facility-assigned participant identifier, such as medical record number, will be maintained at the site and kept in a secure location per site SOP.

A staff member will complete the data abstraction form over the next several days. Once the patient is discharged home and/or seven days from delivery has passed if the participant remains in the facility, the data entry will be considered complete. It is anticipated that some data will be readily available on the first review of the medical chart (e.g. gestational age, type of delivery, etc). Other variables should be finalized at the time of discharge or seven days after delivery if the patient is still admitted to the facility (chorioamnionitis, postpartum hemorrhage, etc.). The research team will keep track of the last time the chart was reviewed through the use of stickers applied to the participants chart (or a comparable system outlined by a site-specific SOP). In this way, researchers will be able to ensure that each chart is assigned a single PTID and complications that might occur in the days after delivery are not missed (chorioamnionitis, etc.)

## **6 STUDY PRODUCT**

This observational study does not have any study product.

## **7 STUDY PROCEDURES**

This observational study does not have any study procedures.

## **8 ASSESSMENT OF SAFETY**

This observational study does not have need for safety assessments.

## **9 CLINICAL MANAGEMENT**

This observational study does not have need for clinical management.

## **10 STATISTICAL CONSIDERATIONS**

### **10.1 Review of Study Design**

The primary aim of this study is to provide an estimate of pregnancy outcome frequencies (term delivery, preterm delivery, still birth). We will use descriptive statistics to summarize the frequency of the primary and secondary outcomes overall and at each of the study hospitals.

## **10.2 Sample Size and Data Collection**

All women delivering at the designated facility or admitted to the facility for postpartum care within seven days of a delivery elsewhere (home, health clinic, etc.) will be included. All subjects should have an identifiable pregnancy outcome (full term delivery, preterm delivery, stillbirth). The time period of 8 weeks was chosen to aid in estimating the rarer rates of pregnancy complications (hemorrhage, hypertension, chorioamnionitis).

## **11 DATA HANDLING AND RECORDKEEPING**

A study data abstraction form will be developed by the MTN SDMC in conjunction with the protocol team. Study data is entered into the electronic CRFs using a data management system compliant with International Council on Harmonization (ICH) Good Clinical Practices (GCP) and CFR Guidelines, which is maintained by the MTN SDMC.

The site investigator will make study documents (e.g., eCRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, the NIAID, the OHRP, the industry supporter, and other local, US, or international regulatory authorities/entities for confirmation of the study data.

## **12 CLINICAL SITE MONITORING**

This observational study does not have need for clinical management.

## **13 HUMAN SUBJECTS CONSIDERATIONS**

There are no anticipated risks to the study subjects.

### **13.1 Informed Consent Waiver**

A waiver of informed written consent is requested as the proposed research presents no more than minimal risk to subjects and involves no procedures for which written consent is normally required outside of the research context. Furthermore, the research could not practically be carried out without the waiver. The number of individuals who deliver at these facilities is large and requiring informed written consent from each woman would make this review unfeasible. Lastly, patients with adverse outcomes would likely be less likely to engage in a research project during a period of illness and or grieving. This would substantially affect the results.

All data will be entered into a password protected de-identified database, where each record will not be traceable to an individual chart. Each chart will be assigned a unique PTID that will be used for all data collection and no participant identifiers will be collected in the database. Each site will maintain a separate log listing that links PTIDs to the facility-assigned participant identifier to avoid duplication of entry, but no names will be recorded.

### **13.2 Risk/Benefit Statement**

#### Risks

This trial will expose human subjects to minimal or no risk. As this is strictly a chart review data collection study, health care at the facilities will in no way be altered. No interventions will be conducted. There will be no interaction between the women and the data collection activity. The only potential risk will be breach of confidentiality. (See Section 13.4)

## Benefits

Women delivering during the study period will have no direct benefit from having their data collected.

### **13.3 Incentives**

There will be no interaction with women who deliver during the study period.

### **13.4 Participant Confidentiality**

Members of the study staff are all trained in patient confidentiality. Health information will only be captured by study number. No names, government issued numbers, or other identifiable information will be recorded into the database. A master log linking participant ID and facility-assigned participant identifier (e.g. medical record number, as outlined in a site specific SOP) will be kept in a secure location under lock and key. Furthermore, only information that directly relates to the outcomes of interest (pregnancy outcomes and specific complications) will be collected.

### **13.5 Special Populations**

#### **13.5.1 Pregnant Women**

Based on an assessment of potential risks and benefits associated with the MTN-042B study, the MTN-042B study team provides the following rationale to support the assertion that this study may be conducted. Final determination rests with each site's local IRB/EC.

As specified in US 45 CFR 46.204, pregnant women or fetuses may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
  - N/A, as is this observational study that does not involve study product.
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.
  - N/A, as is this observational study that does not include interventions or procedures.
3. Any risk is the least possible for achieving the objectives of the research.
  - As an observational study, this study will expose human subjects to minimal or no risk.
4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part.

- As an observational study, this study will expose human subjects to minimal or no risk.
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
    - As an observational study, this study will not provide direct benefit to the fetus.
  6. Each individual providing consent under paragraph (d) I(e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
    - This observational study requests a waiver of informed consent.
  7. For children as defined in 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part.
    - This observational study requests a waiver of informed consent for pregnant females who meet the definition of Children.
  8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
    - Inducements to terminate a pregnancy will not be offered by the MTN-042B study.
  9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
    - Individuals engaged in MTN-042B will have no part in decisions as to the timing, method, or procedures used to terminate a pregnancy by participants.
  10. Individuals engaged in the research will have no part in determining the viability of a neonate.
    - Individuals engaged in MTN-042B will have no part in determining the viability of a neonate.

### **13.5.2 Children**

The NIH has mandated that children be included in research studies when appropriate. Based on an assessment of potential risks and benefits associated with the MTN-042B study, the MTN-042B study team provides the following rationale to support the assertion that this study may be conducted. Final determination rests with each site's local IRB/EC.

As specified in US 45 CFR 46.205, neonates of uncertain viability and non-viable neonates may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
  - N/A, as is this observational study that does not involve study product.
2. Each individual providing consent for the neonate is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
  - This observational study requests a waiver of informed consent.
3. Individuals engaged in the research will have no part in determining the viability of a neonate.

- Individuals engaged in MTN-042B will have no part in determining the viability of a neonate.
4. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research.
    - As an observational study, this study will expose human subjects to minimal or no risk.
  5. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.
    - This observational study requests a waiver of informed consent.

As specified in US 45 CFR 46.405, children may be involved in research of greater than minimal risk but presenting the prospect of direct benefit to the individual subjects if all of the following conditions are met:

1. The risk is justified by the anticipated benefit to the subjects.
  - As an observational study, this study will expose human subjects to minimal or no risk.
2. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.
  - As an observational study, this study will expose human subjects to minimal or no risk.
3. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in § 46.408.
  - This observational study requests a waiver of informed consent.

## **14 PUBLICATION POLICY**

DAIDS/NIAID and MTN policies will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee and DAIDS/NIAID for review prior to submission.

## REFERENCES

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5. Wickremsinhe MN, Little MO, Carter AS, Sullivan KA, Lyerly AD. Beyond "Vessels and Vectors": A Global Review of Registered HIV-Related Clinical Trials with Pregnant Women. *J Womens Health (Larchmt)* 2018.