TECHNICAL REPORT

BEHAVIORAL AND SOCIAL SCIENCE SUPPORT TO CONRAD PHASE III CLINICAL TRIAL 0F CELLULOSE SULFATE 6% GEL

Family Health International

June 2008

Submitted to CONRAD

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Family Health International (FHI) is a nonprofit organization working to improve lives worldwide through research, education, and services in family health.

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Technical Report: Behavioral and Social Science Support to CONRAD Phase III Clinical Trial of Cellulose Sulfate 6% Gel

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Executive Summary

This report documents behavioral and social science (BSS) activities carried out by Family Health International (FHI) and its partners from September 2004 through August 2007 in support of CONRAD's Phase III clinical trial to determine the effectiveness of Cellulose Sulfate 6% in preventing transmission of HIV. Some or all BSS activities were implemented during three phases (Preparedness, On-Going and Exit) in seven sites, including Cotonou, Benin; Bobo-Dioulassa, Burkina Faso; Kampala, Uganda; Durban, South Africa; and Chennai and Bagalkot, India. The objectives of the BSS work were to:

- Advise on data collection instruments and techniques, including informed consent materials and process
- Identify and develop strategies affecting recruitment
- Identify and develop strategies affecting retention
- Examine community understanding of and attitudes toward trial; develop and implement strategies to improve community support
- Document referral medical care sites identified for individuals who seroconvert or who test HIV positive at screening
- Explore former participants' understanding of and adherence to trial requirements, including study gel use, and
- Assess how communities, trial staff, and participants understand the decision to terminate the trial

Local BSS teams were trained in formal and informal qualitative data collection methods and conducted in-depth interviews, focus group discussions, and informal meetings with three categories of respondents: 1) potential participants or other community stakeholders; 2) clinical trial participants and former participants; and 3) clinical trial staff. BSS teams shared the information from their activities with the local clinical teams in an on-going manner. The data were also analyzed in aggregate and presented in this report.

Research findings show the importance of BSS activities in enhancing the implementation of HIV prevention clinical trials. Below are some major findings and recommendations:

Promoting understanding of clinical trials

- The findings highlighted the need to pretest informed consent and counseling information to ensure that explanations are comprehensible and to avoid misunderstandings, particularly regarding gel effectiveness. There is a need to increase research literacy within the community while being mindful of the difficulties that may arise from integrating community stakeholders with different concerns in trial planning and implementation.

Recruitment and retention of trial participants

- The BSS data show that group approaches to recruitment (e.g. community meetings and and informal gatherings) were effective together with the use of outreach workers and peer leaders. It is also essential to adapt recruitment strategies to fit local realities and individual perceptions of risk.

- Identifying and rapidly addressing participant concerns enhance retention rates. Two factors of particular importance include clinical staff's provision of high quality of care and respectful treatment to trial participants.

Gel acceptability and adherence

- Gel acceptability was high among trial participants, especially its lubricating properties.
- The findings also show some cases of partial gel use, particularly concerning the amount of gel to be applied (for fear of detection by partners) and difficulties using the gel with primary partners.
- Condom use was also likely to differ by partner type.

Planning for early closure

- Early closure caused disappointment to participants and staff because of the loss of trial benefits.
- Despite some rumors circulating in the community after the closure of the trial, information on closure was well managed overall and, with the exception of South Africa, did not appear to adversely affect willingness to participate in future trials.

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Acknowledgements

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LIST OF ACRONYMNS

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
BSS	Behavioral and Social Science
CAB	Community Advisory Board
CS	Cellulose Sulfate
CSW	Commercial Sex Worker
CT	Clinical Trial
EVMS	Eastern Virginia Medical School
FGD	Focus Group Discussion
FHI	Family Health International
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
IC	Informed Consent
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
LTF	Loss-to-Follow-Up
N-9	Nonoxynol-9
NGO	Non-Governmental Organization
ORW	Outreach Worker
PE	Peer Educator
PHSC	Protection of Human Subjects Committee
PI	Principal Investigator
PreP	Pre-exposure Prophylaxis
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
TASO	The AIDS Support Organization
UNAIDS	United Nations Joint Program on HIV/AIDS
USAID	United States Agency for International Development
UZ-UCSF	University of Zimbabwe – University of California San Francisco
WHO	World Health Organization

I. Overview and Objectives

A. Overview

This report documents behavioral and social science (BSS) activities carried out by Family Health International (FHI) and its partners from September 2004 through August 2007 in support of CONRAD's Phase III clinical trial to determine the effectiveness of Cellulose Sulfate 6% in preventing transmission of HIV. The BSS activities were undertaken to address some of the logistical, methodological, and ethical issues known to create challenges for successful implementation of Phase III clinical trials. First, HIV prevention trial administrators must be able to identify and recruit individuals who are HIV-negative but at risk of HIV infection. Ideally, this involves situating the trial within a population with high HIV incidence rates but only moderate prevalence rates. (When prevalence rates are high, the cost of screening participants increases rapidly.) Therefore, BSS activities were conducted in some sites to identify the types of women who were both at risk of HIV and willing to participate in a microbicide clinical trial. Second, trial administrators face the challenge of developing systems to encourage participant retention. Clinical trial results are jeopardized when loss-to-follow-up (LTF) rates are high, especially when these rates differ by trial arm. The effectiveness of HIV prevention interventions, like the use of a topical microbicide, cannot be tested unless participants actually use the product and are exposed to HIV. In response to these issues, BSS activities were conducted before and during the clinical trial to identify factors that might affect participants' willingness or ability to remain in the trial and to come consistently for study visits. Third, given the potential of HIV seroconversion during trial participation, a whole host of ethical issues may plague the trial. They include ensuring that participants understand the experimental nature of the trial (that product effectiveness is not known and that participants may be assigned either an active or non-active/placebo product to use); organizing the care and support for participants who seroconvert during the trial; and how to explain the potential risks and benefits of the trial to community members. BSS teams engaged community stakeholders throughout the three-year study to get a better sense of how they understood the trial and its eventual closure.

The following sites participated in one or more phases of the study:

Nairobi, Kenya
Durban, South Africa
Kampala, Uganda
Cotonou, Benin
Bobo-Dioulasso, Burkina Faso

Chennai, India
Bagalkot, India
Harare, Zimbabwe

Initially, the first six sites listed above were identified for participation in the CS trial. One early decision was to drop Kenya as a trial site, add a second site in India (Bagalkot) and increase sample sizes in South Africa and Chennai, India. Later, after the site initiation training but before screening began, Burkina Faso was also dropped from the trial because of low HIV incidence., Finally,l two additional sites were proposed – a second site in South Africa and one in Zimbabwe – but the trial ended prematurely, before the latter two could be initiated.

B. Study Objectives

The objectives of BSS activities were revised at three times or phases: preparedness, ongoing and exit. Initially, BSS activities were to be conducted in each trial site during a six-month Preparedness Phase. Once the trial was initiated in a site, however, the BSS activities were to have ended. Preparedness activities were primarily intended to inform recruitment and retention activities, and advise the refinement of informed consent materials and data collection instruments. Four of the original six sites conducted Preparedness Phase activities: Benin, Burkina Faso, Chennai (India), and Uganda.

