**MTN-003C**

# Household and Community Level Factors Associated with Study Product Adherence in VOICE: A Substudy of MTN-003

**Microbicide Trials Network**

**Sponsored by:**

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

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**A Non-IND Study**

**Protocol Chairs:**

**Jonathan Stadler, MA**

**Ariane van der Straten, PhD, MPH**

**Version 1.0**

**July 15, 2009**

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## List of Tables and Figures

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## LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| ACASI | Audio-Computer Assisted Self-Interview |
| AIDS | Acquired Immunodeficiency Syndrome |
| ARV | antiretroviral |
| BRWG | Behavioral Research Working Group |
| CAB | community advisory board |
| CORE | Coordinating and Operations Center |
| CRF | case report form |
| CWG | Community Working Group |
| DAIDS | Division of AIDS |
| DSMB | Data Safety and Monitoring Board |
| EAE | expedited adverse event |
| EC | Ethics Committee |
| FDA | US Food and Drug Administration |
| FGD | focus group discussion |
| FHI | Family Health International |
| FTC | emtricitabine |
| FTC/TDF | emtricitabine/tenofovir disoproxil fumarate |
| GCP | Good Clinical Practices |
| HIV | human immunodeficiency virus |
| HPTN | HIV Prevention Trials Network |
| IDI | in-depth interview |
| IND | investigational new drug |
| IoR | Investigator of Record |
| IRB | Institutional Review Board |
| MDP | Microbicides Development Programme |
| MIRA | Methods for Improving Reproductive health in Africa trial |
| MTN | Microbicide Trials Network |
| NGO | non-governmental organization |
| NIH | National Institutes of Health |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIMH | National Institute of Mental Health |
| OHRP | Office for Human Research Protections |
| PPD | Pharmaceutical Product Development, Inc. |
| PrEP | pre-exposure prophylaxis |
| PTID | participant identification number |
| QA | quality assurance |
| QC | quality control |
| RCC | Regulatory Compliance Center |

| | |
|---|---|
| SMC | Study Monitoring Committee |
| SSP | study specific procedures |
| STI | sexually transmitted infection |
| TB | tuberculosis |
| TDF | tenofovir disoproxil fumarate |
| VCT | Voluntary Counseling and Testing |
| VOICE | Vaginal and Oral Interventions to Control the Epidemic |

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**INVESTIGATOR SIGNATURE FORM**

**Version 1.0**
**July 15, 2009**

**A Study of the Microbicide Trials Network**

**Sponsored by:**
**Division of AIDS, US National Institute of Allergy and Infectious Diseases**
**US National Institute of Mental Health**
**US National Institutes of Health**

I, the Investigator of Record (IoR), agree to conduct this study in full accordance with the provisions of this protocol. I agree to maintain all study documentation for a minimum of three years after submission of the site's final Financial Status Report to the US Division of Acquired Immunodeficiency Syndrome (DAIDS), unless otherwise specified by 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 made available by the investigators to the MTN Manuscript Review Committee, NIMH, and DAIDS, for review prior to submission.

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-003C**
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## PROTOCOL SUMMARY

**Short Title:** VOICE Community and Adherence Substudy

**Co-Chairs:** Jonathan Stadler, MA and Ariane van der Straten, PhD, MPH

**Sample Size:** Approximately 275 participants per site

**Study Population:** The study population will consist of the following four groups:

- Group 1: VOICE participants at MTN-003C (VOICE-C) site(s) (approximately 150 per site)
- Group 2: Male partners of VOICE participants at VOICE-C site(s) (approximately 60 per site)
- Group 3: Members of Community Advisory Boards (CABs) at VOICE-C site(s) (approximately 15 per site)
- Group 4: Key community stakeholders in the community surrounding VOICE-C site(s) (approximately 50 per site)

**Study Sites:** Sites in sub-Saharan Africa as designated by the MTN Executive Committee

**Study Design:** Exploratory substudy of VOICE using qualitative research methods, including focus group discussions (FGDs), in-depth interview (IDI), ethnography, and observation and note-taking at male partner activities (in the VOICE trial) at participating VOICE-C site(s).

**Study Regimen for Participants:**

| Group | One-time IDI | Ethnography | FGD |
|---|---|---|---|
| **1a. VOICE Participants** | | Offered to randomly selected, eligible participants who do not participate in IDI or FGD during VOICE accrual and follow-up period | |
| **1b: VOICE Participants** | | | One-time exit FGD offered to each VOICE participant randomly selected and eligible to participate in VOICE-C* after VOICE study participation |
| **1c: VOICE Participants** | Offered to each VOICE participant randomly selected and eligible to participate in MTN-003C during VOICE accrual period | | |
| **2a: Male Partners of VOICE Participants** | | | One-time exit FGD offered to current male sexual partners of VOICE participants systematically selected and eligible to participate, and whose female partners consent for him to be contacted after completion of VOICE trial* |
| **2b: Male Partners of VOICE Participants** | Offered to current male sexual partners of VOICE-C participants systematically selected and eligible to participate, and whose female partner consents for him to be contacted during VOICE accrual period** | | |
| **3: CAB Members** | | | Offered to members of CABs affiliated with VOICE-C sites who meet eligibility criteria. The FGDs will be conducted during VOICE accrual and follow-up period |
| **4: Key Community Stakeholders** | | | Offered to key community stakeholders at VOICE-C sites who are purposively selected, by CAB members, community group members, and/or site staff and who meet eligibility criteria during VOICE accrual and follow-up period |
| * IDIs will be an option for eligible participants if they decline to participate in an exit FGD<br>***Participation will be extended to male partners of VOICE (not VOICE-C) participants if recruitment targets are not met* | | | |

**Primary Objectives:**

1. To explore socio-cultural and contextual factors that participants identify as influencing product use (and non-use) in VOICE

2. To determine if factors identified by participants as influencing product use (and non-use) are different between those who are randomized to the vaginal product vs. oral product

3. To elicit Group 1 participants' perceptions of the importance of adherence, and their experiences of barriers and facilitators to adherence

**Secondary Objectives:**

1. To elicit "external" stakeholders' perspectives on the trial, with a focus on its acceptance at the household level and in the community, and views on adherence-related issues among the following groups:

    a. Male partners of study participants (Group 2)
    b. CAB members (Group 3)
    c. Key community stakeholders (Group 4)

2. To solicit the input of external stakeholders on developing and implementing strategies to improve product adherence in the trial

3. To collect feedback from Group 1 and Group 2 participants on their experience with these implemented strategies through specific questions in the exit FGDs

# 1 KEY ROLES

## 1.1 Protocol Identification

Protocol Title: Household and Community Level Factors Associated with Study Product Adherence in VOICE: A Sub-study of MTN-003

Protocol Number: MTN-003C

Short Title: VOICE-C

Date: July 15, 2009

## 1.2 Sponsor and Monitor Identification

Sponsor: DAIDS/NIAID/NIH
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# 2 INTRODUCTION

## 2.1 The VOICE Study

The VOICE Study is designed to assess the safety and efficacy of daily dose oral and vaginal formulations of tenofovir and oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in preventing HIV acquisition. The study design of VOICE also allows limited comparisons of effectiveness, safety, adherence, and associated frequency of viral resistance among HIV seroconverters across formulations.

The VOICE study is a Phase 2B, five-arm, multi-site, randomized, placebo-controlled trial that is double-blinded within each mode of administration, but open-label with respect to the randomly assigned mode of administration (vaginal or oral). Approximately 4200 participants will be randomized to the five study arms in a 1:1:1:1:1 ratio. The VOICE study will be implemented in sub-Saharan Africa.

While investigators and participants will be aware of randomization to either the oral or vaginal administration of study product, they will be blinded to the specific study products randomly assigned. All participants will complete monthly follow-up visits for a period of 12 to 33 months, and will receive ongoing HIV risk reduction counseling, condoms, and diagnosis and treatment of STIs throughout the course of study participation. Participants will also be scheduled for a Termination Visit approximately 8 weeks following completion of their scheduled end-of-study product use.

The proposed substudy, VOICE-C, is ancillary to the VOICE study, and will be implemented at site(s) selected by the MTN Executive Committee, in a subset of VOICE participants, their male partners, CAB members and key community stakeholders.

## 2.2 Adherence and Behavioral Measures in VOICE

The VOICE study includes the following objectives related to study product adherence and behavior:

- To evaluate adherence to daily regimens of vaginal gel (tenofovir 1% gel and placebo) vs. oral tablets (TDF, FTC/TDF, and placebos) used to prevent HIV infection

- To evaluate whether sexual activity, condom use, and intravaginal practices change over time in women who use either daily vaginal gel (tenofovir 1% gel and placebo) or daily oral tablets (TDF, FTC/TDF, and placebos)

These objectives will be assessed using study product counts, face-to-face interviewing (with responses collected on Case Report Forms (CRFs), and Audio-Computer Assisted Self Interview (ACASI), and will focus primarily on individual-level factors that may influence adherence to study product use and other participant behaviors of interest.

However, it is hypothesized that other important social, cultural and contextual factors that operate at the household, organizational and community levels may influence VOICE participants' willingness or ability to adhere to the study product use regimen. The purpose of VOICE-C is to qualitatively explore these additional factors and the level at which they may hinder or facilitate adherence. In addition to being of significant scientific interest in and of itself, collection of this information during implementation of VOICE will allow for rapid response to any identified barriers to adherence that are considered modifiable by the VOICE Protocol Team. In summary, VOICE-C will have two components: a) a descriptive component which involves the qualitative exploration of barriers and facilitators of product adherence among VOICE participants, and the level (household, community, organizational) at which they operate and b) a strategic component, wherein issues identified through the descriptive component will be brought back to the VOICE protocol team, and decisions will be made about the modification or implementation of new adherence strategies across all VOICE sites.

## 2.3 Background

### 2.3.1 Socio-cultural Considerations and the Importance of Community in HIV Prevention Trials

Because the study populations of interest are HIV-negative and generally healthy, HIV prevention trials face a unique adherence challenge as participants are asked to adhere to a regimen to possibly prevent HIV infection, rather than to treat a pathologic condition.[1] Thus the incentive to adhere may be less than in treatment trials in which participants may more directly benefit from treatment. Beyond individual motivation to adhere to a prevention regimen, numerous external factors may influence a participant's willingness and ability to adhere to such a regimen. This study will examine challenges to optimal adherence to two different prevention regimens. This study is informed by a socio-ecological model which recognizes an individual's behavior as influenced by external factors operating at various levels beyond the individual.[2]

Figure 1 and Table 1 present an adapted socio-ecological model of various levels of influence on an individual's adherence to product use. Within the 3 levels considered — household, organizational and community — several factors may influence adherence. Additionally, some factors such as gender norms and HIV-related stigma may pervade all levels. This study aims to explore these external influences and to identify potential strategies to eliminate or mitigate any identified barriers to product use during the VOICE study.

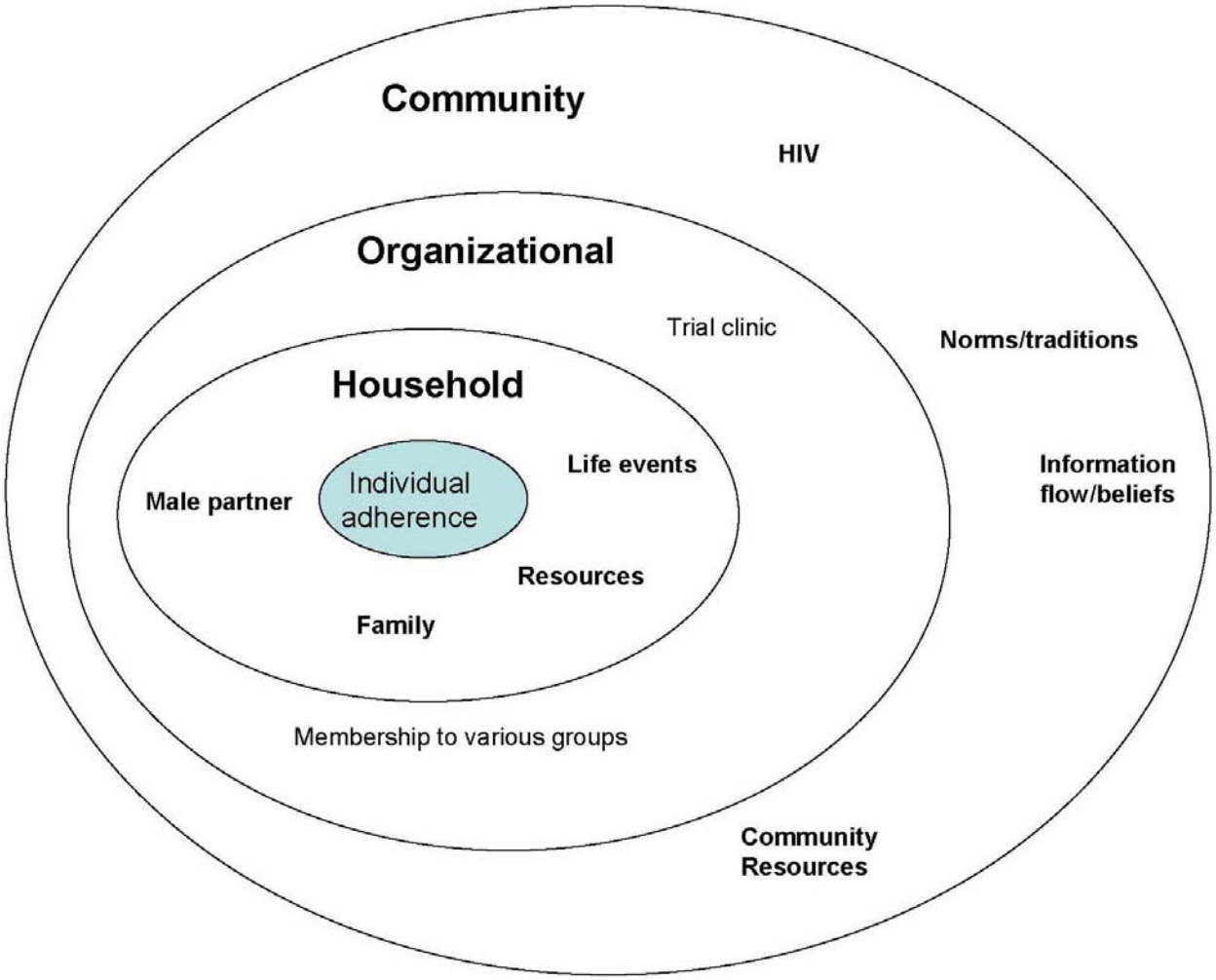


**Figure 1: Socio-ecological Model of Factors Affecting Adherence in VOICE, and Levels of Influence (household, organizational and community)**

### 2.3.2 Household level

"Household" is defined as people (generally family members) living together, sharing relationships and resources. Several studies in Africa have highlighted the important role played by family members, and specifically male partners in women's use of female-initiated HIV prevention methods.[3-6] Qualitative research with men, women and opinion leaders in Southern Africa has universally stressed the importance of involving male partners in any investigation of HIV/STI prevention products.[7-10] Less information is available about the influence of other household or social support network members. In the antiretroviral (ARV) treatment literature, there have been reports that use of "buddy systems" and other social network strategies to improve adherence have been successful.[11] Household resources are also hypothesized to affect adherence. For example, employment may affect participants' ability to attend clinic visits at which product supplies are dispensed and crowded housing situations may inhibit product use if participants have not informed family or household members of their study participation. Life events, such as birth, death, employment, and/or relationship

changes, are likely to impact routine as well as emotional status or HIV risk perception, and thus influence one's ability to adhere to study regimen.