During this time, several FHI-sponsored microbicide/PrEP clinical trials encountered a range of difficulties, including community concerns and opposition in some trial sites and low HIV incidence in others. These difficulties led to a series of decisions affecting the composition of trial sites. In addition, a decision was made to include some on-going BSS activities in each site during trial implementation. While informing recruitment and retention strategies remained important objectives for the ongoing phase, additional objectives were added to monitor local community attitudes toward the clinical trial; to document referral for those who screened out because of HIV or who seroconverted, and to develop an exit strategy for implementation in the event of early closure of the study. A proposed objective to examine participants' adherence to gel use and other trial-related requirements was considered but rejected because of concern about burdening trial participants and difficulties reconciling potentially discrepant data between the clinical trial data and the BSS data.

On January 26, 2007, an Independent Data Monitoring Committee (IDMC) indicated that the use of Cellulose Sulfate could potentially lead to an increased risk of HIV infection as compared with a placebo. While the results were preliminary and a plausible explanation was not apparent, CONRAD decided to halt its Phase III effectiveness trial of Cellulose Sulfate as a precautionary measure. Because the sudden closure of the trial was likely to raise a number of questions and concerns among trial communities, staff, and participants, a third phase of BSS data collection activities was added. In addition to a continued focus on community and staff understandings of and reactions to trial closure, a decision was made to directly examine former participants' understanding of and use of study gel during the trial. The table below summarizes BSS objectives and the three phases in which data were collected to address them.

TABLE 1: OBJECTIVES OF BSS SUPPORT TO CONRAD PHASE III CLINICAL TRIAL OF 6% CELLULOSE SULFATE GEL

Rpt	Objectives	Preparedness	On-Going	Exit
A	Advise on data collection instruments and techniques, including **informed consent** materials and process	✓	✓	
B	Identify and develop strategies affecting **recruitment**	✓	✓	
C	Identify and develop strategies affecting **retention**	✓	✓	
D	Examine **community understanding of and attitudes** toward trial, develop and implement strategies to improve community support	✓	✓	✓
E	Document **referral medical care sites** identified for individuals who seroconvert or who test HIV positive at screening		✓	
F	Explore former **participants' understanding of and adherence** to trial and study gel use			✓
G	Assess how communities, trial staff, and participants **understand decision to terminate the trial**			✓

C. Training

FHI staff conducted BSS training in each site. Training content was modified to fit the needs of the local BSS team and included some or all of the following components: research ethics and review of informed consent materials; study protocol review; review and practice using question guides; data management; theoretical and practical experience with qualitative analysis; and review and practice with qualitative research methods, including observation, in-depth interviewing, and the use of focus group discussion techniques. In addition to these formal trainings, FHI staff helped the local teams coordinate and implement data collection through monitoring trips and regular electronic or telephone communication.

During the Preparedness Phase, FHI staff traveled to Cotonou, Benin, and Chennai, India, to conduct training. The Benin training included staff from Benin and Burkina Faso. A "reconnaissance" trip to Uganda and South Africa was conducted in advance of launching behavioral preparedness work. However, it was determined that a formal training was not required for these two sites.

Between April and August 2005, core training for the clinical trial was conducted jointly by the clinical team and FHI BSS members in Benin, Burkina Faso, Chennai (India), Uganda and South Africa. FHI BSS members returned to Benin, Chennai, Uganda, and South Africa for a detailed refresher training on the on-going behavioral and social science work to be done. Burkina Faso had been closed as a site by this time, so no refresher training was done. The training team was en route to the new site in South Africa for core training when the trial was halted in 2007.

The Exit Phase began in Burkina Faso with work on close-out activities related to the cancellation of the trial at that site because of low HIV incidence. BSS staff members

were on-site to train on the revised exit plan when the trial closure was announced after the IDMC meeting in 2007. Although she did not conduct a formal training in Benin, the site monitor was able to extend her trip in the region and return to Benin to work on broader exit phase activities for the new situation. At the time of trial closure, the Zimbabwe site had just received ethics approval to begin conducting Preparedness and On-Going Phase activities. Therefore, site training for the Exit Phase only was conducted. All other sites conducted Exit Phase activities with guidance provided by the FHI BSS team through e-mail and conference calls.

TABLE 2: BSS TRAINING ACTIVITIES OVER THREE PHASES OF STUDY

Date of Trip	Sites	Date of Trip	Sites
Phase I: Preparedness		**Phase II: On-Going (cont.)**	
2005 January	Benin & Burkina Faso	2005 December	Bagalkot
2005 April	Chennai	2006 January	Benin
Phase II: On-Going		2006 March	Chennai & Bagalkot
2005 April	South Africa	2006 July	South Africa
2005 April	Uganda	2006 July	Uganda
2005 June	Burkina Faso	**Phase III: Exit**	
2005 June	Benin	2007 January	Burkina Faso
2005 August	Chennai	2007 February	Benin
		2007 March	Zimbabwe

D. Human Subjects

The study was approved in compliance with all U.S. federal regulations governing the protection of human subjects, as well as by local country requirements. In total, 12 ethics boards reviewed aspects of the study (see Appendix 1). To allow for the changes within the study, including site variations to the protocol and timeline, the process for Institutional Review Board (IRB) submissions was flexible. FHI's Protection of Human Subjects Committee (PHSC) provided the first level of review, and the relevant ethics boards for each site provided a second level of review.

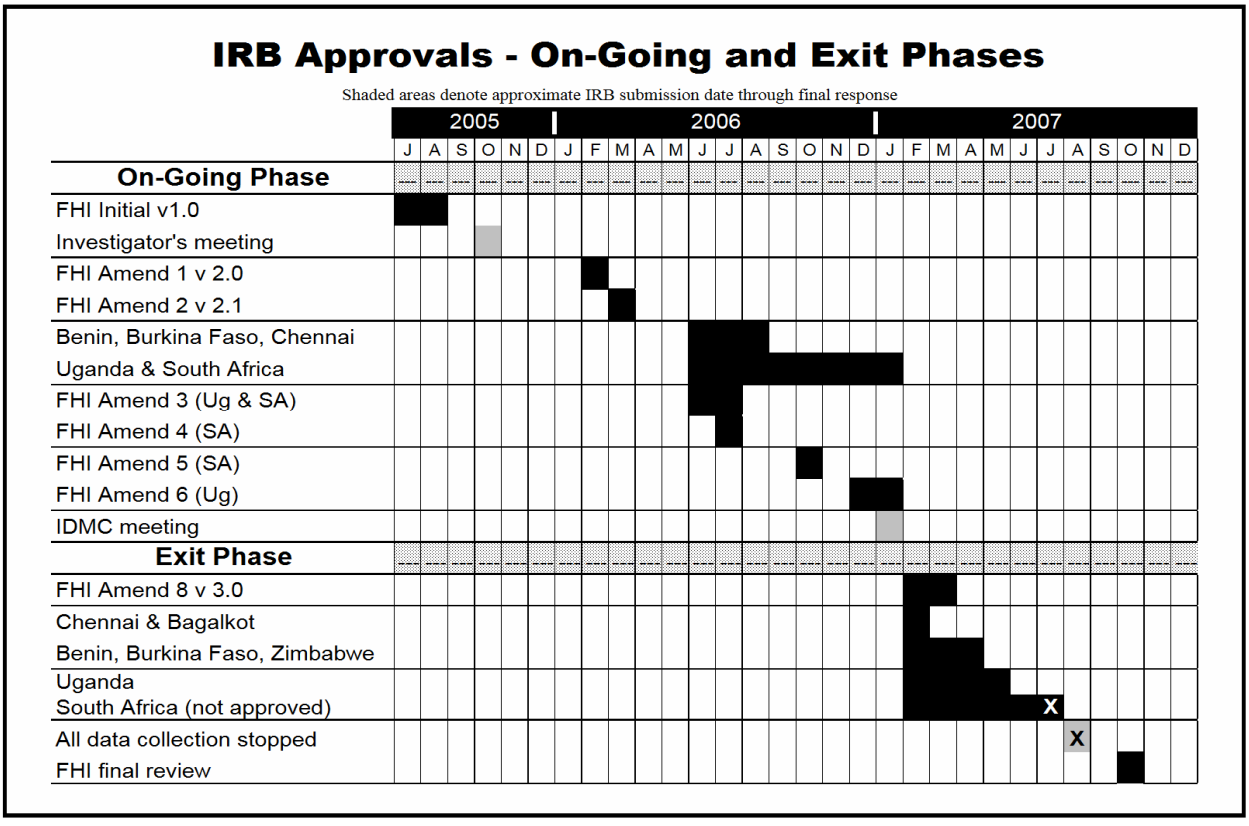
For the Preparedness Phase only, the PHSC reviewed and granted (Sept. 27, 2004) an exemption of the research from further review. The PHSC exemption was forwarded to all sites. The local IRBs for the sites in Uganda, South Africa, and Kenya received the protocol for review. In Uganda and South Africa, the preparedness protocol was submitted with the clinical trial submission. In Kenya, it was part of an addendum to the original clinical review. Other sites did not require a review.

The initial protocol for the On-Going Phase was submitted to the FHI PHSC and the IRB for CONRAD at Eastern Virginia Medical School (EVMS) and approved in August 2005. At the second Investigator's Meeting (October 2005), several recommendations were made. They included removing an earlier objective to assess the adherence patterns of trial participants and adding an objective to evaluate medical facilities to which participants or potential participants would be referred. Protocol version 2.0 was prepared for submission in February 2006. During this time, the EVMS IRB deferred to the FHI PHSC as the governing IRB for the study,

requiring all subsequent amendments and reviews to be through the PHSC only. The protocol was approved by PHSC on April 3, 2006, with the changes made based on recommendations received. In June 2006, it was submitted to five local IRBs. The IRBs in Benin, Burkina Faso, and Chennai, India, received local approvals between two weeks and three months after submission. Uganda and South Africa submitted site-specific protocols at the sites' request. Final approval from the South African IRB was received at the end of September 2006. Ugandan approval was not received until February 2007. In both cases, the sites had minimal to no time to participate in On-Going Phase activities because of the announcement of the clinical trial closure in January 2007. In November 2006, local IRB approval was received for the Zimbabwe site to begin BSS activities. However, no on-going activities took place as the site was still awaiting PHSC approval when the clinical trial was closed.

In February 2007, a final protocol amendment was submitted and approved by the PHSC, describing the addition of Zimbabwe and incorporation of detailed exit strategies regarding the closure of the trial. The sites in Benin, Burkina Faso, Zimbabwe, Chennai, Bagalkot, Uganda, and South Africa submitted amendments to their local IRBs. All but the South Africa site received approvals from the local IRBs. In June 2007, the South Africa site was notified that its IRB did not approve the amendment because of concerns that the study team would not be completely independent from the clinical trial and that the additional activities could contaminate the site. No appeal or modification was attempted. Data collection in all sites was completed by August 2007. Final documentation was submitted to the PHSC in October 2007 for closure of the study.

DIAGRAM 1: TIMELINE OF IRB APPROVALS



II. Study Design

A. Methods and Study Populations

BSS activities included formal and informal data gathering methods. During the Preparedness and Exit phases, formal, in-depth interviews and focus group discussions were conducted with potential and former participants and with community stakeholders in four of the five initial and two newer trial sites (Uganda, Benin, Burkina Faso, Chennai, Bagalkot, and Zimbabwe). These interviews and FGDs were conducted in the local language, tape-recorded, transcribed, and translated into English or French (in Benin and Burkina Faso) and then typed into word processing files for analysis. In Chennai, India, some formal data collection was also conducted during the On-Going Phase. In addition to these formal BSS activities, information collected during staff and community meetings was shared informally with the clinical trial team and, in some sites, recorded in field notes or weekly reports. The South Africa BSS team relied almost exclusively on informal activities; Benin also relied on a weekly reporting system during the On-Going Phase.

Three types of participants were involved in BSS activities: 1) potential participants or other community stakeholders; 2) clinical trial participants and former participants; and 3) clinical trial staff. Each local BSS team determined how to identify and interview individuals from the community. In several sites, staff developed a list of community groups who were either involved in or potentially affected by the clinical trial and began a regular dialogue with them. These included NGOs that represent the rights of HIV-positive persons or vulnerable women; healthcare providers who might provide contact points for recruitment or to whom participants might be referred; representatives of political, religious or educational institutions; and local employers or neighborhood groups through which trial participants may be recruited or followed up during the trial. Throughout the BSS phases, community groups were contacted formally and informally to assess their understanding of and concerns related to the clinical trial. Some sites also conducted formal interviews with potential participants to understand their motivations and disincentives for trial participation and identify factors likely to influence retention and gel adherence.

No formal in-depth interviews were conducted with clinical trial participants during the On-Going Phase. However, during this time, BSS staff accompanied outreach workers to locate participants who had missed a visit in order to find out the reasons for the missed visit and how the staff could assist the participants in continuing in the trial (for women who agreed to visits or contacts). During the Exit Phase, many sites conducted in-depth interviews with former trial participants to assess their experiences as clinical trial participants; their understanding or trial closure; and their likely adherence to gel and condoms during the trial.

Finally, BSS staff conducted informal meetings with CT staff during the On-Going Phase and more formal interviews with some staff members during the Exit Phase to understand their experiences and perspectives related to recruitment and retention.

B. Data Collection

Table 4 summarizes formal and informal data collection activities in the seven sites that participated in at least one phase of BSS activities. Figures in the table below reflect the number of data files (either transcripts of IDIs or FGDs, textual reports or field notes) that were received and analyzed. In all, they represent 369 sets of notes from seven countries over three time periods.

TABLE 3: NUMBER OF BSS DATA COLLECTION ACTIVITIES BY SITE

Categories	SA	Uganda	Benin	BF	Chennai	Bagal	Zim
Phase I: Preparedness							
Potential Participants		3	10	29	20		
Opinion Leaders		2	23	22	5		
Other activities			12				
Phase II: On-Going							
Staff	3				9		
Participants (Missed visits or HIV referral)	3				3		
Community	2				13		
Weekly Reports	(20*)		19				
Phase III: Exit							
Staff		6	16	12	0	10	n/a
Former Participants		20	10	n/a	16	10	n/a
Community		3	11	34	6	1	21
Peer Leaders		15					

* Weekly reports in South Africa were shared with the local team, but not typed or sent to FHI, and therefore not included in analysis.

C. Data Analysis

Based on the need to quickly use data collected on retention and recruitment issues, qualitative data collection and analysis was an iterative process throughout the study. Immediately after terminating each field interview, interviewers were encouraged to summarize for their team the field interaction to identify the key types of information that emerged during the interview, noting questions that required modification or further probing, and highlighting any potential insights regarding research questions. Interviewers were then responsible for expanding notes or transcribing their tape-recorded interviews within two days of conducting each interview, community meeting, or discussion with clinical trial staff. Electronic transcripts were scheduled to be e-mailed to the FHI BSS staff within a week after the interview. FHI BSS staff then worked directly with the local BSS staff to improve data collection and to translate findings from these interviews into strategies for the clinical trial.