### 2.3.3 Organizational Level

The organizational level refers to the sphere of influence that is beyond the household, but representative of a smaller, more specific group of individuals than the broader community as a whole. For example, women's membership in a church, market group or the VOICE trial itself may influence adherence through personal interactions, peer pressure or exposure to information, education and group norms. A qualitative study in Soweto that compared attitudes between the general community and trial participants reported that while those in the community expressed Acquired Immunodeficiency Syndrome (AIDS) information "fatigue" and fatalism about knowing one's serostatus, those who joined a microbicide trial ascribed to their participation a sense of self-worth, and empowerment to protect oneself from HIV.[12]

In this study, we will explore organizational-level factors, and specifically, the influence of the clinical trial site. Although we recognize its importance, the organizational level will not be the main focus of VOICE-C. While the VOICE-C Substudy staff will be different from the VOICE clinical team, it will still be viewed as associated with the larger VOICE trial. Therefore, an inherent bias may exist when gathering data on the role of the trial, study procedures and clinical staff on participants' product use. We will, however, have opportunities to observe and collect information on this sphere of influence, particularly during the ethnography visit and IDIs with Group 1 participants.

### 2.3.4 Community level

Of particular interest to this study are community-level factors that may influence product adherence. "Community" is a broad term with multiple dimensions and definitions.[13] For purposes of this substudy, "community" is taken to refer to a physically and geographically discrete place with an organization and structure that is broadly recognized by a government and the individuals who live there. However, it is recognized that within a "geographic community" there may exist many distinct or overlapping "communities" that are defined entirely differently, e.g. by sex, religion, tribe, or other characteristics or social ties.[13] This substudy will focus on community as defined by geographic location, and will consider community-level factors, including HIV- prevalence in the community, acceptance of HIV-positive individuals and stigma. The substudy will also examine norms and traditions around bridewealth, gender and sexual relationships, all of which impact women's autonomy and decision-making ability for contraception, disease prevention and other health-related behaviors.[14-19] Information flow through formal and informal community networks can greatly influence perceptions about study participation, willingness to participate in studies, and willingness and ability to adhere to study product use.[20, 21]

All HIV prevention trials are situated in communities. Therefore, trials may be intrinsically impacted by their communities and vice versa. Research that fails to

adequately respect and consider this relationship runs the risk of misunderstandings and rumors that could deleteriously impact trial conduct, or lead to premature closure of trial, as with the tenofovir trials closures in 2005.[22] Following these events, guidelines for researchers to better engage communities in clinical trials have been published. In the recently completed Methods for Improving Reproductive Health in Africa (MIRA) study, qualitative assessments of trial experiences with participants while the trial was ongoing, as well as continuous communication with CABs played a major role in dispelling rumors about the intentions of the research, and helped overcome recruitment and retention challenges.[20]

Several microbicide preparedness studies have elicited input from community leaders, men or other "stakeholders" to inform the future acceptability and use of candidate products.[7-9] However, this initial work was based on hypothetical products, and was not able to report on the community's role on trial participation and product adherence over an extended (3 months or greater) follow-up period. An ancillary study to the HIV Prevention Trials Network (HPTN) 035 trial explored microbicide acceptability from the perspective of participants, their partners, as well as community stakeholders (religious leaders, non-governmental organization (NGO) leaders, civil servants) and health-care professionals (traditional healers, nurses, doctors, counselors) as the trial was ongoing. Although the two are linked the focus of that study was more on product acceptability than on adherence.[23] Indeed, the critical importance of product adherence was perhaps taken for granted five years ago, but with several recent trials reporting lower-than-anticipated adherence and no effect[24, 25], the importance of further researching reasons for non-use and addressing suboptimal adherence is paramount.

All pre-exposure prophylaxis (PrEP) trials planned or ongoing have had extensive consultations with the communities where they are implemented. In addition, some have incorporated socio-behavioral and community research components to their activities. For example, in Botswana, the Truvada PrEP trial is conducting a multi-phased community monitoring study to assess understanding (and misunderstanding) of the trial. It uses a mix of methods, including general community surveys using venue-based random sampling, as well as qualitative interviews with key community members and with trial participants (K. Chillage, personal communication). Similarly, in FEM-PreP, which will be conducted in five Sub-Saharan African countries, extensive formative work as well as ongoing qualitative interviews with participants during trial implementation will be conducted, among other things, to foster community involvement, help develop adherence messages and to explore issues related to product adherence and trial participation.[26]

Additionally, ethnographic research methods provide further insight into factors that impact participant adherence. According to the American Anthropological Association, *ethnography refers to the description of cultural systems or an aspect of culture based on fieldwork in which the investigator is immersed in the ongoing everyday activities of the designated community for the purpose of describing the social context, relationships and processes relevant to the topic under consideration*.[27] The ethnographic method has been used successfully in the Microbicides Development Programme (MDP) 301

social science research. For example, at one point although the quantitative data started to show a decline in adherence at one site, the IDIs and ethnography showed that this decline in adherence was due to women running out of gel rather than dissatisfaction with the product or trial fatigue.[28] As a result of these findings, the study team increased the amount of gel dispensed at clinic visits or delivered the study gel to participants who could not otherwise come to the clinic.

As mentioned above, community responses, particularly negative rumors regarding clinical trials are widespread and often require in-depth investigation.[29] These rumors are not always readily reported in formal interviews. Ethnographic research into rumors surrounding the MDP 301 trial in Johannesburg led researchers to conclude that the rumors were not supported by trial participants and may have little impact on enrollment and retention.[30] Ethnographic research was also conducted with community members and trial participants to assist in developing messages and to provide an early warning system in the case of extraordinary events such as the closure of the Cellulose Sulfate Trial and the closure of the 2% arm of the MDP 301 trial.

In summary, based on previous microbicide and PrEP studies, it seems critical for the VOICE trial to also include a qualitative substudy assessing the various socio-cultural and contextual factors that impact participant adherence to study product(s).

## 2.4 Study Hypotheses and Rationale for Study Design

### 2.4.1 Study Hypothesis

This is primarily an exploratory descriptive study that is not designed to test a hypothesis. However, the objectives of the study are based on the assumption that various levels of influence beyond the individual (i.e. household, organizational and community level factors) will impact VOICE participants' adherence to study product use, and that these external influencing factors may differ by route of product administration (vaginal vs. oral).

### 2.4.2 Rationale for Study Design

The proposed study will be an important complement to the behavioral component of VOICE. As depicted in the conceptual framework (Figure 1) several factors are hypothesized to influence adherence at the household, organizational and community levels. However, the mechanism of action for their influence is not well understood or straightforward, and there are undoubtedly other factors that have not yet been identified.

For the descriptive component of VOICE-C, qualitative research is ideally suited to explore these domains in rich details. The proposed study utilizes a unique structure and combines the behavioral expertise of the MTN Behavioral Research Working Group (BRWG) with the community experience of the MTN Community Working Group (CWG)

as well as the expertise in ethnographic research methods of an anthropologist with over fifteen years of research experience, involved in VOICE-C.

Ethnographic research is proposed as an appropriate method to provide a detailed understanding of the three spheres of influence on adherence in this study: the household, clinic and community (as experienced by the Group 1 participants). In particular, ethnographic research may provide insight into the ways in which relations within these contexts shape adherence that may be missed in the more formal methods of FGDs and IDIs. Ethnographic research will also provide a valuable means to triangulate data collected through IDI and FGD.

Ethnographic research involves a range of methods, which can include informal interviews, direct observation, and participation in daily life, collective discussions, documents and life histories. It is undertaken over a long period of time, and provides the researcher more opportunities to observe and interpret information. A strength is that the researcher can identify discrepancies between what people say and believe and what actually happens.[31, 32] Ethnography can also uncover the hidden aspects of social reality.[32] Therefore, ethnographic research can be a powerful check against what people report about themselves during interviews and FGDs. It is often in more informal settings where issues that are usually concealed may be revealed.[33] Ethnographic research typically does not rely on large numbers of participants. Instead, what may be lost in terms of representation is made up for in terms of depth of understanding. Ethnographic research may be well suited to a study of adherence in the context of a clinical trial. Ethnographic research on tuberculosis (TB) medication adherence, for example, has been shown to reveal unanticipated barriers to treatment.[34]

Focus group discussions are a well suited methodology to explore normative behavior, beliefs, and levels of influence on behavior beyond the level of the individual. These will be conducted with Group 1 and Group 2 participants after study exit to avoid any "clustering" effect during VOICE trial implementation.

In-depth-interviews, will be conducted during the accrual phase of VOICE, and are best suited to provide insight on personal experience, opinions and feelings on sensitive topics, and to explore in-depth circumstances around specific events (i.e. circumstances surrounding use and non-use of products).[31] In the MDP 301 phase III trial of PRO2000/5 microbicide gel, a mixed method approach is currently being used to better understand adherence issues and increase the accuracy of adherence data, which includes conducting in-depth-interviews with a subset of trial participants and their male partners (as is similarly planned in VOICE-C with Group 1 and Group 2 participants).[35] Indeed, because qualitative methods enable rapid identification and nuanced understanding of salient issues that are affecting adherence, they can also fulfill the strategic goal of VOICE-C as action can be taken to respond to these quickly, as the study is progressing.

The insight culled from the qualitative research in VOICE-C, regarding the complex and multitude of factors that impact product adherence will be used to examine, and if

needed, modify or implement new adherence strategies as appropriate across all VOICE sites. Should the VOICE-C team discover particular factors that can be addressed in the VOICE trial to improve product adherence, they will inform the VOICE team of their findings, and the VOICE team will decide on the most appropriate way to address the adherence issues at the VOICE-C site as well as across all sites.

# 3 OBJECTIVES

## 3.1 Primary Objectives

1. To explore socio-cultural and contextual factors that participants identify as influencing product use (and non-use) in VOICE

2. To determine if factors identified by participants as influencing product use (and non-use) are different between those who are randomized to the vaginal product vs. oral product

3. To elicit VOICE participants' perceptions of the importance of adherence, and their experiences of barriers and facilitators to adherence

## 3.2 Secondary Objectives

1. To elicit "external" stakeholders' perspectives on the trial, with a focus on its acceptance at the household level and in the community, and views on adherence-related issues among the following groups:

    a. Male partners of study participants (Group 2)
    b. CAB members (Group 3)
    c. Key community stakeholders (Group 4)

2. To solicit the input of external stakeholders on developing and implementing strategies to improve product adherence in the trial

3. To collect feedback from Group 1 and Group 2 participants on their experience with these implemented strategies through specific questions in the exit FGDs

# 4 STUDY DESIGN

## 4.1 Identification of Study Design

VOICE-C will be a substudy of VOICE. It is an exploratory study using qualitative research methods, which will be conducted at site(s) selected by the MTN Executive Committee, with 4 groups of participants (see Table in Protocol Summary for details). VOICE female participants (Group 1) who have been in the trial for at least 12 weeks will be offered participation in VOICE-C which will involve one of the following three activities: a) a single visit during which they will participate in a FGD (conducted at study exit, after completing their time in the trial) b) a single visit during which they will participate in an IDI (conducted as the trial is unfolding) or c) long term (1 year for a total of approximately 4 visits) ethnographic research. We will also conduct male partner IDIs during the trial and FGDs with male partners (Group 2) of participants who have exited the trial. FGDs with CABs (Group 3) and key community stakeholders (Group 4) will also be conducted at several times during trial implementation.

All data collection activities for the descriptive component (ethnographic visits, IDIs, and FGDs) of the study will aim to identify factors facilitating or impeding women's optimal adherence to study product, and the levels at which they operate. If applicable, strategies to address impediments that are modifiable may be implemented over the course of the trial and across all sites, through regular feedback and consultation with the Investigators and the Protocol Team of the main VOICE study (strategic component of VOICE-C).

## 4.2 Summary of Major Outcomes of Interest

The main outcomes of interest will be the barriers and enablers to optimal adherence with a focus on factors operating at the household and community levels. We will also indirectly examine factors operating at the organizational level. As detailed in Table 1, we will examine household, organizational and community level factors that are hypothesized to affect product adherence in the VOICE trial, or that will emerge through the qualitative data collection process, including coded textual data from the ethnographic visits, FGDs, and the IDIs.

**Table 1: Household, Organizational, and Community-level Factors Potentially Affecting Adherence**

| Level | Factors | Topics/Themes |
|---|---|---|
| **Household level** | Male partner/husband | Partner's role in sexual decision-making dominance |
| | | Domestic violence |
| | | Type of sexual relationship (mutual or one-sided monogamy, polygamy) |
| | | Partner's approval of PrEP and vaginal microbicides |
| | | Decision making and disclosure about trial participation |
| | | Decision making and disclosure about product use |
| | Family | Decision making and disclosure about trial participation |
| | | Decision making and disclosure about product use |
| | | Family structure and relationships |
| | | Influential family members' approval of PrEP and vaginal microbicides |
| | | Health/HIV status of family members and care-taking responsibilities |
| | Household resources | Income/financial resources |
| | | Work and migration |
| | | Household size/crowding |
| | | Access to health care (and ARV) for family members |
| | Life events | Birth, death/funerals, employment changes |
| | | Changes in relationships |
| **Organizational level** | Clinical trial site | Perceived quality of services received from clinical staff and relationships with clinical staff |
| | | Networking/support among participants |
| | | Perceived positive expectations from trial participation |
| | | Messages received re: protection from study products |
| | | Physical infrastructure (e.g., access to study site) |
| | Membership to various groups | Participation in women's groups, church groups, support groups, micro-credit groups, etc. |
| **Community level** | HIV/AIDS | HIV/AIDS prevalence in the community<br>HIV/AIDS acceptance/stigma |
| | Community resources | Existence of Voluntary Counseling and Testing (VCT), Non-Governmental Organizations (NGO) and other social services |
| | | Physical infrastructure (e.g. access to health and other services, public transportation) |
| | Cultural norms and traditional practices | Bridewealth, gender and sexual norms, monogamy/polygamy |
| | | Traditional practices around insertion of vaginal products, pill/medication taking |
| | Information flow and beliefs | Rumors/beliefs about trial, HIV transmission |
| | | Other traditional and institutional belief systems (churches, etc.) |
| | | Informal and formal (CABs) social and community networks |

## 4.3 Description of Study Population

VOICE Participants at VOICE-C sites (~150 per site)

At each VOICE-C site, following enrollment into VOICE, women will be invited to participate in VOICE-C throughout three accrual periods, and if eligible, they will be randomly assigned to one of three VOICE-C subgroups in the following proportion (1:3:1): an ethnography group (approximately n=30), an exit FGD group (approximately n=90), or an IDI group (approximately n=30). We anticipate that because of the random selection procedure, the subgroups will have balanced proportions of women across the five study arms in VOICE.