FHI staff also followed an iterative, team-based process to finalize results presented in this report. The process was modified slightly based on the phase of the study,

type of report (i.e. interim results at an investigators' meeting versus end of study results), and quantity of data to be analyzed. Data analysis generally proceeded through a process of four inter-related steps: reading, coding, data display, and data reduction (Ulin et al. 2005[1]). An initial coding scheme, corresponding to study objectives, was developed before the study began and modified as necessary throughout the study. It included codes to capture information such as perceived risks and benefits of the microbicide trial, recruitment, retention and adherence issues, acceptability, and comprehension of informed consent. During the data display step, researchers read each coding report and identified the dimensions of each code (as expressed in local terms) and examined issues related to the credibility of the data collected. A second level of more emergent codes was developed. Depending on the report, this was done through a process that was formal (e.g. codebook modification and another round of coding) or informal (grouping themes within the coding report). The final data reduction included identifying differences between sub-groups, such as countries, within specific codes and synthesizing information into the reports. Unless otherwise specified, numbers presented in the findings section represent the minimum number of **BSS transcripts** within which a theme arose, rather than the number of people who endorsed a theme. **These numbers in no way correspond to the number of clinical trial participants** from a given site, since only small numbers of former trial participants were included in BSS exit activities.

III. Results

Results have been organized into sections corresponding to the objectives described in Table 1. In this section, we present findings related to A) Informed Consent and Supplementary Materials; B) Recruitment; C) Retention; D) Community Understanding of the Clinical Trial; E) HIV Referral Systems; F) Acceptability and Adherence; G) Early Closure; and an additional topic area H) Recommendations for Future Trials.

A. Informed Consent (IC) and Supplementary Materials

The FHI BSS team worked with local BSS teams during the Preparedness Phase to develop and pre-test a flip chart that presented information contained in the IC document, but in a simpler and more concise way. The flip chart relied primarily on pictures to portray important concepts; words were kept to a minimum and formatted in bullet form. An artist hired through FHI developed the pictures used in the African sites (South Africa, Uganda, Benin, and Burkina Faso); the Chennai site hired its own artist to develop pictures that were more culturally appropriate for the South Asian site. Counseling staff were trained during the site core and initiation training visit to

[1] Ulin, Priscilla; Robinson, Elizabeth; Tolley, Elizabeth. Qualitative Methods in Public Health: A Field Guide for Applied Research. (2005), Jossey-Bass: San Francisco.

use the flip chart in parallel with the official IC document in order to facilitate explanations and check on comprehension. However, some sites expressed concern about using the flip chart during the IC counseling session without exceeding the 45 minutes to one hour already needed. Some sites developed an IC checklist that included all information items to be covered in the written IC document and then used the flip chart to discuss each item. Other sites chose not to use the flip chart. In such cases, no written materials except a copy of the official IC document were distributed to individuals who presented themselves for trial participation. The flip charts were approved by the local IRBs before being used. There was no formal evaluation of the flip chart or its value in the consent process.

The study team also developed a set of questions to be administered after the IC process in order to check women's understanding of trial participation as explained in the IC document. The original set of IC questions was later revised to more comprehensively assess the required eight elements of informed consent. The intention had been for the local BSS team to periodically evaluate a sample of these IC questionnaires and assess how well participants were able to correctly answer the IC questions on the first attempt. However, some sites did not record failed first or second attempts on the questionnaire, but only final results. Because responses to the questionnaire were recorded differently in each site, this activity was never implemented.

The IC process emerged as a topic of discussion during BSS on-going and exit activities in a few sites. A former participant in Benin and one in Uganda, as well as a witness[2] in Bagalkot, reported favorably about the IC process, highlighting the efforts to ensure women understood the information and to ensure that *"nobody was forced in the study."* In Bagalkot, three witnesses reported that counselors made special efforts to ensure that women understood the information, despite their illiteracy. To this end, they would read the consent materials and ask the women to explain the same thing back to them. If women were unable to do this, counselors would repeat the explanations *"in their own language."* Witnesses suggested that women generally understood the information the first time, with the exception of some women from the rural areas.

Nevertheless, a few criticisms of the IC forms or process were reported. In Benin and Burkina Faso, staff felt that the consent form should have been better tailored to the different types of women recruited into the study. Their concerns related primarily to the sexual behavior criteria (on average three sex acts per week and three or more sexual partners in the past three months) described in the consent form. The language made it particularly difficult to recruit women involved in clandestine sex work, because they were reluctant to identify themselves.

Community members in Zimbabwe had more general comments about the process of informed consent, given their experiences with other microbicide clinical trials. For example, in one FGD participants discussed the fact that "microbicide" does not have

[2] In each site, witnesses were made available to non-literate women during the screening and enrollment processes, in case these women were not accompanied by a trusted friend or family member. These local, literate volunteers assisted potential participants during the IC process to provide independent verification that all information in the written IC document was verbally explained to the potential participant.

a local translation in Shona. In a different trial (HPTN035) they tried to resolve this by explaining that two microbicides – Buffergel and Pro2000 – are chemical components … but still they wonder: "*What is it called in Shona?"* and *"I think some of the medical terms make it difficult and they actually worsen some of the assumptions that people might have."*

In a separate discussion, one community member said:

> I don't know how many (medical terms) have been translated into vernacular. How many of those women who are participating are able to read and understand, not only just reading, but reading to understand what I am putting myself into? And how many are going to be able to push the fifty dollars – the fifty thousand dollars – aside and think of the implications of the exposure should they seroconvert?

B. Recruitment

Decisions about how to operationalize eligibility criteria may greatly affect a trial's ability to achieve its aims. Effectiveness trials of new HIV prevention products must identify and recruit participants who are HIV-negative, but also likely to be exposed to HIV during the trial. Unless enough new infections are detected (in this trial 66 infections were targeted) to determine whether any observed differences in HIV acquisition are significant between those assigned to the experimental and comparison study arms, the trial will not be able to conclude whether the new product is more protective than the placebo or comparator product. The CONRAD CS trial aimed to recruit women at high risk of HIV infection. Except in South Africa, where a generalized epidemic meant that women of all backgrounds were likely to face some risk, high-risk women were considered those with multiple sexual partners. Specifically, the study aimed to recruit women who had had three or more sexual partners in the three months before screening, and who had on average three or more sex acts per week. This section presents data on the types of women considered to have sexual and risk behaviors; potential participants' motivations and disincentives for enrolling in a microbicide effectiveness trial; and strategies used by the different sites to recruit high-risk women.

1. Sexual and Risk Behaviors

During the Preparedness Phase, several sites conducted research to help identify women at high risk of HIV and the locations from which to recruit them. Overall, community participants were most likely to identify brothel-based sex workers as those most likely to fit the sexual behavior criteria and most easy to recruit. In Benin, several community participants referred to Jonquet, a section of Cotonou where numerous brothels (*"maisons de passe"*) were located. In Chennai, sex workers appeared to be less associated with individual brothels as they were with sections of town. For example, participants listed numerous places where women "ply their services" including at bus stands, in front of theaters and wine shops, in lodges and houses or on the beach. One potential participant from India explained that women like her who work through brothels may have 10 different partners in a day. She worked through four different brothels in different parts of town, rather than take her clients to lodges because of police problems. In Benin and Burkina Faso, women who worked in hotels, bars, and nightclubs were often included in a similar category – as

"des travailleuses de sexe affichées" (commercial sex workers). Nevertheless, some BSS participants argued against a strategy of recruiting women who identified themselves as involved in sex work. For example, one community FGD participant from Benin argued that formal prostitutes protect themselves better than other women do. In addition, some self-identified sex workers in Benin argued that the number of sexual partners included in the study's eligibility criteria was far too low for them; this criterion would be applicable to other types of women. In Chennai, a community stakeholder suggested it was better not to go with commercial sex workers because they often migrate. She further stated:

> What you consider as high risk might not be considered as high risk by them. I can have four partners, but I might not consider it as high risk … you should have certain criteria so that it need not be just the commercial sex workers.

In all three sites, community participants identified other categories of women who might have high risk behaviors and therefore be included in recruitment efforts. Some focused on the need to recruit women involved in "clandestine" sexual behavior. In Benin, at least seven participants specifically listed students among those categories of women with high risk sexual behaviors. For example, one potential participant in a FGD in Benin stated:

> I especially think about students in private junior high schools, because they are now ready for anything, even (younger) students, waitresses and prostitutes – especially those who do it clandestinely.

Similarly, a Beninese community stakeholder felt that recruitment should be directed toward *"bar girls, streetwalkers, hairdressers and even students – in other words the girls who do informal prostitution*." Still, some participants wondered how easy it would be to identify and recruit women who did not see themselves as sex workers. In Burkina Faso, one community stakeholder pointed out the difficulty of identifying these multi-partnered women. She commented: *"I don't know, I would not be open to identifying myself as a woman with multiple partners."* Later in the discussion another FGD participant suggested that they should invite any woman who felt vulnerable.

Finally, while a few participants in Chennai mentioned that married women are also involved in sex work and could be included in recruitment strategies, participants in Benin and Burkina Faso were more likely to feel that the study was targeting "free women" – those who were not married, because they either were still in school or worked as sex workers. It would be difficult to join the study (given sexual criteria) and have a steady partner.

2. Motivations and Concerns Related to Trial Participation

Motivations and concerns related to clinical trial participation were assessed among potential participants and community members during the Preparedness Phase in several sites, and retrospectively among former trial participants during the Exit Phase. While many of the same themes arose among BSS participants at both times (preparedness and exit), the relative importance of themes changed – perhaps based on experience in the trial. Also, there were some interesting differences among sites.

***Trial's association with HIV prevention*:** Because the study is about HIV/AIDS, women were concerned that people would think they were HIV seropositive. Furthermore, participants were afraid of being associated with the trial out of fear that people would find out about the sexual behavior criteria, which included having three or more sexual partners in the three months before screening and having on average three or more sex acts per week. In Benin, about a third of the opinion leaders interviewed in the Preparedness Phase anticipated that women would deny having multiple sex partners because it was not well regarded socially: *"They are thought of as worthless women, without honor, carriers of the most serious illnesses."* In particular, this created some tensions for women to accept the presence of witnesses during the informed consent process, as they didn't want anyone to know they were participating. Three former participants in Chennai and two in Uganda were initially concerned that people would discover they worked as sex workers, but were reassured when this did not happen.

In contrast to these negative associations, a few potential participants in Benin and Burkina Faso indicated their desire to participate in a study that might stop the proliferation of HIV/AIDS. In the words of a Burkinabe potential participant, if a woman participates and the trial succeeds: *"It means that this woman has saved the honor of the whole world, isn't that right?"* Several Beninese participants and two Ugandan women further endorsed the idea of clinical trials during the exit phase, with one Beninese woman saying: "*If they test the products and they're good, if it works, that can help us tomorrow – in the future."*

***Clinical care associated with the trial*:** Before the trial, approximately one-quarter of potential participants in Burkina Faso and one in Benin suggested that gaining access to health care was one reason to join the trial. As one potential participant in Burkina Faso explained, joining the trial proved that *"You love life, because if you continue to go there, you won't get a lot of illnesses."* However, overall, women were more likely to express fear rather than appreciation of certain aspects of clinical care associated with trial participation. Of most concern were the trial's requirements for HIV testing and regular pelvic exams. For example, while a few women considered the HIV testing requirement a benefit of trial participation (and indeed, several participants from Chennai and Uganda appeared to have screened for the trial in order to get a second opinion about their HIV status), it was reported to be a recruitment barrier by half of the potential participants in Benin and a few in Burkina Faso. In particular, women worried about the stigma they would face if confidentiality of a positive test result were breached. In Benin, one woman suggested that it would be better not to know one's status, because:

> I am very afraid. If, for example, I learn that I have it, what would I do? Commit suicide or what? It's the beginning of worry. So, I think you should live without knowing that you have AIDS.

Similarly, during exit interviews, some staff members in Bagalkot and six peer leaders in Uganda described the difficulty that HIV testing created for trial recruitment. One Ugandan peer leader suggested that some women would only approach peer leaders about trial participation once they had been tested somewhere else and knew they were seronegative. In Bagalkot, former participants reported initial fear of learning their status because they had never been tested before and knew that their behavior was at high risk.

Fear of pelvic exams was also a disincentive to trial participation – particularly in Bagalkot. One staff member from this site estimated that 60% of women worried about both HIV testing and pelvic exams, and about half of the staff cited difficulties convincing participants to undergo tests. An outreach worker attributed this reluctance to the fact that women felt generally healthy:

> If at all they observe some symptoms and if they face some problems they come on their own to get all these tests done. But it was not like that here. Bringing normal women here and making them ready to undergo all these tests was a big challenge to all of us.

This fear was at least partially caused by misunderstanding and lack of prior experience. Some women, for instance, thought that the doctor's hands would go inside their uterus. In Bagalkot, only three of 15 outreach workers and one peer leader were women, and it is not clear if any of them had ever had a pelvic exam, which limited the possibility of sharing experiences with participants.

Despite concerns expressed during the Preparedness Phase, appreciation of access to free, high quality, and readily available health care became particularly obvious in the exit interviews. About one-fifth of participants in Benin, but two-thirds or more of participants in Bagalkot, Chennai, and Uganda, stated their appreciation of the care they received. In Bagalkot, one former participant explained:

> Initially we felt afraid about the project as they told we have to undergo urine test, blood test and vaginal examination. If at all it comes as positive, we were afraid of it. If it comes as negative then nothing will happen. … If at all I had that disease and if I did not have that test done, it would have remained inside me. So, it is good that I underwent that test. … It was good for us to undergo all the check ups.

Another explained that if a woman goes to a private hospital with burning urination or a rash, they will not do tests. The study clinic, however, was developed exclusively for women who do sex work, and the clinic would treat them. She also suggested that private hospitals saved money by giving injections that were *"half water"* – here women were cured the first time without need for a follow-up visit. Similarly, one Ugandan participant indicated: *"They have helped us and saved us from a lot of sickness; women have a lot of diseases but they removed them."*

Gel use: During the Preparedness Phase, women who worried about potential side effects saw gel use as a disincentive to trial participation, while those who focused on the potential for HIV protection considered gel use a reason to join the trial. Although lubricants were available and used in the West African sites, some potential participants in those two sites worried that the use of the study gel might negatively affect their fertility – or perhaps even cause them to get HIV. Potential participants who were interviewed as part of the Preparedness Phase in Chennai also worried about gel use, in part because they had never used a vaginal product. At exit, several participants in Bagalkot, Benin, Chennai, and Uganda admitted to having been afraid initially but stated that they were reassured by the staff. One Ugandan woman explained:

> I feared and said something like that how can they research on us human beings? Why don't they first test it before they are sure it is safe? ... By good luck, when I

> continued listening to the doctors, and so on, I grew strong and I participated in the study.