Male Partners of VOICE Participants (~60 per site)

Female participants in VOICE-C will be asked permission to have their current male sexual partner contacted for participation in an IDI or an exit FGD. Male partners will be

systematically invited to participate in VOICE-C only if their female partner consents for them to be contacted. In the event that accrual of male partners from VOICE-C participants is too slow or doesn't meet target numbers, we will extend recruitment to include random selection of male partners from all VOICE participants at the VOICE-C site.

CAB Members (Up to 15 per site)
CAB members are those individuals who have been affiliated with VOICE-C sites for a minimum of 3 months. Eligible CAB members will be purposively selected and invited to join the VOICE-C Substudy, until 15 individuals accept to participate. As participating CAB members will participate in several bi-annual FGDs, in case one individual has to terminate early his/her participation into VOICE-C, he or she will be replaced by another eligible CAB member.

Key Community Stakeholders (~50 per site)
Key community stakeholders are those individuals who are identified as such by CAB members, community group members and site staff. Key community stakeholders will be purposively selected to participate in one FGD at a given time during trial implementation.

## 4.4 Time to Complete Accrual

The data collection activities for this substudy are one-time-only events, except for CAB FGDs and the ethnographic component. The data collection timeline is synchronized with the accrual and follow-up period of the main VOICE trial. Data collection through IDIs with Group 1 (female participants) and Group 2 (male partners) participants will begin shortly after Month 3 of study implementation at the site, and will continue at regular intervals during the accrual period. Data collection with Group 1 participants randomized to the ethnographic component will begin after Month 3 as well. Each participant in this component of the study will receive a home visit every 3 months for one year. At study exit, FGDs will be conducted with Group 1 participants (separately for oral and vaginal product administration groups) and separate FGDs will be conducted with male partners of exited VOICE participants. Data collection with CABs and key community stakeholders will be on an approximately semi-annual schedule for the duration of the study.

## 4.5 Study Groups

Study groups will include the following individuals:

- Group 1: VOICE participants at VOICE-C sites. Female VOICE participants will be randomly selected to participate in ethnographic visits, exit FGDs, or IDIs. Approximately 150 individuals per site will have the opportunity to participate in one of these three VOICE-C activities

- Group 2: Male partners of study participants: VOICE-C participants will be asked to give permission for study staff to contact their current primary sexual partner for participation in an exit FGD (after the trial) or IDI (during the trial). Study staff will only contact male partners if the woman has given permission. Approximately 60 male partners per site will have the opportunity to attend either one of approximately four exit FGDs or participate in an IDI

- Group 3: Members of the CABs at VOICE-C sites: Approximately 15 CAB members who have been serving for at least 3 months will be invited to attend 5 consecutive FGDs, including a FGD at the outset of the substudy

- Group 4: Key community stakeholders: CAB members, community-group members (i.e. women's groups, church groups, market groups) and site staff will help identify and purposively select approximately 50 key community stakeholders at each site, for the 5 FGDs (with 10 members each) conducted throughout trial implementation with this group

The timeline for participant accrual is as follows:

**Table 2: VOICE-C Accrual Plan**

| Group | VOICE Accrual Period | VOICE Follow-up Period |
|---|---|---|
| **1** | 30 (IDIs) | 90 (FGDs)* |
| | Approximately 30 participants will be accrued during the VOICE accrual and follow-up periods for the ethnographic component | |
| **2** | 12 (IDIs) | 48 (FGDs) |
| **3** | Up to 15 participants | N/A |
| **4** | 40 | 10 |

*FGDs will take place among individuals who have exited the study, but during the follow-up period of the VOICE trial.

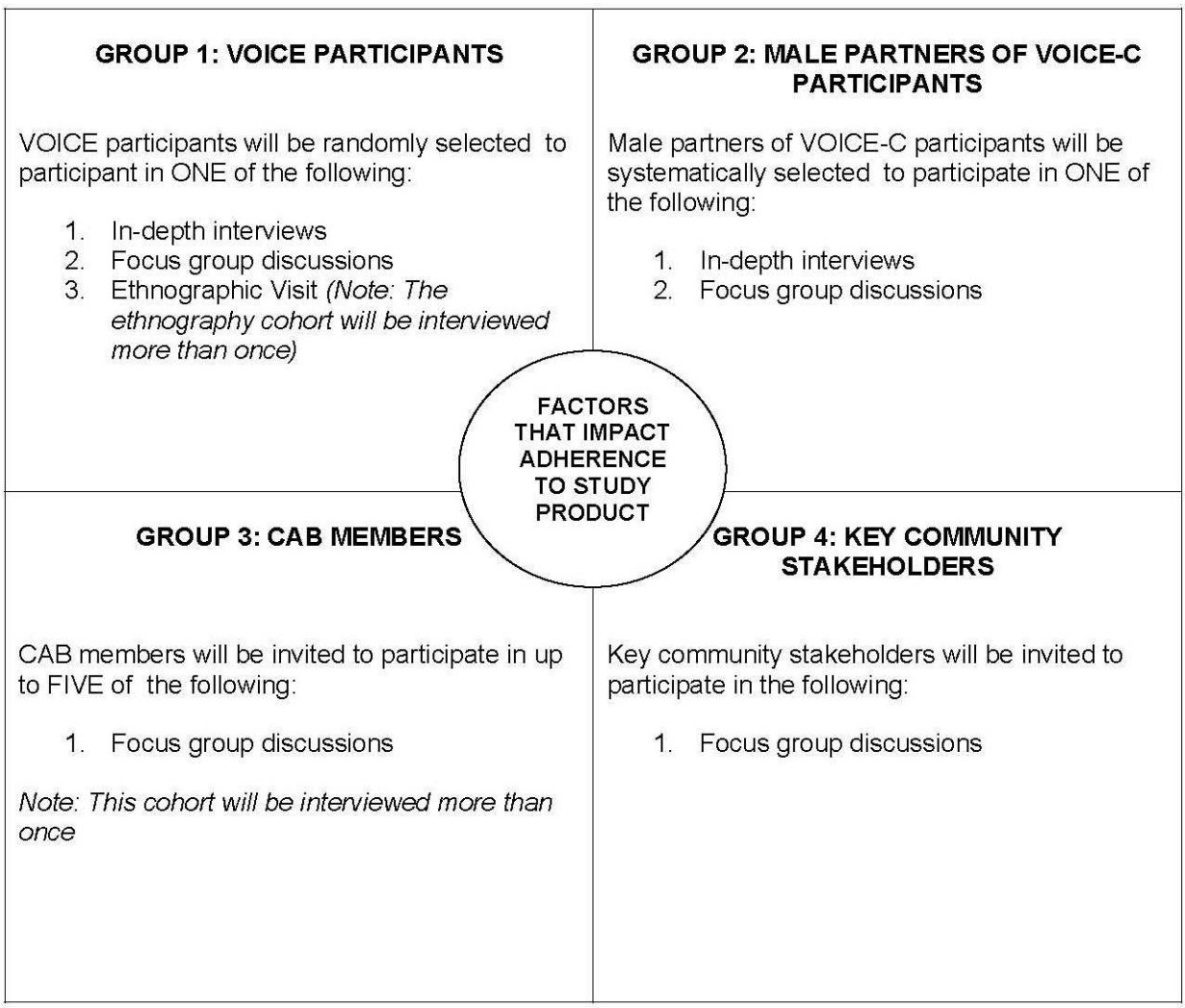


**Figure 2: MTN-003C Study Groups**

## 4.6 Expected Duration of Participation

Group 1 and Group 2 participants will partake in an exit FGD or an IDI only once for a duration of up to 2 hours for an IDI or 2-3 hours for a FGD. Informal interviews for the ethnographic visit will not last more than 3 hours, and will be repeated up to 4 times (over one year) with each participant. Key community stakeholders will participate in a FGD only once for a duration of up to 2-3 hours. CAB members will be invited to attend up to five successive FGDs that will last up to 2-3 hours each, which includes a FGD at the outset of the substudy to discuss topics that the VOICE-C team may want to consider exploring in the context of the IDIs.

## 4.7 Sites

Study site(s) will be located in sub-Saharan Africa and will be selected by the MTN Executive Committee. Sites will be selected based on participation in VOICE as well as capacity.

# 5 STUDY POPULATION

## 5.1 Selection of the Study Population and Recruitment

The inclusion and exclusion criteria in Sections 5.2 and 5.3 will be utilized to ensure the appropriate selection of study participants

**Group 1 (VOICE participants):**
As described in Sections 4.3 and 10.4, at each VOICE-C site, every woman who has been enrolled in VOICE for at least 12 weeks will be invited to participate in VOICE-C. If eligible and willing to participate, she will be randomly assigned to one of 3 VOICE-C subgroups in the following proportion (1:3:1). At each VOICE-C site, we expect to enroll approximately 150 women in VOICE-C. It is anticipated that relatively balanced proportions of women from both the oral and vaginal study product groups will be selected to participate in VOICE-C.

Ethnography
Randomly selected women who have been participating in VOICE for at least 12 weeks will be approached and invited to participate in the ethnographic component of the VOICE C study. The first meeting will take place at the clinic where informed consent will be completed and a detailed explanation will be provided regarding the procedures for the ethnographic component. Once a participant agrees to participate, an appointment will be made for subsequent meetings at their home or a venue of their choice. The participants will be followed up for a year, with a total of four visits. Approximately 30 women per site will participate in this component of the study.

Exit Focus Group Discussions
Approximately 90 women per site will participate in FGDs. This corresponds to 10-12 participant identification numbers (PTIDs) for each of 8 FGDs at each site. Each randomly selected participant will only be allowed to participate once. Separate FGDs will be conducted for women in the oral study product group and those in the vaginal study product group in VOICE.

The files of women randomly pre-selected for MTN-003C FGDs will be flagged, and at the visit prior to study exit or at the exit visit, study staff will remind participants of their initial eligibility to participate in the VOICE-C Substudy and will invite them to join a group-specific (e.g. oral or vaginal study product) FGD. Prior to recruitment, we will assess additional exclusion and inclusion criteria of the randomly pre-selected participants such as long term or permanent product discontinuation and HIV seroconversion. The allowable number of FGD participants per group will be 6-15 participants. Therefore, by inviting 15 per planned FGD, we will be able to absorb the losses due to product discontinuation, refusal to participate, unavailability or loss to follow up. A brief description of the activity will be given at the regularly scheduled VOICE study visit, and a more comprehensive description, including informed consent, at the VOICE-C study visit.

At regular intervals, a new set of randomly selected FGD participants will be invited to participate in the exit FGDs.

In-Depth Interviews

As described above, women who have been enrolled in VOICE for at least 12 weeks, will be approached and will be invited to join VOICE-C. The first meeting will take place at the clinic where a detailed explanation of IDI study procedures will be provided, and the IDI informed consent will be reviewed. The IDI will either take place that day at the clinic or an appointment will be made for a subsequent visit at the clinic or at a venue of their choice. Those who agree and are randomized to the IDI subgroup will be asked to provide written informed consent and will then participate in an IDI to discuss personal experiences, challenges and facilitators to product adherence (approximately 30 women per site). To identify adherence issues early on in the VOICE trial, the majority of IDIs will be conducted during early study accrual, with the option of a final round scheduled for the end of the study to assess long term issues related to product adherence. Women who participated in an IDI will not be eligible to participate in another VOICE-C activity. A brief description of the IDI activity will be given during the initial contact about VOICE-C, and a more comprehensive description, including informed consent will take place at the IDI VOICE-C study visit.

**Group 2 (Male partners)**

Recruitment of male partners for IDIs during trial implementation will be done through the female VOICE-C participant. Women who are randomly selected to participate in IDIs (sampling described above) will be asked to provide permission for study staff to invite their primary male partner for an IDI, which will be scheduled at a mutually convenient time. Similarly, women randomly selected for FGDs will be asked to provide permission to contact their partner to join an FGD (after the trial). A "permission to contact" form will be created by RTI that will document female participants' willingness (or not) for staff to contact her male partner. Participants will initial this form to confirm their consent for the partner to be contacted, and partner name and contact details will be recorded on this form. The forms will be stored in a secured location, accessible only by key study personnel. Study staff will only contact male partners if the woman gives permission for the study staff to do so. Staff will verify that male partners meet inclusion and exclusion criteria (i.e. female partner on product, not seroconverted) prior to making contact. Based on previous studies, we estimate that about two-thirds of VOICE-C (or VOICE) participants will give their permission to contact their partner. If there are recruitment challenges, IDIs and FGDs will be opened up to male partners of other VOICE (not VOICE-C) participants (see MTN-003C SSP manual for details). These partners will be systematically contacted by staff for IDIs during the accrual phase of the trial (one partner IDI per quarter per treatment group, for a total of approximately of 12 per site), or after the woman has exited the trial (approximately 48 male partners for 4 FGDs, with 2 FGDs per treatment group per site). Staff will contact these partners by telephone or in-person visit two weeks prior to the scheduled interview or FGD. Prospective participants will have the opportunity to ask questions about the purpose of the meeting at the time of recruitment. A more comprehensive

description, including informed consent, will be provided at the scheduled IDI visit or FGD meeting.

Additional male partner activities:
At each site, the VOICE trial will hold regular informational and educational meetings with VOICE participants and/or their male partners, and the VOICE-C Substudy team will attend these meetings, to observe, take notes and summarize key discussion items, although no individually-linked or identifying data will be collected. VOICE-C staff will also have access to summary reports or notes from these activities if available.

**Group 3 (CABs)**
CAB members who will participate in this study will be recruited from the existing local CAB. Prior to study initiation, a VOICE-C staff member will attend a regular CAB meeting and explain the study, and solicit interest and participation. CAB members who meet eligibility criteria and are willing to participate will be asked to provide written informed consent at the first FGD.

**Group 4 (Key community stakeholders)**
A list of potential key community stakeholders will be generated through study contacts (i.e. via staff, CAB, etc.). Potential participants will be contacted by telephone or through in-person meetings, and invited to come to the clinic for a FGD. Potential participants may ask questions about the purpose of the FGD at the time of recruitment. Further detailed information will be offered during the informed consent process preceding the FGDs.