A community stakeholder in Zimbabwe had heard rumors that ‘‘*This study closes the womb and that they brought medicines that were not good for people.”* On the other hand, about half of potential participants in Benin and one in Burkina Faso appeared to be driven by false expectations about the gel’s effectiveness to prevent HIV. Three Beninese participants were under the impression that the gel was being tested because researchers were certain that it would be effective. Exit interviews indicate that at least a third of the women in Bagalkot got involved in the trial for similar reasons. One participant clearly explained: *“We have not come here thinking that we get the salary from here. We have come here just to protect our lives and body.*”

Monetary and other incentives: Community stakeholders were more likely to discuss money during the Preparedness Phase than were the potential participants. In general, they were concerned that money might motivate women to join the trial when trial participation was not in their interest. Interestingly, while the theme emerged strongly in the Benin, Uganda, and Zimbabwe BSS work, only two Indian participants mentioned financial compensation, both in Chennai. During exit interviews, almost half of Ugandan participants and staff, as well as one former participant in Benin, reported how important the money was to women. A Beninese staff member explained that women *“base a whole set of activities on this money. There are women who survive, thanks to this small change.”* One Ugandan participant reported using the money to put her child through school: *“I would help my child at school, I knew that if I attended in a month, I would be able to pay for some school requirements … although it was little.”* The relative lack of discussion about money among potential and former participants in most sites is likely due to self-presentation bias – the fact that people do not want to portray themselves as being driven by less than altruistic reasons. In Benin, the boyfriend of a trial participant reported that his girlfriend went to the clinic every Tuesday to bring back condoms and 2000 francs (about $4.00).

3. Recruiting Process

Local sites used a combination of strategies to identify and recruit high-risk women into the trial. In addition, some approaches developed more spontaneously. Both planned and spontaneous approaches had advantages, as well as difficulties.

Multiple approaches**:** In general, multiple approaches toward recruiting potential participants were found to be successful. In Bagalkot, the recruitment process started with community meetings. During these meetings, a presentation giving an overview of the trial was provided, followed by discussions. The audience was then invited to visit the clinic before making a decision about participation in the trial. This strategy was implemented because staff felt that potential participants’ lack of familiarity with healthcare facilities made them feel intimidated – creating an additional barrier to enrollment. Once a woman decided to participate in the study, she was very likely to recruit others in her community. In addition to community meetings, peer educators and outreach workers were used in Bagalkot. Although the outreach workers were better educated about HIV/AIDS and explained the trial better, the peer educators were better at developing trust, as they were usually from the same community as the potential participants.

Several approaches were also used in Benin. Field workers recruited high-risk women to come to the clinic and provided details about the trial. They also recruited potential participants at brothels and outside nightclubs and "hotspots" next to the clubs. Assistance with recruitment was also sought from peer leaders – two brothel-based sex workers from Nigeria and one clandestine sex worker. The Nigerian sex workers were very good and helped reach the English speaking population. Their compensation was based on both the number of women they sent to the clinic and how long these women stayed in the study.

***Peer leader/recruiter model*:** As in Bagalkot and Benin, peer leaders were also used in Uganda. Peer leaders believed that this model was essential for gaining access to the sex worker communities. One Ugandan peer leader stated:

> I don't know how you would have got these women if you had not used us. Because us, we are close to these women and we talk to them. You know what they are doing is illegal, so they do it in hiding. It is good you used us.

Another peer leader mentioned that holding community sensitization meetings – an approach suggested initially – would have caused a lot of stigma. Instead, she emphasized the benefit of the peer leader model, as peer leaders were also commercial sex workers and knew where other high risk women lived and worked.

Although this approach appeared successful in recruiting potential participants, there were also problems. In Uganda, some peer leaders reported that they were scorned and treated badly by potential participants. One peer leader said she had a bucket of water poured over her head while trying to reach a potential participant (who later apologized). Two peer leaders also reported being arrested by the police while trying to recruit participants. The provision of formal identification cards showing a peer leader's affiliation with the clinic assisted greatly in eliminating the earlier problems. Also, some participants in Uganda were jealous of peer leaders, thinking mistakenly that they were being compensated very well for their work. In fact, the peer leaders were only compensated with transport and cell phone airtime reimbursements. As one of the trial participants illustrated:

> The grievance I had is the little money they gave to us compared to the peer leaders and yet, the participants in my view were at the center of the study and they would determine the outcome.

Participants refer others to the trial: In all sites, trial participants played an important role in addressing their friends' and acquaintances' fears about the trial and in referring them to the study. A peer leader in Uganda mentioned that some women were worried that the intention of the trial was to kill them off *"but eventually they realized that their friends go and it works out well; then they would come and tell us that they want to go to the clinic."* In Benin, the staff thought that clandestine sex workers were recruited through their friends who were trial participants. And in Bagalkot, a clinic staff member said she hoped that potential participants' HIV results would be negative so that trial participants would then refer their friends to the trial:

> I prayed to God after all those HIV tests that the result should come as negative so that we will get many women to be enrolled for our study and they in turn will develop faith in the study and will bring many more women for the clinic.

***Collaboration with providers of contraceptive services*:** In Benin, steps were taken to collaborate with two providers of contraceptive services so that they could not only refer clients to the trial but also provide contraceptive services to trial participants.

Overcoming barriers to recruitment: Trial staff used different approaches to overcoming women's concerns about HIV testing and other trial requirements. In Bagalkot, staff invited potential participants to visit the clinic before enrollment. During these visits, women could meet clinical trial staff and learn more about the trial procedures, before making a decision about participation.

C. Retention

Participant retention is essential to the success of longitudinal clinical trials because high loss-to-follow-up rates can bias results. Understanding the factors that cause participants to miss visits or drop out of the study is thus critical. In this section, we discuss the factors that affected participant retention in the trial. Some issues are known from participants' experiences and relate to various aspects of the trial. Other issues describe challenges staff had to contend with in their continuing attempts to keep participants coming to their visits. These include a list of circumstantial factors preventing visits, and the need to maintain the confidentiality of participants.

1. Aspects of the Trial

Although, overall, trial participants were satisfied with the benefits they received and the way they were treated by the staff, some women reported issues and concerns with some aspects of the trial. In particular, such concerns were raised in Uganda, where three-fourths of participants and 13 peer leaders included some discussion on this topic. Some of the issues built on concerns identified at the recruitment stage (e.g., fear of HIV testing or pelvic exams), but others arose during the trial.

Long wait times and slow pace of visits: Several participants in Benin and Uganda said they spent too much time at the clinic, and staff and peer leaders at these sites confirmed receiving complaints about the slow pace and long waiting hours of the visits. Similarly, one outreach worker in Bagalkot suggested that the wait time was long. According to women and staff, a single visit could take 2 to 3 hours, and up to 5 hours in some extreme cases. Two participants and two peer leaders in Uganda indicated that women sometimes had to miss work because they had to be at the clinic for too long. In Bagalkot, an outreach worker reported problems with *"women's organizations, lovers, or gharwalis* [madams]," who asked many questions and complained that the "work" was not getting done. In some cases, the long duration of clinic visits led women to terminate their clinic visits early – without completing all study procedures – or to miss clinic visits entirely. For example, two Beninese participants, who were interviewed after missing clinic visits, reported not completing their visits because of the waiting time. The first explained that she had refused to complete all her gynecological exams during a visit because she had already wasted too much time but, as an excuse, told the doctor she was menstruating. The second

was told to come back on a different day because the doctor was too tired, but she did not return until her following visit. The clinics in Bagalkot, Benin, Chennai, and Uganda began to provide food or drinks and visual entertainment to make the wait time more pleasant, and several Beninese staff members reported that complaints subsequently lessened. Furthermore, several participants and staff in Benin and Uganda suggested that delays were reduced after the first few visits.

Insufficient compensation: According to nine women and five peer leaders in Uganda, the compensation for their participation was insufficient. Participants specifically complained that they were not receiving enough money in relation to the time spent away from work, the tests they had to undergo, and transportation costs. One participant explained her frustration:

> They invite you to be a specimen! ... That examination; they gave us little money, because you abandoned your work; sometimes you stay there the whole day from 8 a.m. to 6 p.m. for example … it wasn't enough so it made us impatient.

The money was later increased from 10,000 to 20,000 shillings (about $5.60 to $11.20) to assuage women's complaints, but three participants and one peer leader indicated that the raise in fact created bitterness because the earlier-recruited participants were paid less than those recruited later in the trial. One peer leader further reported that some of the participants who had already completed the study before the raise thought that the clinic staff had taken some of their money. In Benin, two staff members suggested that some participants complained about not receiving enough money when they first started the study. According to one staff member, for instance, some new participants received 500 CFA (about $1.00) but claimed that they were paid 2,000 CFA at screening and 2,500 or 3,000 CFA for enrollment, and thus expected to receive 3,500 CFA for their second follow-up visit. In contrast, there were no complaints in Bagalkot and Chennai. One participant in Chennai explained that she was in fact pleased with the benefits participants received:

> Monthly once if we access your organization and if we don't go to work we would have a compensation for that particular day of an amount of 100 rupees (about $2.50) one time meals so we would access by consoling this type of compensation. We would access here happily without any hesitation by providing good and appropriate medical treatment and by providing good meals and that day's wages…

Complaints related to free condoms and drugs: Participants liked receiving free condoms in Bagalkot (1), Benin (2), Chennai (2), and Uganda (5). In Benin, however, one participant complained that condom distributions went down from six per visit to three and that no additional condoms would be provided if she had already visited that month. In Uganda, one participant and two peer leaders similarly indicated that participants were not given enough condoms to tide them over between visits. Although participants could go back to the clinic to get more, one participant explained that the clinic was too far and that it was in fact less expensive for her to buy additional condoms. In Uganda, one participant and three peer leaders also reported that medicines were sometimes out of stock and participants had to buy them from pharmacies. One peer leader suggested that women *"thought that they just didn't want to give them the drugs but it was there."*

The importance of being treated well by staff: In the Preparedness Phase, several women and opinion leaders in Benin and Burkina Faso emphasized the need to treat participants with respect and to make them feel welcome to encourage them to stay in the trial. At times, their own words emphasized the lack of respect that women from the trial population faced in their daily lives. For example, One Beninese opinion leader explained the need to be patient and nice:

> because these girls…they are undisciplined, capricious, prepared to do anything, and they are of all kinds: some are thieves, some are rude, some are witches, some are overworked, some are underprivileged…

Exit interviews confirmed that the degree of respect women received from the staff was important in keeping them in the study. In Bagalkot and Chennai, several staff members and a few participants reported that women felt they were treated better and with more respect at the clinic than at government or private hospitals. During the On-Going Phase of the trial, one clinical staff member in Chennai explained that women liked that their questions were answered and that they were asked for their consent to participate and that because of this, they showed an interest in the study. Two staff members and one participant in Bagalkot indicated that women were generally looked down upon in other hospitals because *"All the big doctors think that sex workers means very bad and dirty"* but that they were cared for in the study clinics. According to one outreach worker, the women:

> tell even if they go to private clinics they don't get this much respect. They tell me this much facility is not there. In our hospital it was like a family relationship. There was no differentiation.

Seven participants and 10 peer leaders in Uganda similarly reported that the doctors treated the women well and made them feel welcome: *"We would come to the clinic and the reception was always warm. … The way they cared for us: we were like their children at home."*

Conversely, mistreatment – or fear of mistreatment by staff jeopardized continuation of visits in a few cases. One Ugandan peer leader stated that some women would stay away if they missed an appointment because they were afraid of *"retribution from the health workers."* In South Africa, a participant progressively lost interest in coming to the clinic because the staff mocked her for being illiterate and struggling to be consistent when signing forms. Moreover, she recounted that whenever she missed a visit and came on an unscheduled date, the staff would laugh at her and say that she always had excuses.

Gender of doctors: Two participants in Chennai indicated their preference for female doctors because they felt more comfortable discussing their health status with a woman. According to two staff members in Benin and participants (4) and peer leaders (2) in Uganda, standing naked in front of a doctor was a problem, and women were particularly uncomfortable with male doctors. A Beninese staff member recounted that when the clinic's female doctor left on vacation, women were reluctant to be examined by her male substitute, and some of them missed their scheduled visits. The issue, however, was one not only of gender, but also confidentiality. Clandestine sex workers generally preferred to see the same doctor at each of their visits because of their need for secrecy. In Uganda, women felt shy exposing

themselves in front of the doctors, especially men, and one peer leader described some participants' concerns that staff were discussing the women among themselves. One woman in particular complained to her that *"some of the men would chat with each other and share their experiences and some of them were saying that maybe during the process of examining, men look at them critically."* Two participants, however, explained that they got over their discomfort once they realized that *"the doctors keep it a secret and even if you are created differently, they keep it to themselves."* Furthermore, participants were able to choose which doctor examined them, and one woman reported switching from a male to a female doctor. However, although most women were thus satisfied, a peer leader indicated that *"some complain that their requests to see some particular doctors who they prefer are denied."*

Fear of pelvic exams: Fear of pelvic exams was identified as an issue for recruitment in Uganda and Bagalkot, and continued to be an obstacle in the On-Going Phase of the trial. Complaints about pelvic exams were particularly frequent in Uganda, where almost three-fourths of the participants reported pain, at least initially, and three peer leaders were suspicious that some participants missed visits because they were afraid of the "*machine*" (speculum). Exit interviews furthermore highlighted a few misunderstandings. For instance, one participant thought that the purpose of the exam was to remove dirt from her stomach. Another believed that the speculum triggered monthly periods, because it made her bleed. A peer leader also reported that women were afraid that the speculum could transmit infections from one person to another. Not all women, however, had problems with the pelvic exams. One peer leader suggested that only one out of ten women persistently complained, and half of the participants who initially experienced pain stated that they got used to the exams. One participant explained that she found the speculum painful the first time and refused to submit to the exam again, but a different doctor examined her and used a technique that made it painless:

> He told me that what caused pain for me the other time, he told me that I had not coughed…the vagina opens well when you cough, he inserted it so well, I did not get any problems. Since that time I love the machine.