### 5.2 Inclusion Criteria: Group 1 (VOICE Participants)

Potential participants in Group 1 must meet all of the following criteria to be eligible for inclusion in the study:

1) Enrolled in VOICE and randomized to study product in VOICE at least 12 weeks prior to enrollment in the VOICE-C Substudy

2) Able and willing to provide informed consent for participation in the VOICE-C Substudy

### 5.3 Exclusion Criteria: Group 1 (VOICE Participants)

Potential participants in Group 1 who meet the following criteria will be excluded from the study:

1) Permanently or long term (> 2 months) discontinued from study product use by the site Investigator of Record (IoR)/designee, per the specifications of the VOICE protocol, by the time of the scheduled ethnographic visit, IDI, or FGD

2) Has any condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

3) Has HIV-seroconverted prior to the time of the VOICE-C IDI or exit FGD or start of ethnography

### 5.4 Inclusion Criteria: Group 2 (Male Partners)

Potential participants in Group 2 must meet the following criterion to be eligible for inclusion in the study:

1) 18 years of age or older, male, able and willing to provide informed consent for participation in the VOICE-C Substudy

2) Identified as a partner of a female VOICE or VOICE-C participant who meets eligibility criteria for VOICE-C (i.e. on product, no seroconversion)

3) Identified by a VOICE or VOICE-C participant in either arm of the trial as a current sexual partner (current is defined as a sexual partner by the VOICE or VOICE-C participant at the time she is asked permission to contact him)

4) Identified by the VOICE or VOICE-C participant as someone she is willing to have the study team to contact

### 5.5 Exclusion Criteria: Group 2 (Male Partners)

Potential participants in Group 2 who meet the following criterion will be excluded from the study:

1) Has already participated in a VOICE-C male partner IDI (for FGDs only)

2) Has any condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

### 5.6 Inclusion Criteria: Group 3 (CAB Members)

Potential participants in Group 3 must meet the following criteria to be eligible for inclusion in the study:

1) 18 years of age or older, able and willing to provide informed consent for participation in the VOICE-C Substudy

2) At the time of enrollment, has been a member of a CAB affiliated with the site for at least 3 months as reported by the site CAB liaison

3) At the time of enrollment, is considered an active CAB member as reported by the site CAB liaison

### 5.7 Exclusion Criteria: Group 3 (CAB Members)

Potential participants in Group 3 who meet the following criterion will be excluded from the study:

1) Has any condition that, in the opinion of the IoR or designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

2) CAB members who have been involved in the VOICE-C protocol development process

### 5.8 Inclusion Criteria: Group 4 (Key Community Stakeholders)

Potential participants in Group 4 must meet the following criteria to be eligible for inclusion in the study:

1) 18 years of age or older, able and willing to provide informed consent for participation in the VOICE-C Substudy

2) Lives or works within the community in which the parent study is being conducted

### 5.9 Exclusion Criteria: Group 4 (Key Community Stakeholders)

Potential participants in Group 4 who meet the following criterion will be excluded from the study:

1) Has any condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

2) Current CAB member at that site

### 5.10 Co-enrollment Guidelines

For this substudy, all participants in Group 1 will be participants in the VOICE trial. Therefore, the VOICE guidelines for co-enrollment into other studies apply to this substudy.

There are no co-enrollment restrictions for participants in Groups 2, 3 and 4.

# 6 STUDY PRODUCT

No additional study product considerations are applicable for the VOICE-C Substudy.

# 7 STUDY PROCEDURES

Additional information on visit-specific study procedures is presented in this section. Detailed instructions to guide and standardize procedures across sites are provided in the MTN-003C SSP Manual available at www.mtnstopshiv.org.

## 7.1 Pre-Screening

Pre-screening for all data collection activities will include oral or written confirmation that participants meet their respective inclusion and exclusion criteria. The study team will create checklists to ensure this is consistently documented.

## 7.2 Screening and Enrollment

### 7.2.1 Administrative, Behavioral, and Regulatory Procedures

- Informed consent
- Eligibility information
- Demographic information
- Locator information
- Reimbursement

### 7.2.2 Ethnographic Research Procedures

Ethnographic research will focus around the participant's everyday life as it relates to adherence and the clinical trial more generally. The primary site for ethnographic research will be the participant's household and surrounding community. Trained and experienced researchers will first meet participants randomized to the ethnographic research after their scheduled visit at the clinic. They will arrange a time and place to meet, preferably at home. However, some participants may not want to draw attention to their involvement in the trial and therefore neutral venues in the community will be used for these purposes. Participants will be asked to participate in four ethnographic visits.

At the first meeting the researcher will collect a life history, social and economic background, and a sexual biography, and reasons for enrolling in VOICE by interviewing the participant. The second and subsequent meetings will monitor the following issues: significant events in the community (for example political disturbances), physical experiences related to gel use or pill use; barriers to gel use or pill use; rumors about the trial; neighborhood conversations about their participation in the trial; gossip overheard in the clinic waiting room. In addition, observations of the household and the use of space will be recorded.

These discussions will be recorded in a notebook and field notes will be transcribed into a word processor that day or within five days of the interview to minimize lost data. Notes will be filed according to participant enrollment number and date of ethnographic data collected and field visit. A monthly report will be prepared based on these field notes and presented and discussed with the social science research team per the key themes outlined above.

**Table 3: Enrollment and Visits for Ethnographic Research Component**

| Year | Year 1 | | | | Year 2 | | | | Year 3 | | | | Year 4 | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Quarters** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** | **1** | **2** | **3** | **4** | |
| **Target enrollment** | 4 | 2 | 2 | 2 | 4 | 2 | 2 | 2 | 4 | 2 | 2 | 2 | 0 | 0 | 0 | 0 | 30 |
| **Total enrolled per year** | | | | 10 | | | | 10 | | | | 10 | | | | 0 | 30 |
| **Cumulative quarterly visits** | 4 | 6 | 8 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 6 | 4 | 2 | 0 | |
| **Total participants** | | | | | | | | | | | | | | | | | **30** |

### 7.2.3 Focus Group Discussion Procedures

VOICE Participants and Male partners of VOICE-C Participants

The FGDs will be conducted in an appropriate meeting room that is conducive to the number of participants, privacy, and the need to audio-record the session. To maximize confidentiality and privacy, if logistically possible, the FGDs should be located at a different physical location from the clinic site or scheduled at the clinic site during off-hours. Upon arrival at the scheduled meeting time, FGD participants will be greeted, presented with an informed consent document to review while awaiting the arrival of the remaining participants, and will be offered refreshments. Staff will be available to answer questions. When all participants have arrived, a staff member will read the entire informed consent document and explain it in detail to ensure that participants fully understand the FGD process. Participants will be encouraged to ask questions. Once participant questions are thoroughly addressed, participants who wish to participate in the FGD will be asked to sign or make their mark on the informed consent document, and remain present for the FGD. Those not willing to provide consent will be reimbursed for their transport expenses only and will not participate in the FGD. The facilitator will then initiate the FGD by first explaining that the session will be audio-recorded and later transcribed and translated. Ground rules for conduct will be described (i.e. no interruptions, cell phones, confidentiality). The facilitator will then conduct the session, starting with an ice breaker, and then will follow the appropriate FGD guide. FGDs guides will be structured, but will allow opportunity for probing and exploration of spontaneously generated themes. The note-taker will take notes during the session as a back-up to the audio-recording, and to record non-verbal information. At the end of the FGD, participants will be thanked and reimbursed for their transport expenses and time.

Immediately following each FGD, the facilitator and note-takers will be asked to complete a one-page debriefing form that will list some basic statistics about the session (i.e. duration, mood of interview, number of participants, people present, etc.) as well as a summary report of the discussion, which will include staff's impressions of

key issues (i.e. barriers and enabling factors, and the level at which they operate) related to the main outcome of adherence. Each debriefing report will thus represent a summary and extraction of the full data that can be used in "real-time". This will allow access to pertinent findings while the data goes through the longer process of QA, coding and more formal qualitative analysis.

CAB Members

FGDs with CAB members will occur every six months for the duration of the study. CAB members who have been active members of the CAB for at least three months will be invited to attend, and will be asked to provide written informed consent. FGDs with CAB members will explore the ongoing relationship of the community and the trial. Additionally a FGD with CAB members will be conducted at the outset of the substudy to discuss topics that the VOICE-C protocol team should consider exploring in the context of the IDIs. Issues of adherence and challenges to adherence will be discussed. This is the only group of informants that will be interviewed at several time points, and thus it will be important to provide information on perceived changes over time in community outlook and external factors affecting adherence. The procedures will follow those outlined above, although the informed consent process will only be conducted one time per individual.

Key Community Stakeholders

The goal of the Key Community Stakeholder FGDs is to gain a wide-array of perspectives from community members that are neither part of the trial nor formerly affiliated with the trial, as CAB members are. We will identify potential participants using referrals from CAB members and study staff, and will approach community contacts, i.e. church groups, public health clinics, etc., keeping in mind the following guiding definition of stakeholders:

Stakeholders are those people or organizations affected by the outcome of a biomedical HIV prevention trial, negatively or positively, or those who can affect the outcome of proposed research. This includes the population that will be approached to participate in the trial, as well as communities and individuals who are not physically located where the research takes place, including advocates, activists, and/or groups representing specific constituencies. In addition, key stakeholders can potentially include educators, medical professionals, media professionals, and, in the immediate community, family members, and people whose age and/or gender make them ineligible for study participation. [36]

For practical reasons, key community stakeholders in VOICE-C will be selected among individuals living in the general surrounding area where the VOICE-C site is located. The procedures will follow those outlined above.

### 7.2.4 In-Depth Interview Procedures for Group 1 and Group 2 Participants

The IDIs will be conducted in private meeting rooms that are quiet enough for audio-recording. The IDIs should be located in a confidential private location, which may be at

the clinic, or another venue preferred by the participant. If requested or preferred by the participant, the IDI can be arranged at the participant's home, or at a different outside location. Upon arrival for the IDI, participants will be greeted and offered refreshments. The study staff member will then go through the informed consent document, allowing the participant an opportunity to ask questions. If and when written informed consent is completed, the facilitator will lead the interview. The IDI will follow an IDI guide, but will allow for iteration, probing and digression on relevant themes. Additional activities may be conducted with participants during the IDIs, such as free listing, pile sorting and rating exercises (see Section 10.5.2). IDIs will be audio-recorded and later transcribed and translated. Ideally a note-taker will be present to take notes during the session, but if only a facilitator is available, the IDI may still go on, and the facilitator will take brief notes as the interview is ongoing (these will be immediately expanded by the facilitator, after completing the IDI). Following the IDI, the participant will be thanked for his/her time and reimbursed for his/her travel and time.

Immediately following each IDI, the facilitator will be asked to complete a one-page debriefing form that will list some basic statistics about the session (i.e. duration, mood of interview, people present, etc.) as well as a summary report of the interview, which will include staff's impressions of key issues (i.e. barriers and enabling factors, and the level at which they operate) related to the main outcome of adherence. As with the FGDs (see Section 7.2.3 for details), each debriefing report will thus represent a summary and extraction of the full data that can be used in "real-time". This will allow access to pertinent findings while the data goes through the longer process of quality assurance (QA), coding and more formal qualitative analysis.

### 7.2.5 Participant Observation Procedures at Male Partner Activities During the VOICE Trial

As described above at each VOICE trial site, it is expected that VOICE participants and/or their male partners will be invited to attend regularly scheduled VOICE-sponsored informational/educational meetings. These meetings will be arranged as a forum to provide information and answer questions about the main VOICE trial. No formal data collection is planned for these meetings. However, it is expected that one VOICE-C staff member will have access to summary reports and notes from these meetings and/or have the opportunity to attend each of these meetings as a participant-observer, and will take notes and summarize key issues raised by attendees. If it is determined that the presence of VOICE-C staff is affecting or otherwise hindering the planned meeting/activity, the VOICE-C staff member(s) will no longer attend said meeting/activity at that site. No personal identifiers will be collected, and male partner attendance to these meetings will not be recorded. The VOICE trial CRFs will include a question to record whether a woman's male partner attended these meetings.

# 8 ASSESSMENT OF SAFETY

VOICE-C is a qualitative descriptive 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 Institutional Review Board (IRB)/Ethics Committees (EC), of any unanticipated problem involving risks to subjects or others. No safety events will be captured in the study database.

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; 2) this study does not involve a study drug or intervention; and 3) adverse events are not primary or secondary objectives of the study. Nonetheless, events meeting Expedited Adverse Events (EAE) reporting requirements by Group 1 participants will be reported by VOICE-C staff to the parent protocol (MTN-003).

Participants may experience **social harms** — non-medical adverse consequences — as a result of their participation in the study. 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, a note will be placed in the participant file and the participant will be referred to a counselor in the main VOICE trial. 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. RTI will provide listings of social harms reported by study participants to the protocol team at a minimum of every 6 months per any applicable DAIDS requirements. Additionally, an SOP (Standard Operating Procedure) for emergency procedures will be developed for the VOICE-C research team to be used in situations of social harm and when situations that require immediate attention are identified, including domestic violence, suicidal ideation or behavior. The procedures will provide clear guidelines for researchers to refer participants in these situations to the relevant institution/body and to provide feedback to senior personnel in the main VOICE trial.

Relationship to study participation or procedures will be assessed by the site IoR, or designee, based on the following definitions:

- **Definitely related:** unanticipated problem and study participation/procedures are related in time, and a direct association can be demonstrated with study participation/procedures

- **Probably related:** unanticipated problem and study participation/procedures are reasonably related in time, and the unanticipated problem is more likely explained by study participation/procedures than by other causes

- **Possibly related:** unanticipated problem and study participation/procedures are reasonably related in time, and the unanticipated problem could be explained equally well by causes other than study participation/procedures

- **Probably not related:** A potential relationship between an unanticipated problem and study participation/procedures could exist (i.e., the possibility cannot be excluded), but the unanticipated problem is most likely explained by causes other than study participation/procedures

- **Definitely not related:** The unanticipated problem is clearly explained by another cause not related to study participation/procedures

# 9 CLINICAL MANAGEMENT

There are no additional clinical management considerations for participants enrolled in the VOICE-C Substudy.

# 10 ANALYTICAL CONSIDERATIONS

## 10.1 Overview and Summary of Design

VOICE-C is an exploratory substudy of VOICE using qualitative research methods, including ethnography, FGDs, and IDIs, at participating VOICE-C site(s). Data collection will occur at various time points at selected sites during VOICE trial implementation with four groups of informants: VOICE participants (randomly assigned to three subgroups: ethnography, exit FGDs, and IDIs), male partners of VOICE-C participants (systematically selected in equal numbers as partners of VOICE-C participants in oral and vaginal groups), CAB members (purposively selected) and Key Community Stakeholders (purposively selected). Aside from CAB members who will participate in several (approximately five-monthly) FGDs throughout the duration of the VOICE trial and those participants who are randomized to the ethnographic portion of the study, all other informants will only be interviewed once. VOICE-C participants and male partners will participate in IDIs during the VOICE accrual phase and FGDs after study completion; FGDs with Key Community Stakeholders will occur throughout the implementation period of VOICE. If possible, participant observation will be conducted throughout the trial at regularly scheduled VOICE educational/informational meetings with male partners.

## 10.2 Study Endpoints

The main outcomes of interest in VOICE-C will be the barriers and enablers to optimal adherence with a focus on factors operating at the household and community levels. We will examine household, organizational and community level factors that are hypothesized to affect product adherence in the VOICE trial, or that will emerge through the qualitative data collection and analysis process, including through coded textual

data from ethnographic visits, FGDs, IDIs, and participant observation field note reports (see Section 10.5.2).

Consistent with the descriptive objectives of this ancillary study, the endpoints for the primary objectives 1 and 2 will be coded data for socio-cultural and contextual factors influencing product use and non-use in VOICE, from transcripts of VOICE-C participants in the oral and vaginal groups. The endpoints for objective 3 will be coded data for the meanings and importance of product adherence, and for personal experiences with barriers and enablers of adherence from transcripts of VOICE-C participants. Endpoints for secondary objective 1 will be coded data regarding trial acceptance as well as product-adherence from transcripts of male partners, CAB members and key community stakeholders.

## 10.3 Primary Study Hypotheses

This is a descriptive and exploratory study, which is not designed to test a hypothesis. However, we do theorize that there will be factors beyond the individual, and more specifically at the household and community level, that will influence VOICE participants' study product adherence, and that these may differ by route of administration.

## 10.4 Number of Participants

The sample size per site is estimated in Table 4.

**Table 4: Target Number of Participants Per Group and Site**

| Group | Description | Number of Participants per Site | Details per site |
|---|---|---|---|
| 1a | VOICE participants ethnography | ~30 | Cohort totaling 30 participants; enrolled at month 3 of study participation. One visit per quarter over a 12 month period |
| 1b | VOICE participants exit FGDs | ~90 | 8 groups of about 10-12 participants each* |
| 1c | VOICE participants IDIs | ~30 | 1-2 participants/month (from month 3 to ~month 21 of VOICE) |
| 2a | Male Partner exit FGDs | ~48 | 4 groups of about 10-12 participants each* |
| 2b | Male partner IDIs | ~12 | 1 partner/study product group/ quarter for 6 quarters (from month 3 to ~ month 21 of VOICE) |
| 3 | CAB FGDs | Up to 15 maximum | 5 groups, same ~15 participants each per site* |
| 4 | Key Community Stakeholders | 50 | 5 groups, ~10 participants each* |
| | **Total** | **~275 per site** | |

*Acceptable number of participants ~6-15 per group

Participants in Group 1(a, b, c) will be randomly selected from the enrolled women in the VOICE trial. In order to select women from different accrual periods, the selection will be stratified into 3 accrual periods of 6 months each where approximately 50 women will be sequentially enrolled in each period until the target accrual is reached, and randomized to Group 1a, 1b, and 1c using a 1:3:1 allocation (10, 30, and 10 participants in Group 1a, 1b, and 1c, respectively). Specifically, at the beginning of each of the three accrual periods, each woman enrolled in VOICE will be asked to participate in the VOICE-C Substudy until we reach the target of ~50 women for each of these accrual periods.

We expect a low refusal rate (of no more than 10%) and thus anticipate recruiting 10% more women in Group 1 than needed to achieve the number of participants in this target group. Number of women recruited may be adjusted if refusal rate is substantially different from 10%. If the refusal rate is low, this random selection scheme should allow an approximate equal number of participants from each of the 5 arms of the VOICE trial while providing participants from 3 different accrual periods. If the accrual in the VOICE trial at the selected site is substantially slower or faster than the VOICE target accrual rate, the accrual cohorts in the above plan may need to be adjusted.

Following a similar approach as for Group 1a, 1b, 1c, in Group 2, the primary male partners of women who consent for them to be contacted and who consent to participate in the trial, will be assigned to Group 2a and 2b in a 4:1 allocation. Therefore, 20 male partners will be enrolled per each of the 3 accrual periods. A total of 60 males will be recruited, 48 and 12 in Group 2a and 2b, respectively.

No random selection of participants will be performed for Group 3 and 4. All CAB members and key community stakeholders will be invited to participate.

## 10.5 Data, Study Monitoring and Analysis

### 10.5.1 Study Monitoring Committee (SMC)

No Data and Safety Monitoring Board (DSMB) oversight is planned for this observational study. The MTN SMC will conduct periodic reviews of study progress including rates of participant accrual. These reviews will take place approximately every 12 months or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. The SMC may consider recommending termination of this study if recruitment is lower than targeted. If the SMC deems that accrual targets are not being met for male partners of VOICE-C participants, recruitment of this population will be extended to male partners of other VOICE participants, who were previously not selected to participate in VOICE-C.

### 10.5.2 Data Analysis

We will use the following descriptive statistics to assess the characteristics of the participants in each of the four study groups of VOICE-C: the number and percent in each category for categorical variables, (i.e. marital status, employment, and for VOICE participants: oral vs. vaginal group, self-reported product use per VOICE CRF), and the mean or median and range for continuous variables (i.e. age, education). No formal statistical testing will be conducted. Building on these assessments, the success of the VOICE-C randomization scheme will be evaluated by comparing the behavioral and demographic characteristics of the following three groups: 1) VOICE-C participants 2) eligible women who refused participation in VOICE-C and 3) the remaining non-VOICE-C sample (women from VOICE who were not enrolled into VOICE-C). We will also describe changes in sexual behavior and product use among women enrolled in the ethnographic research component at quarterly intervals, and will compare them to those of the remaining VOICE sample at the study site(s). This information combined with the demographic features of the women enrolled in the ethnographic research component, will allow the study team to assess the representation of the women randomly selected to participate in the ethnographic research versus those who either refused to participate in this component of the study or were not selected to participate in the substudy.

**Qualitative Analysis: Data Types**

Data types

The qualitative data from VOICE-C will include several data types:

- Transcripts from audio recorded IDIs or FGDs
- Handwritten notes (brief field notes, summary notes, debriefing reports) from ethnographic field notes, FGDs, and IDIs
- List of terms generated through free listing and pile sorting exercises during IDIs
- Participant observation notes or summary reports from male partner meetings, if available

**Qualitative Data Analysis**

Detailed description of the qualitative analysis will be presented in the study analysis plan. Briefly, the primary source of qualitative data in VOICE-C will be raw textual data. Qualitative data require interpretation, and texts are coded as a primary analytical approach, for data reduction, that is, to summarize, extract meaning, and condense the data. [37, 38] The VOICE-C transcripts will be coded first through descriptive coding for key themes and topics, using a preliminary codebook (see section on Codebook Development and Coding Process below). [39] Additional codes will be identified through an iterative process of reading the textual data to identify emergent themes, and the codebook will be modified accordingly. In addition to descriptive codes, pattern codes, which achieve a greater level of abstraction, will be used to start linking themes and topics together. [37] We will then seek to identify relationships between these various codes and how they are linked to product adherence, within a given level of the socio-ecological framework, in order to build a revised conceptual model that incorporates the

themes that were empirically identified during analysis. The analysis will be done by the investigative team, working interactively through emails, regular phone and face-to-face meetings. The findings and interpretations of the data will be critically discussed, until there is group consensus on the dominant themes and meanings contained in the data. For each VOICE-C group, the revised conceptual model will be validated through feedback from new "knowledgeable" informants during later rounds of exit FGDs.[40]

In addition to the textual data discussed above, systematic qualitative data collection methods, including free-listing, pile sorting and rating exercises may be conducted during the IDIs with VOICE participants and their male partners. [38, 41, 42] These methods will help to elicit terms encapsulating salient aspects of product adherence (or lack of thereof), factors influencing adherence, a classification of these factors in terms of negative or positive influence on use; and a rating of them, in terms of their relative importance with respect to product use. These data will then be aggregated and summarized for each study group (Group 1 and Group 2 participants) using cluster analysis.

As indicated above, the various data sources in VOICE-C will include transcripts from all of study groups, using multiple methods of data collection, including participant observations of male partners meetings and ethnographic research. Comparing findings and making linkages between these various data sources will allow confirmation, corroboration and validation of study results through triangulation.[37] We will also compare study sites and explore differences or similarities in response to the trial and the study regimen due to different social, economic and geographical contexts.

Final outputs of the qualitative analyses will include:

- A synthesized report with representational quotes that will describe the subjective personal experiences of trial participants in using the gel or the pill and how this influences adherence, household, (organizational) and community factors that influence product adherence. Differences in results by "stratifying" groups or variables will be described
- A refined conceptual model of products adherence, factors influencing product use/non-use and levels at which they operate, integrating the perspectives of each group of VOICE-C participants
- A typology of patterns of product use/adherence (as identified by VOICE-C participants and their partners) and the meanings participants associate with each aspect of use and pattern (i.e. non-use, sporadic use, intermittent use, consistent use, etcetera)
- A summary matrix displaying factors influencing adherence, motivators for use/non use, and the strength/importance of their association, including a count of how often these were mentioned (via content analysis) and illustrative quotes from the coded transcripts
- When data collection in the main VOICE trial is completed and available, we plan to conduct secondary analyses in VOICE-C Group 1 (and Group 2 if applicable), stratifying our qualitative analyses by women's reported level of adherence in the

VOICE trial. Additionally, we plan to qualitatively look at discrepancies between quantitative and qualitative reports of adherence among VOICE-C participants (Group 1), as appropriate

In summary, qualitative analyses from VOICE-C study will use a variety of techniques to provide exploratory and descriptive findings that will describe, in depth, the barriers and facilitators to adherence for 2 types of HIV prevention products (vaginally inserted gel and oral tablets). Illustrations of similar types of outputs from qualitative ancillary studies have been presented or published from several HIV prevention trials, including HPTN 035 [23, 43], MIRA ,[44] ,MDP 301[35] and others. [45, 46] The findings from VOICE-C may in turn inform future trials of this nature. Specifically, the data may suggest modifications to enable more accurate measurement of adherence in clinical trials, strategies for higher product uptake, consistent and sustained use, more effective male partner and community engagement processes in trials, and future roll-out or scale-up strategies. Findings from VOICE-C may also identify key issues that need to be systematically researched through future confirmatory quantitative studies.

**Codebook Development and Coding Process [47]**

Staff at RTI in collaboration with designated VOICE-C protocol team members and site staff, will develop a codebook and detailed guidelines/study procedures for coding and analysis of all of the textual data from MTN-003C in a qualitative software package such as Nvivo.

During the study development stage, a set of preliminary codes will be developed based on the research questions and the socio-ecological framework of this study (Table and Figure 1). The analysis coding structure will be hierarchical, and will reflect the levels, factors and topics/themes, as identified in Table 1. When the first 2-3 rounds of interviews is completed each group member will apply this initial set of thematic codes to a common transcript, discuss their coding experiences (over email, a meeting or conference calls), and agree on expanding and modifying code names and definitions when necessary. We will generate substantive and conceptual categories through an iterative process of reading the data, and generating codes based on the data and on key themes or topics identified *a priori*, applying the codes to the data, and refining these as we continue to read and code the data. Thus, codes will reflect the conceptual framework of the study, and will be centered on the main topic of interest (adherence) and the hypothesized spheres of influence at the household, organizational and community levels. However, by nature, the qualitative research process is iterative, and the Nvivo software allows for the generation of new codes for emergent themes that were not identified *a priori* by the research team. The software also allows for coders to insert descriptive comments and memos to themselves and others as they are working, and to code for concepts not spelled out in verbatim text, such as “contradiction”, when a participant or participants contradicts oneself.

Once finalized, the codebook will be used for a final recoding all of the transcripts. Comprehensive listings of all coded quotations for every code (as well as “families” of related codes) will be generated in Nvivo. We will consider the coded dataset in

entirety, and "stratify" the coded quotations by the study groups (VOICE participants, male partners, CAB, key community stakeholders), interview type (ethnography, FGD, IDI), site, respondent gender and study product group (e.g. oral vs. vaginal). Depending on findings from the cluster analysis, we may conduct additional grouping and stratifications of the data.

The coding process will involve a core group of 4-5 analysts who will frequently communicate (via email, phone or in person meetings) and discuss their use of the codebook and application of the codes during the coding process. A pre-selected number of texts will be double-coded by two coders (one at RTI, one at the site) to establish intra-coder and inter-coder reliability. These measures can be automatically generated in Nvivo. Following this process, the coding team will discuss (via teleconference) the coding discrepancies, which will ultimately be resolved through consensus. Ideally, there will be the opportunity for the coding and analysis team to meet in person several times during MTN-sponsored meetings. This process will continue until the inter-coder reliability is sufficiently high 80% or above. Thereafter each remaining text will be coded by one analyst only within Nvivo. Regular discussions among the coding team will ensure that coding remains standardized and reliable.

**Quality Assurance and Data Management**

The study will generate a large quantity of rich textual data that will include field notes, debriefing and summary reports, and verbatim transcriptions of IDIs, ethnographic field notes, and FGDs, transcribed and translated into English, using a standardized protocol.[13] During the data collection procedure, the data will be quality-checked by an external reviewer for grammatical and typographical errors, as well as clarifications on cultural meanings and conversation nuances, resulting in a textual dataset of several hundred pages of documents.

All these documents will be uploaded and managed in the qualitative software package Nvivo, which will also be used to code all the textual data. Once coded, all the pieces of textual data can later be retrieved through query tools, summarized in reports, and related to other codes and concepts using theoretical diagramming structures.

Coding is thus essential process for data reduction necessary for the management and interpretation of large amount of qualitative data. To ensure the quality of the coding, staff at RTI in collaboration with site staff and other VOICE-C team representative will develop a codebook and study procedures for coding and analysis of all of the qualitative data from MTN-003C in Nvivo. Each code will be operationally-defined and refined in an iterative way, as needed. Qualitative data coding is a subjective process, thus it is imperative that every coder and member of the research team is vigilant about being systematic and self-critical, so as to minimize the effects of imposing one's own biases or potentially erroneous interpretations of meaning. At the same time it is imperative that a coder does not only *read* text verbatim, but interprets some sense of meaning in the text, so that important elements of the data are not overlooked.

# 11 DATA HANDLING AND RECORDKEEPING

## 11.1 Data Management Responsibilities

Study CRFs will be developed by RTI in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by RTI to the study sites for verification and resolution. As part of the study activation process, each study site must identify all CRFs to be used as source documents.

RTI will act as a hub, and manage all data for the study. A convention for file naming will be developed, and all data will be labeled according to this process. Study sites will email original language and translated transcripts to RTI on a weekly or monthly basis. All files will be password-protected.

RTI will save all versions of all files on a secure, password-protected server. RTI will upload final coded and uncoded versions of all transcripts on a secure web-based share site that can be globally accessed.

## 11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/SourceDocPolicy.pdf).

For the VOICE-C Substudy, source documentation will include recruitment logs, records of attendance, seating charts, original audio files and facilitator notes. Essential documentation for the study also includes all versions of the protocol, informed consent forms, operating procedures and communication with the protocol team, including minutes, memos and emails. In accordance with U.S regulations and those outlined in the VOICE trial, each IoR/designee 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 parent 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 (QC) and Quality Assurance

At the site level, the social science coordinator will check the site's transcripts and translations for QA to ensure that the translation reflected the content of the focus group or interview, and then send each transcript to RTI for QC. During the first rounds of data collection, the coordinator will check the full content of the transcripts against the source. Once the site coordinator is satisfied with the accuracy and completeness of the transcription, the QC can be done on a random sample of the transcripts (or a randomly selected section from each transcript).

Staff at RTI will then check each English-language transcript for a second round of quality assurance, include their queries in track changes, and send the transcripts back to the site coordinators to address the queries. Queries will likely address issues ranging from questions to clarify a translation to corrections on spelling of English words. Once resolved, transcripts will be uploaded into Nvivo.

All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/QMPPolicy.pdf)

# 12 CLINICAL SITE MONITORING

Study monitoring will be carried out by PPD (Wilmington, NC) in accordance with all applicable DAIDS guidance for monitoring of substudies. Please refer to the VOICE (DAIDS Protocol #10622) Clinical Site Monitoring Section (Section 12) for additional applicable details.

# 13 HUMAN SUBJECTS PROTECTIONS

Site investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR will have obtained IRB/EC approval. The IoR will permit audits by the NIH or any of their appointed agents.

Accurate and thorough community education efforts may enhance participants' understanding of HIV prevention studies and of clinical research in general. The MTN CORE Community Program staff has initiated and plans continuation of strategies to inform site community representatives and community educators on important issues related to the VOICE-C study.

## 13.1 Institutional Review Boards/Ethics Committees

Each participating institution is responsible for assuring that this protocol, the associated site-specific informed consent forms, and study-related documents (such as participation education and recruitment materials) are reviewed by an IRB/EC responsible for oversight of research conducted at the study sites. Any amendments to the protocol must be approved by the responsible IRBs/ECs prior to implementation.

Subsequent to the initial review and approval, the responsible IRBs/ECs must review the study at least annually. Each IoR/designee will make safety and progress reports to the IRBs/ECs at least annually and within three months after study termination or completion. These reports will include the total number of participants enrolled in the

study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office in accordance with the most current DAIDS policies at the time of registration.

### 13.2 Protocol Registration

Each study site will also complete protocol registration in accordance with the most current DAIDS policies at the time of registration. Protocol registration material can be sent electronically to epr@tech-res.com. For questions regarding protocol registration, please call (301) 897-1707 or email Protocol@tech-res.com. For additional information, refer to the protocol registration documents located at http://rcc.tech-res.com/forms.htm. Protocol registration must occur as a condition for site-specific study activation; no participants may be screened or enrolled in this study prior to obtaining protocol registration approval and completing all other study activation requirements. MTN CORE (FHI) 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. The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chairs and DAIDS Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB/EC(s) and the RCC prior to implementing the amendment.

### 13.3 Study Coordination

Close coordination between protocol team members is necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chairs and DAIDS Medical Officer. Study implementation will also be guided by a common Study-Specific Procedures (SSP) manual that provides further instructions and operational guidance on conducting study procedures and associated data processing. Individual FGDs and IDIs will be conducted according to detailed interviewer guides that will be provided to the site staff by RTI. Standardized study-specific training will be provided to all sites by the MTN CORE, RTI, and other designated members of the Protocol Team.

### 13.4 Risk Benefit Statement

#### 13.4.1 Risks

Participation in research includes the risks of loss of confidentiality and discomfort with the personal nature of questions. 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. FGD participants may disclose what other participants said during the discussion. All FGD participants will be asked and strongly encouraged to respect each other's confidentiality. Furthermore, all FGD participants will be asked to use pseudonyms for themselves and for anyone they may talk about during the course of the FGD.

### 13.4.2 Benefits

Participants in this study may experience no direct benefit. Participants and others may benefit in the future from information learned from this study. For example, information learned in this study may contribute to the development of better ways to conduct HIV prevention studies and/or educate communities about HIV prevention studies. Participants also may appreciate the opportunity to contribute to the field of HIV prevention research.

## 13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to enrollment. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to Good Clinical Practices (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 will be 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 the Appendices 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 forms into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

## 13.6 Participant Confidentiality

With the exception of the FGDs, all study procedures will be conducted in private. Nonetheless, every effort will be made to protect participant privacy and confidentiality to the greatest 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. Notes will not contain any identifying information, and will also be stored on a password protected computer. Furthermore, all participant information will be stored in locked 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 the following:

- DAIDS, NIMH, and/or its contractors, including study monitors
- Representatives of the MTN CORE
- Representatives of RTI
- US government and regulatory authorities
- Site IRBs/ECs
- CONRAD
- Gilead Sciences, Inc.

## 13.7 Special Populations

### 13.7.1 Pregnant Women

While Group 1 participants who are pregnant will not be enrolled in MTN-003C, pregnancy is not exclusionary for women in Group 3 or Group 4. No pregnancy-related risks are anticipated in MTN-003C.

### 13.7.2 Children

The NIH has mandated that children be included in research trials when appropriate. This study meets "Justifications for Exclusion" criteria for younger children as set forth by the NIH. Specifically, "insufficient data are available in adults to judge potential risk in children" and "children should not be the initial group to be involved in research studies." This study does not plan to enroll children under 18 years old.

## 13.8 Compensation

Pending IRB/EC approval, participants will be compensated for time and effort.

## 13.9 Study Discontinuation

This study may be discontinued at any time by NIAID, the MTN, the Office for Human Research Protections (OHRP), other government or regulatory authorities, or site IRBs/ECs.

# 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, DAIDS, and NIMH for review prior to submission.

# 15 APPENDICES

**APPENDIX I: Sample Informed Consent Document (Ethnographic Visit-VOICE-C Participants)**

**SAMPLE INFORMED CONSENT FORM**
**DIVISION OF AIDS, NIAID, NIH**

**MTN-003C**
**Household and Community Level Factors Associated with Study Product Adherence in VOICE: A Substudy of MTN-003**

**Version 1.0**
**July 15, 2009**

**PRINCIPAL INVESTIGATOR:** [insert name]
**PHONE:** [insert number]
**Short Title for the Study:** Vaginal and Oral Interventions to Control the Epidemic (VOICE) Community and Adherence Substudy

**INFORMED CONSENT**
You are being asked to volunteer for the research study named above. This study is for women who have already agreed to be in the VOICE study at this site, their male partners, and community members.

**YOUR PARTICIPATION IS VOLUNTARY**
Before you decide whether to be in the Community and Adherence Substudy, we would like to explain the purpose of the substudy, the risks and benefits, what is expected of you, and what you can expect from us. This consent form might contain some words that are unfamiliar to you. Please ask questions about anything you do not understand or anything you want to learn more about. Once you understand the substudy, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep.

Before you learn about the substudy, it is important to know the following:

- It is up to you whether or not you join the Community and Adherence Substudy. If you decide not to join this substudy, you can still be in the VOICE study

- You may decide not to join this substudy, or you may choose to leave this substudy at any time, without losing the benefits of your regular medical care. If you choose to leave this substudy, you can still stay in the VOICE study

**PURPOSE OF THE STUDY**
The main purpose of the Community and Adherence Substudy is to find out what issues at your home and in your community might be encouraging or discouraging your use of

gel or tablets in the VOICE study. The [local authority] has permitted the substudy to be conducted. The United States National Institutes of Health is funding this substudy. Approximately 275 participants at this site [insert study site] will be invited to join the substudy. The whole substudy will take about 4 years to finish. Results and other medical information collected from participants in the main study may be used to help researchers understand the results of this substudy.

**STUDY PROCEDURES**

If you decide to join the Community and Adherence Substudy, your visit will start today, after you read, discuss, and sign or make your mark on this form.

If you agree, the following procedures will occur:

- You will participate in an informal conversation with a research staff member(s) at your home, or at an alternative venue of your choosing. These interactions will last no more than three hours and will take place every three months for one year
- Over the length of the study you may be asked to participate in 4 of these informal interactions
- You will also tell study staff or fill a sheet with some information about yourself before the start of the interview
- During these interactions you will talk about your experiences of participating in the VOICE study, and will be asked to talk about how this has influenced your use of the gel or tablets
- During the interview, you will discuss with the interviewer your use of gel or tablets in the VOICE study and about your situation at home and the community in which you live
- During the interaction, a research staff member will write down what you say. The notes will not contain your name or other identifying information; they will only be labeled with a study number, and will be stored on a computer that is password protected
- During the interaction, a research staff member may also ask for your permission to record what you say using a handheld digital voice recorder. The recordings will be destroyed when other source documents from the study are destroyed. A source document is a type of document where information is first collected or written down for a research study

**RISKS AND/OR DISCOMFORTS**

During these interactions we will ask you some questions about your private life and personal practices regarding product use and your relationships that may cause you to feel embarrassed or uncomfortable. You can decline answering questions at any time. It is also possible that people may find out that you are participating in this study and as a result, people may treat you unfairly, discriminate against you, and you may encounter problems in being accepted by your family and/or community.

**NEW INFORMATION**
You will be told about new information from this or other studies that may affect your health, welfare or willingness to stay in this study.

**BENEFITS**
There are no direct benefits in this substudy. However, the information that you provide may help health professionals better understand the issues women face when using vaginal gels and tablets for HIV prevention studies.

**REASONS WHY YOU MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR CONSENT**
You may be removed from this substudy without your consent for the following reasons:

- The substudy and/or main study is stopped or canceled
- The study staff feels that staying in the substudy would be harmful to you
- You are not able to attend substudy visits or complete the substudy procedures
- You have not used the study gel or study tablet(s) for 2 months or more at the time of your substudy visit
- You are diagnosed with HIV before the first informal conversation with research staff
- Other administrative reasons

**ALTERNATIVES TO PARTICIPATION**
There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about.

**COSTS TO YOU**
There is no cost to you for being in this substudy.

**REIMBURSEMENT**
[*Sites to insert information about local reimbursement:*]
You will receive [$xx] at each visit for your time, effort. This reimbursement will be separate from what you will receive for participation in the VOICE study.

**CONFIDENTIALITY**
We will do our best to make sure that the personal information gathered for this study is kept private. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this substudy will not use your name or identify you personally.

Your records may be reviewed by any or all of the following:

- The study staff
- The study monitors
- [insert names of applicable Institutional Review Boards/Ethics Committees]
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]

- The organization that supplies tenofovir 1% gel
- The company that makes tenofovir tablets and Truvada® tablets
- The United States Food and Drug Administration (FDA)
- The United States National Institutes of Health (NIH)

**PROBLEMS OR QUESTIONS**

If you ever have any questions about this study, you should contact [insert name of the investigator or other study staff] at [insert telephone number and/or physical address].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert telephone number and/or physical address of above].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member [staff will decide which] at [insert telephone number and/or physical address].

**SIGNATURES**

*[Insert signature blocks as required by the local IRB/EC:]* If you have read this consent form, or had it read and explained to you, and you understand the information, and voluntarily agree to participate in the study, please sign your name or make your mark below. All other information that is contained in the main study consent that you signed also applies to this substudy consent.

Please mark one of the following boxes if you choose to participate in this substudy:

☐ I agree to participate in this substudy, but do not wish to have my visits audio-recorded

☐ I agree to participate in this substudy and give the research staff permission to audio-record my visits

| _____ | _____ | _____ |
|---|---|---|
| Participant Name (print) | Participant Signature or Mark | Date |
| _____ | _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature | Date |
| _____ | _____ | _____ |
| Witness Name | Witness Signature | Date |

## APPENDIX II: Sample Informed Consent Document (FGDs-VOICE-C Participants)

**SAMPLE INFORMED CONSENT FORM**
**DIVISION OF AIDS, NIAID, NIH**

**MTN-003C**
**Household and Community Level Factors Associated with Study Product Adherence in VOICE: A Substudy of MTN-003**

**Version 1.0**
**July 15, 2009**

**PRINCIPAL INVESTIGATOR: [insert name]**
**PHONE: [insert number]**
**Short Title for the Study: Vaginal and Oral Interventions to Control the Epidemic (VOICE) Community and Adherence Substudy**

**INFORMED CONSENT**
You are being asked to volunteer for the research study named above. This study is for women who have already agreed to be in the VOICE study at this site, their male partners, and community members.

**YOUR PARTICIPATION IS VOLUNTARY**
Before you decide whether to be in the Community and Adherence Substudy, we would like to explain the purpose of the substudy, the risks and benefits, what is expected of you, and what you can expect from us. This consent form might contain some words that are unfamiliar to you. Please ask questions about anything you do not understand or anything you want to learn more about. Once you understand the substudy, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep.

Before you learn about the substudy, it is important to know the following:

- It is up to you whether or not you join the Community and Adherence Substudy. If you decide not to join this substudy, you can still be in the VOICE study

- You may decide not to join this substudy, or you may choose to leave this substudy at any time, without losing the benefits of your regular medical care

**PURPOSE OF THE STUDY**
The main purpose of the Community and Adherence Substudy is to find out what issues at your home and in your community might be encouraging or discouraging women's use of gel or tablets in the VOICE study. The [local authority] has permitted the substudy to be conducted. The United States National Institutes of Health is funding this substudy.

Approximately 275 participants at this site [insert study site] will be invited to join the substudy. The whole substudy will take about 4 years to finish. If you agree to participate, you will take part in the substudy for one visit only. Results and other medical information collected from participants in the main study may be used to help researchers understand the results of this substudy.

**STUDY PROCEDURES**

- If you decide to join the Community and Adherence Substudy, your visit will start today, after you read, discuss, and sign or make your mark on this form.

If you agree, the following procedures will occur:

- You will participate in a focus group discussion with up to 14 other women in a private place. The discussion will last about two to three hours and will be facilitated by a trained female staff member. To protect your privacy, you will be asked to use a made-up name for yourself and anyone you might talk about during the discussion
- You will also tell study staff or fill a sheet with some information about yourself before the start of the discussion
- During the focus group discussion, we will discuss women's use of gel or tablets in the VOICE study and about women's situation at home and the community in which you live
- During the group discussion a research staff member will write down what everyone says. We will also record the session using a voice recorder. We will use a recorder to make sure we record exactly what everyone says. The notes and the recording will not contain your name or other identifying information; they will only be labeled with a study number, and will be stored on a computer that is password protected. The recordings will be destroyed when other source documents from the study are destroyed. A source document is a type of document where information is first collected or written down for a research study

**RISKS AND/OR DISCOMFORTS**

During the group discussion, other participants will hear what you say. We will not reveal your full name to other participants, and at no time during the group discussion will your name be written down in connection with the information you have provided. We will ask you to use only your made-up name. We will also ask every participant not to tell anyone outside of the group what any person said during the discussion. While it is not at all likely that your discussion will be made public, we cannot guarantee that everyone will keep the discussion private. You are free to decline answering any questions you do not wish to answer and you may leave the discussion at any time.

During the discussion, some questions may be about your private life and personal practices regarding your product use and your relationships. This may cause you to feel embarrassed or uncomfortable. You can decline answering questions during the discussion at any time.

It is also possible that people may find out that you are participating in this study and as a result, people may treat you unfairly, discriminate against you, and you may encounter problems in being accepted by your family and/or community.

**NEW INFORMATION**
You will be told about new information from this or other studies that may affect your health, welfare or willingness to stay in this study.

**BENEFITS**
You may get no direct benefit from being in this substudy. However, the information that you provide may help health professionals better understand/learn more about the issues women face when using vaginal gels and tablets for HIV prevention studies.

**REASONS WHY YOU MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR CONSENT**
You may be removed from this substudy without your consent for the following reasons:

- The substudy and/or main study is stopped or canceled
- The study staff feels that staying in the substudy would be harmful to you
- You have not used the study gel or study tablet(s) for 2 months or more at the time of your substudy visit
- You are diagnosed with HIV before the Focus Group Discussion takes place
- Other administrative reasons

**ALTERNATIVES TO PARTICIPATION**
There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about.

**COSTS TO YOU**
There is no cost to you for being in this substudy.

**REIMBURSEMENT**
[*Sites to insert information about local reimbursement:*]
You will receive [$xx] for your time, effort, and travel for your Community and Adherence Substudy visit. This reimbursement will be separate from what you will receive for participation in the VOICE study.

**CONFIDENTIALITY**
We will do our best to make sure that the personal information gathered for this study is kept private. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this substudy will not use your name or identify you personally.

Your records may be reviewed by any or all of the following:

- The study staff
- The study monitors

- [insert names of applicable Institutional Review Boards/Ethics Committees]
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- The organization that supplies tenofovir 1% gel
- The company that makes tenofovir tablets and Truvada® tablets
- The United States Food and Drug Administration (FDA)
- The United States National Institutes of Health (NIH)

**PROBLEMS OR QUESTIONS**

If you ever have any questions about this study, you should contact [insert name of the investigator or other study staff] at [insert telephone number and/or physical address].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert telephone number and/or physical address of above].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member [staff will decide which] at [insert telephone number and/or physical address].

**SIGNATURES**

*[Insert signature blocks as required by the local IRB/EC:]* If you have read this consent form, or had it read and explained to you, and you understand the information, and voluntarily agree to participate in the study, please sign your name or make your mark below. All other information that is contained in the main study consent that you signed also applies to this substudy consent.

| _____ | _____ | _____ |
|---|---|---|
| Participant Name (print) | Participant Signature or Mark | Date |
| _____ | _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature | Date |
| _____ | _____ | _____ |
| Witness Name | Witness Signature | Date |

## APPENDIX III: Sample Informed Consent Document (FGDs-Male Partners)

**SAMPLE INFORMED CONSENT FORM**
**DIVISION OF AIDS, NIAID, NIH**

**MTN-003C**
**Household and Community Level Factors Associated with Study Product Adherence in VOICE: A Substudy of MTN-003**

**Version 1.0**
**July 15, 2009**

**PRINCIPAL INVESTIGATOR: [insert name]**
**PHONE: [insert number]**
**Short Title for the Study: Vaginal and Oral Interventions to Control the Epidemic (VOICE) Community and Adherence Substudy**

**INFORMED CONSENT**
You are being asked to volunteer for the research study named above. This study is for women who have already agreed to be in the VOICE study at this site, their male partners, and community members.

**YOUR PARTICIPATION IS VOLUNTARY**
Before you decide whether to be in the Community and Adherence Substudy, we would like to explain the purpose of the substudy, the risks and benefits, what is expected of you, and what you can expect from us. This consent form might contain some words that are unfamiliar to you. Please ask questions about anything you do not understand or anything you want to learn more about. Once you understand the substudy, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep.

Before you learn about the substudy, it is important to know the following:

- It is up to you whether or not you join the Community and Adherence Substudy. Your decision about whether to join this substudy will not impact your partner's participation in the VOICE study or this substudy

- You may decide not to join this substudy, or you may choose to leave this substudy at any time, without losing the benefits of your regular medical care

- Your partner has given permission to the study staff to contact you regarding the Community and Adherence Substudy

**PURPOSE OF THE STUDY**

The main purpose of the Community and Adherence Substudy is to find out what issues at your home and in your community might be encouraging or discouraging women's use of gel or tablets in the VOICE study. The [local authority] has permitted the substudy to be conducted. The United States National Institutes of Health is funding this substudy.

Approximately 275 participants at this site [insert study site] will be invited to join the substudy. The whole substudy will take about 4 years to finish. If you agree to participate, you will take part in the substudy for one visit only. Results and other medical information collected from participants in the main study may be used to help researchers understand the results of this substudy.

**STUDY PROCEDURES**

- If you decide to join the Community and Adherence Substudy, your visit will start today, after you read, discuss, and sign or make your mark on this form.

If you agree, the following procedures will occur:

- You will participate in a focus group discussion with up to 14 other men in a private place. The discussion will last about two to three hours and will be facilitated by a trained male staff member. To protect your privacy, you will be asked to use a made-up name for yourself and anyone you might talk about during the discussion
- You will also tell study staff or fill out a sheet with some information about yourself before the start of the discussion
- During the focus group discussion, we will discuss your partner's use of gel or tablets in the VOICE study and about women's situation at home and the community in which you live
- During the group discussion a research staff member will write down what everyone says. We will also record the session using a voice recorder. We will use a recorder to make sure we record exactly what everyone says. The notes and the recording will not contain your name or other identifying information; they will only be labeled with a study number, and will be stored on a computer that is password protected. The recordings will be destroyed when other source documents from the study are destroyed. A source document is a type of document where information is first collected or written down for a research study

**RISKS AND/OR DISCOMFORTS**

During the group discussion, other participants will hear what you say. We will not reveal your full name to other participants, and at no time during the group discussion will your name be written down in connection with the information you have provided. We will ask you to use only your made-up name. We will also ask every participant not to tell anyone outside of the group what any person said during the discussion. While it is not at all likely that your discussion will be made public, we cannot guarantee that

everyone will keep the discussion private. You are free to decline answering any questions you do not wish to answer and you may leave the discussion at any time.

During the discussion, some questions may be about your private life and personal practices regarding your partner's product use and your relationships. This may cause you to feel embarrassed or uncomfortable. You can decline answering questions during the discussion at any time.

It is also possible that people may find out that you are participating in this study and as a result, people may treat you unfairly, discriminate against you, and you may encounter problems in being accepted by your family and/or community.

**NEW INFORMATION**
You will be told about new information from this or other studies that may affect your health, welfare or willingness to stay in this study.

**BENEFITS**
You may get no direct benefit from being in this Substudy. However, the information that you provide may help health professionals better understand/learn more about the issues women face when using vaginal gels and tablets for HIV prevention studies.

**REASONS WHY YOU MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR CONSENT**
You may be removed from this substudy without your consent for the following reasons:

- The substudy and/or main study is stopped or canceled
- The study staff feels that staying in the substudy would be harmful to you.
- Other administrative reasons

**ALTERNATIVES TO PARTICIPATION**
There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about.

**COSTS TO YOU**
There is no cost to you for being in this substudy.

**REIMBURSEMENT**
[*Sites to insert information about local reimbursement:*]
You will receive [$xx] for your time, effort, and travel for your Community and Adherence Substudy visit.

**CONFIDENTIALITY**
We will do our best to make sure that the personal information gathered for this study is kept private. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this substudy will not use your name or identify you personally.

Your records may be reviewed by any or all of the following:

- The study staff
- The study monitors
- [insert names of applicable Institutional Review Boards/Ethics Committees]
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- The organization that supplies tenofovir 1% gel
- The company that makes tenofovir tablets and Truvada® tablets
- The United States Food and Drug Administration (FDA)
- The United States National Institutes of Health (NIH)

**PROBLEMS OR QUESTIONS**

If you ever have any questions about this study, you should contact [insert name of the investigator or other study staff] at [insert telephone number and/or physical address].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert telephone number and/or physical address of above].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member [staff will decide which] at [insert telephone number and/or physical address].

**SIGNATURES**

*[Insert signature blocks as required by the local IRB/EC:]* If you have read this consent form, or had it read and explained to you, and you understand the information, and voluntarily agree to participate in the study, please sign your name or make your mark below.

| _____ | _____ | _____ |
|---|---|---|
| Participant Name (print) | Participant Signature or Mark | Date |
| _____ | _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature | Date |
| _____ | _____ | _____ |
| Witness Name | Witness Signature | Date |

## APPENDIX IV: Sample Informed Consent Document (FGDs-CAB Members)

**SAMPLE INFORMED CONSENT FORM**
**DIVISION OF AIDS, NIAID, NIH**

**MTN-003C**
**Household and Community Level Factors Associated with Study Product Adherence in VOICE: A Substudy of MTN-003**

**Version 1.0**
**July 15, 2009**

**PRINCIPAL INVESTIGATOR: [insert name]**
**PHONE: [insert number]**
**Short Title for the Study: Vaginal and Oral Interventions to Control the Epidemic (VOICE) Community and Adherence Substudy**

**INFORMED CONSENT**
You are being asked to volunteer for the research study named above. This study is for women who have already agreed to be in the VOICE study at this site, their male partners, and community members.

**YOUR PARTICIPATION IS VOLUNTARY**
Before you decide whether to be in the Community and Adherence Substudy, we would like to explain the purpose of the substudy, the risks and benefits, what is expected of you, and what you can expect from us. This consent form might contain some words that are unfamiliar to you. Please ask questions about anything you do not understand or anything you want to learn more about. Once you understand the substudy, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep.

Before you learn about the substudy, it is important to know the following:

- It is up to you whether or not you join the Community and Adherence Substudy
- You may decide not to join this substudy, or you may choose to leave this substudy at any time without losing the benefits of your regular medical care

**PURPOSE OF THE STUDY**
The main purpose of the Community and Adherence Substudy is to find out what issues in women's homes and in your community might be encouraging or discouraging women's use of gel or tablets in the VOICE study. The [local authority] has permitted

the substudy to be conducted. The United States National Institutes of Health is funding this substudy.

Approximately 275 participants at this site [insert study site] will be invited to join the substudy. The whole substudy will take about 4 years to finish. If you agree to participate, you will take part in 5 focus group discussions. Results and other medical information collected from participants in the main study may be used to help researchers understand the results of this substudy.

**STUDY PROCEDURES**

- If you decide to join the Community and Adherence Substudy, your visit will start today, after you read, discuss, and sign or make your mark on this form.

If you agree, the following procedures will occur:

- You will participate in a focus group discussion with up to 14 other persons in a private place. The discussion will last up to two to three hours and will take place approximately every six months for the duration of the study, facilitated by a trained staff member. To protect your privacy, you will be asked to use a made-up name for yourself and anyone you might talk about during the discussion
- You will also tell study staff or fill a sheet with some information about yourself before the start of the discussion
- During the focus group discussion, we will discuss women's use of gel or tablets in the VOICE study and about women's situation at home and the community in which you live

During the group discussion a research staff member will write down what everyone says. We will also record the session using a voice recorder. We will use a recorder to make sure we record exactly what everyone says. The notes and the recording will not contain your name or other identifying information; they will only be labeled with a study number, and will be stored on a computer that is password protected. The recordings will be destroyed when other source documents from the study are destroyed. A source document is a type of document where information is first collected or written down for a research study.

**RISKS AND/OR DISCOMFORTS**

During the group discussion, other participants will hear what you say. We will not reveal your full name to other participants, and at no time during the group discussion will your name be written down in connection with the information you have provided. We will ask you to use only your made-up name. We will also ask every participant not to tell anyone outside of the group what any person said during the discussion. While it is not at all likely that your discussion will be made public, we cannot guarantee that everyone will keep the discussion private. You are free to decline answering any questions you do not wish to answer and you may leave the discussion at any time.

**NEW INFORMATION**
You will be told about new information from this or other studies that may affect your welfare or willingness to stay in this study.

**BENEFITS**
You may get no direct benefit from being in this substudy. However, the information that you provide may help health professionals better understand/learn more about the issues women face when using vaginal gels and tablets for HIV prevention studies.

**REASONS WHY YOU MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR CONSENT**
You may be removed from this substudy without your consent for the following reasons:

- The substudy and/or main study is stopped or canceled
- The study staff feels that staying in the substudy would be harmful to you
- You are not able to attend substudy visits or complete the substudy procedures
- Other administrative reasons

**ALTERNATIVES TO PARTICIPATION**
There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about.

**COSTS TO YOU**
There is no cost to you for being in this substudy.

**REIMBURSEMENT**
[*Sites to insert information about local reimbursement:*]
You will receive [$xx] at each visit for your time, effort, and travel for your Community and Adherence Substudy visit.

**CONFIDENTIALITY**
We will do our best to make sure that the personal information gathered for this study is kept private. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this substudy will not use your name or identify you personally.

Your records may be reviewed by any or all of the following:

- The study staff
- The study monitors
- [insert names of applicable Institutional Review Boards/Ethics Committees]
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- The organization that supplies tenofovir 1% gel
- The company that makes tenofovir tablets and Truvada® tablets
- The United States Food and Drug Administration (FDA)
- The United States National Institutes of Health (NIH)

**PROBLEMS OR QUESTIONS**

If you ever have any questions about this study, you should contact [insert name of the investigator or other study staff] at [insert telephone number and/or physical address].
If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert telephone number and/or physical address of above].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member [staff will decide which] at [insert telephone number and/or physical address].

**SIGNATURES**

*[Insert signature blocks as required by the local IRB/EC:]* If you have read this consent form, or had it read and explained to you, and you understand the information, and voluntarily agree to participate in the study, please sign your name or make your mark below.

| _____ | _____ | _____ |
|---|---|---|
| Participant Name (print) | Participant Signature or Mark | Date |
| _____ | _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature | Date |
| _____ | _____ | _____ |
| Witness Name | Witness Signature | Date |

**APPENDIX V: Sample Informed Consent Document (FGDs-Key Community Stakeholders)**

**SAMPLE INFORMED CONSENT FORM**
**DIVISION OF AIDS, NIAID, NIH**

**MTN-003C**
**Household and Community Level Factors Associated with Study Product Adherence in VOICE: A Substudy of MTN-003**

**Version 1.0**
**July 15, 2009**

**PRINCIPAL INVESTIGATOR: [insert name]**
**PHONE: [insert number]**
**Short Title for the Study: Vaginal and Oral Interventions to Control the Epidemic (VOICE) Community and Adherence Substudy**

**INFORMED CONSENT**
You are being asked to volunteer for the research study named above. This study is for women who have already agreed to be in the VOICE study at this site, their male partners, and community members.

**YOUR PARTICIPATION IS VOLUNTARY**
Before you decide whether to be in the Community and Adherence Substudy, we would like to explain the purpose of the substudy, the risks and benefits, what is expected of you, and what you can expect from us. This consent form might contain some words that are unfamiliar to you. Please ask questions about anything you do not understand or anything you want to learn more about. Once you understand the substudy, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep.

Before you learn about the substudy, it is important to know the following:

- It is up to you whether or not you join the Community and Adherence Substudy
- You may decide not to join this substudy, or you may choose to leave this substudy at any time, without losing the benefits of your regular medical care

**PURPOSE OF THE STUDY**
The main purpose of the Community and Adherence Substudy is to find out what issues in women's homes and in your community might be encouraging or discouraging women's use of gel or tablets in the VOICE study. The [local authority] has permitted

the substudy to be conducted. The United States National Institutes of Health is funding this substudy.

Approximately 275 participants at this site [insert study site] will be invited to join the substudy. The whole substudy will take about 4 years to finish. If you agree to participate, you will take part in the substudy for one visit only. Results and other medical information collected from participants in the main study may be used to help researchers understand the results of this substudy.

**STUDY PROCEDURES**

- If you decide to join the Community and Adherence Substudy, your visit will start today, after you read, discuss, and sign or make your mark on this form.

If you agree, the following procedures will occur:

- You will participate in a focus group discussion with up to 14 other persons in a private place. The discussion will last up to two to three hours and will be facilitated by a trained staff member. To protect your privacy, you will be asked to use a made-up name for yourself and anyone you might talk about during the discussion
- You will also tell study staff or fill a sheet with some information about yourself before the start of the discussion
- During the focus group discussion, we will discuss women's use of gel or tablets in the VOICE study and about women's situation at home and the community in which you live
- During the group discussion a research staff member will write down what everyone says. We will also record the session using a voice recorder. We will use a recorder to make sure we record exactly what everyone says. The notes and the recording will not contain your name or other identifying information; they will only be labeled with a study number, and will be stored on a computer that is password protected. The recordings will be destroyed when other source documents from the study are destroyed. A source document is a type of document where information is first collected or written down for a research study

**RISKS AND/OR DISCOMFORTS**

During the group discussion, other participants will hear what you say. We will not reveal your full name to other participants, and at no time during the group discussion will your name be written down in connection with the information you have provided. We will ask you to use only your made-up name. We will also ask every participant not to tell anyone outside of the group what any person said during the discussion. While it is not at all likely that your discussion will be made public, we cannot guarantee that everyone will keep the discussion private. You are free to decline answering any questions you do not wish to answer and you may leave the discussion at any time.

**NEW INFORMATION**
You will be told about new information from this or other studies that may affect your welfare or willingness to stay in this study.

**BENEFITS**
You may get no direct benefit from being in this substudy. However, the information that you provide may help health professionals better understand/learn more about the issues women face when using vaginal gels and tablets for HIV prevention studies.

**REASONS WHY YOU MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR CONSENT**
You may be removed from this substudy without your consent for the following reasons:

- The substudy and/or main study is stopped or canceled
- The study staff feels that staying in the substudy would be harmful to you
- Other administrative reasons

**ALTERNATIVES TO PARTICIPATION**
There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about.

**COSTS TO YOU**
There is no cost to you for being in this substudy.

**REIMBURSEMENT**
[*Sites to insert information about local reimbursement:*]
You will receive [$xx] for your time, effort, and travel for your Community and Adherence Substudy visit.

**CONFIDENTIALITY**
We will do our best to make sure that the personal information gathered for this study is kept private. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this substudy will not use your name or identify you personally.

Your records may be reviewed by any or all of the following:

- The study staff
- The study monitors
- [insert names of applicable Institutional Review Boards/Ethics Committees]
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- The organization that supplies tenofovir 1% gel
- The company that makes tenofovir tablets and Truvada® tablets
- The United States Food and Drug Administration (FDA)
- The United States National Institutes of Health (NIH)

**PROBLEMS OR QUESTIONS**

If you ever have any questions about this study, you should contact [insert name of the investigator or other study staff] at [insert telephone number and/or physical address].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert telephone number and/or physical address of above].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member [staff will decide which] at [insert telephone number and/or physical address].

**SIGNATURES**

*[Insert signature blocks as required by the local IRB/EC:]* If you have read this consent form, or had it read and explained to you, and you understand the information, and voluntarily agree to participate in the study, please sign your name or make your mark below.

| _____ | _____ | _____ |
|---|---|---|
| Participant Name (print) | Participant Signature or Mark | Date |
| _____ | _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature | Date |
| _____ | _____ | _____ |
| Witness Name | Witness Signature | Date |

## APPENDIX VI: Sample Informed Consent Document (IDIs-VOICE-C Participants)

**SAMPLE INFORMED CONSENT FORM**
**DIVISION OF AIDS, NIAID, NIH**

**MTN-003C**
**Household and Community Level Factors Associated with Study Product Adherence in VOICE: A Substudy of MTN-003**

**Version 1.0**
**July 15, 2009**

**PRINCIPAL INVESTIGATOR:** [insert name]
**PHONE:** [insert number]
**Short Title for the Study:** Vaginal and Oral Interventions to Control the Epidemic (VOICE) Community and Adherence Substudy

**INFORMED CONSENT**
You are being asked to volunteer for the research study named above. This study is for women who have already agreed to be in the VOICE study at this site, their male partners, and community members.

**YOUR PARTICIPATION IS VOLUNTARY**
Before you decide whether to be in the Community and Adherence Substudy, we would like to explain the purpose of the substudy, the risks and benefits, what is expected of you, and what you can expect from us. This consent form might contain some words that are unfamiliar to you. Please ask questions about anything you do not understand or anything you want to learn more about. Once you understand the substudy, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep.

Before you learn about the substudy, it is important to know the following:

- It is up to you whether or not you join the Community and Adherence Substudy. If you decide not to join this substudy, you can still be in the VOICE study

- You may decide not to join this substudy, or you may choose to leave this substudy at any time, without losing the benefits of your regular medical care. If you choose to leave this substudy, you can still stay in the VOICE study

**PURPOSE OF THE STUDY**
The main purpose of the Community and Adherence Substudy is to find out what issues at your home and in your community might be encouraging or discouraging women's use of gel or tablets in the VOICE study. The [local authority] has permitted the

substudy to be conducted. The United States National Institutes of Health is funding this substudy.

Approximately 275 participants will be invited to join the substudy at this site [insert study site]. The whole substudy will take about 4 years to finish. If you agree to participate, you will take part in the substudy for one visit only. Results and other medical information collected from participants in the main study may be used to help researchers understand the results of this substudy.

**STUDY PROCEDURES**
If you decide to join the Community and Adherence Substudy, your visit will start today, after you read, discuss, and sign or make your mark on this form.

If you agree, the following procedures will occur:

- You will participate in an interview with a research staff member(s) at the clinic or at a location of your choice. The interview will last approximately one to two hours. To protect privacy, you will be asked to use a made-up name for anyone you might talk about during the interview. You will be asked to participate in only one interview
- You will also tell study staff or fill a sheet with some information about yourself before the start of the interview
- You will discuss with the interviewer about your use of gel or tablets in the VOICE study and about your situation at home and the community in which you live
- During the interview a research staff member will write down what you say. We will also record the session using a voice recorder. We will use a voice recorder to make sure we record your words exactly how you said them. The notes and the recording will not contain your name or other identifying information; they will only be labeled with a study number, and will be stored on a computer that is password protected. The voice recordings will be destroyed when other source documents from the study are destroyed. A source document is a type of document where information is first collected or written down for a research study

**RISKS AND/OR DISCOMFORTS**
During the interview we will ask you some questions about your private life and personal practices regarding product use and your relationships that may cause you to feel embarrassed or uncomfortable. You can decline answering questions in the interview at any time. It is also possible that people may find out that you are participating in this study and as a result, people may treat you unfairly, discriminate against you, and you may encounter problems in being accepted by your family and/or community.

**NEW INFORMATION**
You will be told about new information from this or other studies that may affect your health, welfare or willingness to stay in this study.

**BENEFITS**
There are no direct benefits in this substudy. However, the information that you provide may help health professionals better understand the issues women face when using vaginal gels and tablets for HIV prevention studies.

**REASONS WHY YOU MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR CONSENT**
You may be removed from this substudy without your consent for the following reasons:

- The substudy and/or main study is stopped or canceled
- The study staff feels that staying in the substudy would be harmful to you
- You have not used the study gel or study tablet(s) for 2 months or more at the time of your substudy visit
- You are diagnosed with HIV before the in-depth interview takes place
- Other administrative reasons

**ALTERNATIVES TO PARTICIPATION**
There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about.

**COSTS TO YOU**
There is no cost to you for being in this substudy.

**REIMBURSEMENT**
[*Sites to insert information about local reimbursement:*]
You will receive [$xx] for your time, effort, and travel for your Community and Adherence Substudy visit. This reimbursement will be separate from what you will receive for participation in the VOICE study.

**CONFIDENTIALITY**
We will do our best to make sure that the personal information gathered for this study is kept private. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this substudy will not use your name or identify you personally.

Your records may be reviewed by any or all of the following:

- The study staff
- The study monitors
- [insert names of applicable Institutional Review Boards/Ethics Committees]
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- The organization that supplies tenofovir 1% gel
- The company that makes tenofovir tablets and Truvada® tablets
- The United States Food and Drug Administration (FDA)
- The United States National Institutes of Health (NIH)

**PROBLEMS OR QUESTIONS**

If you ever have any questions about this study, you should contact [insert name of the investigator or other study staff] at [insert telephone number and/or physical address].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert telephone number and/or physical address of above].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member [staff will decide which] at [insert telephone number and/or physical address].

**SIGNATURES**

*[Insert signature blocks as required by the local IRB/EC:]* If you have read this consent form, or had it read and explained to you, and you understand the information, and voluntarily agree to participate in the study, please sign your name or make your mark below. All other information that is contained in the main study consent that you signed also applies to this substudy consent.

| _____ | _____ | _____ |
|---|---|---|
| Participant Name (print) | Participant Signature or Mark | Date |
| _____ | _____ | _____ |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature | Date |
| _____ | _____ | _____ |
| Witness Name | Witness Signature | Date |

## APPENDIX VII: Sample Informed Consent Document (IDIs-Male Partners)

**SAMPLE INFORMED CONSENT FORM**
**DIVISION OF AIDS, NIAID, NIH**

**MTN-003C**
**Household and Community Level Factors Associated with Study Product Adherence in VOICE: A Substudy of MTN-003**

**Version 1.0**
**July 15, 2009**

**PRINCIPAL INVESTIGATOR:** [insert name]
**PHONE:** [insert number]
**Short Title for the Study:** Vaginal and Oral Interventions to Control the Epidemic (VOICE) Community and Adherence Substudy

**INFORMED CONSENT**
You are being asked to volunteer for the research study named above. This study is for women who have already agreed to be in the VOICE study at this site, their male partners, and community members.

**YOUR PARTICIPATION IS VOLUNTARY**
Before you decide whether to be in the Community and Adherence Substudy, we would like to explain the purpose of the substudy, the risks and benefits, what is expected of you, and what you can expect from us. This consent form might contain some words that are unfamiliar to you. Please ask questions about anything you do not understand or anything you want to learn more about. Once you understand the substudy, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep.

Before you learn about the substudy, it is important to know the following:

- It is up to you whether or not you join the Community and Adherence Substudy. Your decision about whether to join this substudy will not impact your partner's participation in the VOICE study or this substudy

- You may decide not to join this substudy, or you may choose to leave this substudy at any time, without losing the benefits of your regular medical care

- Your partner has given permission to the study staff to contact you regarding the Community and Adherence Substudy

**PURPOSE OF THE STUDY**
The main purpose of the Community and Adherence Substudy is to find out what issues at your home and in your community might be encouraging or discouraging women's use of gel or tablets in the VOICE study. The [local authority] has permitted the substudy to be conducted. The United States National Institutes of Health is funding this substudy.

Approximately 275 participants will be invited to join the substudy at this site [insert study site]. The whole substudy will take about 4 years to finish. If you agree to participate, you will take part in the substudy for one visit only. Results and other medical information collected from participants in the main study may be used to help researchers understand the results of this substudy.

**STUDY PROCEDURES**
If you decide to join the Community and Adherence Substudy, your visit will start today, after you read, discuss, and sign or make your mark on this form.

If you agree, the following procedures will occur:

- You will participate in an interview with a research staff member(s) in a private place. The interview will last approximately one to two hours. To protect privacy, you will be asked to use a made-up name for anyone you might talk about during the interview. You will be asked to participate in only one interview
- You will also tell study staff or fill a sheet with some information about yourself before the start of the interview
- You will discuss with the interviewer your partner's use of gel or tablets in the VOICE study and your situation at home and the community in which you live
- During the interview a research staff member will write down what you say. We will also record the session using a voice recorder. We will use a voice recorder to make sure we record your words exactly how you said them. The notes and the recording will not contain your name or other identifying information; they will only be labeled with a study number, and will be stored on a computer that is password protected. The voice recordings will be destroyed when other source documents from the study are destroyed. A source document is a type of document where information is first collected or written down for a research study

**RISKS AND/OR DISCOMFORTS**
During the interview we will ask you some questions about your private life and personal practices regarding product use and your relationships that may cause you to feel embarrassed or uncomfortable. You can decline answering questions in the interview at any time. It is also possible that people may find out that you are participating in this study and as a result, people may treat you unfairly, discriminate against you, and you may encounter problems in being accepted by your family and/or community.

**NEW INFORMATION**
You will be told about new information from this or other studies that may affect your health, welfare or willingness to stay in this study.

**BENEFITS**
There are no direct benefits in this substudy. However, the information that you provide may help health professionals better understand the issues women face when using vaginal gels and tablets for HIV prevention studies.

**REASONS WHY YOU MAY BE WITHDRAWN FROM THE SUBSTUDY WITHOUT YOUR CONSENT**
You may be removed from this substudy without your consent for the following reasons:

- The substudy and/or main study is stopped or canceled
- The study staff feels that staying in the substudy would be harmful to you
- Other administrative reasons

**ALTERNATIVES TO PARTICIPATION**
There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about.

**COSTS TO YOU**
There is no cost to you for being in this substudy.

**REIMBURSEMENT**
[*Sites to insert information about local reimbursement:*]
You will receive [$xx] for your time, effort, and travel for your Community and Adherence Substudy visit.

**CONFIDENTIALITY**
We will do our best to make sure that the personal information gathered for this study is kept private. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any publication of this substudy will not use your name or identify you personally.

Your records may be reviewed by any or all of the following:

- The study staff
- The study monitors
- [insert names of applicable Institutional Review Boards/Ethics Committees]
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- The organization that supplies tenofovir 1% gel
- The company that makes tenofovir tablets and Truvada® tablets
- The United States Food and Drug Administration (FDA)
- The United States National Institutes of Health (NIH)

**PROBLEMS OR QUESTIONS**

If you ever have any questions about this study, you should contact [insert name of the investigator or other study staff] at [insert telephone number and/or physical address].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert telephone number and/or physical address of above].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member [staff will decide which] at [insert telephone number and/or physical address].

**SIGNATURES**

*[Insert signature blocks as required by the local IRB/EC:]* If you have read this consent form, or had it read and explained to you, and you understand the information, and voluntarily agree to participate in the study, please sign your name or make your mark below.

| | | |
|---|---|---|
| Participant Name (print) | Participant Signature or Mark | Date |
| Study Staff Conducting Consent Discussion (print) | Study Staff Signature | Date |
| Witness Name | Witness Signature | Date |

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