Two other women indicated that while the exam was painful, it was very helpful because it detected diseases. A few participants, however, remained uncomfortable with the speculum, claiming that it was too big or made them bleed. In Bagalkot, a participant had to undergo surgery during the trial and blamed her problems on pelvic examinations, although the doctors told her that it was not related:

> These people put the pipe no? It might have injured my organ. … The doctor here told me it is not because, I have come here. … That doctor told it had happened because of some rough handling.

The participant, however, essentially seemed to be frustrated at the cost of the operation and did not bear a grudge against the trial or staff. In spite of the initial fears of pelvic exams encountered at the recruitment stage in Bagalkot, there were no other complaints.

Blood draws: Several staff members in Benin and three peer leaders in Uganda indicated that participants complained about blood draws. One Ugandan peer leader

explained: *"The main challenge was getting blood from participants; they used to say that they get too much blood from them."* In Benin, a few staff members also reported that participants complained about the amount of blood being taken, particularly for screening and enrollment, with some participants requesting food at the time of blood draw to replace the blood that was taken. In one instance, a participant refused to get blood drawn during a visit because she was on the last day of her period and thought she had already lost enough blood through menstruating. According to one staff member, complaints about blood draws were a recurring issue, but one that was cultural and not specific to the CS study. Comments by an opinion leader and a potential participant during the Preparedness Phase in fact revealed that women worry about the effect that taking blood will have on their health: *"Some say that they have no blood in their body to give."*

In response to these fears, Beninese counselors started using empty tubes to show participants how much blood was drawn. Several staff members indicated that complaints lessened after the screening stage and once food started to be provided, and most women accepted blood draws during specified follow-up visits. One staff member, however, suggested that some participants continued to miss visits because of their fears of getting their blood drawn, and one participant reported feeling nervous after each visit in which blood was taken, which she attributed to the blood draw.

Study procedures: One participant in Benin and three peer leaders in Uganda indicated that women did not like the many questions they were asked, or that the questions were always the same. Staff in Benin further indicated that some participants thought that being reminded of study procedures at each visit suggested they were "*morons*."

Seroconversion: One South African participant who seroconverted refused to come back. In Benin, a seroconverter who had been lost to follow-up was relocated and came in for some tests but declined to participate in the care for those who seroconvert, especially the CD4 test. During the Preparedness Phase, one participant in Benin and one in Burkina Faso further suggested that the seroconversion (or absence thereof) in some participants may influence the retention of other women.

2. Context of Participants' Daily Lives

Participants faced several challenges to continuing follow-up visits. These factors do not directly relate to aspects of the trial, but rather to the context of participants' daily lives, such as their social circle, work, or family.

Negative influence from social circle: Staff and participants in Benin recognized that some women faced pressure from their families, partners, or employers to withdraw from the trial. For instance, a participant – described as having been suspended from the study for not using the gel regularly, explained that her boyfriend and a regular customer complained about the gel causing too much vaginal discharge and the *"enlargement"* of her vagina. Some Beninese participants also faced pressure from their employers. A participant missed three straight visits and expressed concerns about returning to the clinic because her employer threatened

her once she discovered she was part of the trial. Another participant missed a visit because her employer was prejudiced against the trial and started rumors that the gel caused infertility. Finally, a Beninese staff member reported a series of incidents with the inhabitants of a house near the clinic who stigmatized the clinic as a meeting point for prostitutes and stared at participants to the point of making them feel uncomfortable. In South Africa, a participant reported that her parents did not approve of her participation in the trial and that her mother assured her that it would bring her bad luck. In Uganda, a peer leader similarly indicated that some participants' parents told them that *"the studies are bad and that you might end up dying"* and mentioned that one of her colleagues was prevented from visiting a participant by the woman's parents.

Frequent changes in women's employment or social life: Women's temporary or long-term changes in employment also contributed to missing visits. Some staff and peer leaders in Uganda and Benin reported that sex workers had difficulties keeping their appointments because they had relocated to places with better work that were sometimes far from the clinic. In Benin, 15 participants of Togolese, Nigerian, or Ghanaian origin missed visits because they returned to their countries for various reasons (e.g., pregnancy, marriage, sickness, or family problems). Similarly, a South African participant missed visits because she had found a temporary job. When the job was over, she did not know that she could come back to the clinic after missing many visits. Two participants and three peer leaders in Uganda and one staff member in Benin further stated that it was difficult for some women who were up working all night to come in early for their visit. In Benin, two participants justified missing their visit because of professional obligations or lack of time.

Informing women about their visit times: According to some Beninese staff members and two peer leaders in Uganda, women would sometimes miss visits because they would forget their appointment dates. One Ugandan peer leader explained that women would misplace or hide their appointment cards and not check the dates again. Staff in Benin emphasized the particular challenge faced by illiterate women and the need to remind them of their appointment times, as they could not use the card as a reminder.

Seasonal changes: In Benin, the end-of-the-year holidays are a period of rest and travel for sex workers, and there were concerns about participants not coming to their visits. Staff reported making efforts to plan follow-up visits around these holidays, in order to lessen their impact. On the other hand, Beninese staff reported that the rainy season kept women from coming to the clinic.

Transportation: One staff member in Benin and several peer leaders in Uganda cited lack of transportation as an obstacle to visits. During the Preparedness Phase, one Beninese opinion leader stressed the importance of giving participants taxi money and a focus group of male bar managers suggested hiring a vehicle to collect participants. In Uganda, four peer leaders and one participant identified paying for transport as an obstacle. One peer leader reported that health workers started to provide transportation after some women threatened not to come. According to two peer leaders, it also seems that women stopped complaining about transport after their allowance increased.

Physical symptoms: One peer leader in Uganda explained that when participants were sick, they would be picked up and treated so that there would be no loss-to-follow-up. Another peer leader, however, reported that women missed visits when they had a sick child or parent, or lost someone. Menstruation was also sometimes a problem. Two peer leaders in Uganda reported that some participants did not go to the clinic during their menses. In Benin, one participant came to her visit six days late because she had been menstruating. A staff member reported that one participant refused to have blood drawn at a visit because she was menstruating. However, it appears that menstruation may sometimes be used as an excuse to avoid unpleasant aspects of the study visit. For example, a second Beninese participant did not complete all her gynecological exams during a visit because she was supposedly menstruating. In fact, she told a friend that she had refused to complete her exams because she had already wasted too much time.

3. Confidentiality

Because ensuring participants' confidentiality in the community was important to women in Benin and Uganda, interacting with participants outside the clinic posed challenges.

Follow-up contacts: How to make follow-up contacts was sometimes an issue. Although women in Benin and Burkina Faso generally indicated a preference for home visits in the Preparedness Phase, a few preferred to be reached at work or on their cell phone. A Beninese woman explained that being contacted at home could bother some women because of stigmatization and suggested making visits at night. At exit, five Ugandan peer leaders reported that some women, particularly the ones who were married or lived with their parents, did not like peer leaders coming to their homes. In addition to not wanting people in their communities to find out that they were sex workers, one peer leader explained that health visitors made home visits to seropositive people and that women were thus worried that their neighbors would think they were infected.

Home deliveries: In Benin, several staff members and a participant indicated that women were unsatisfied with doctors for arranging for delivery of drugs to their home. Because of a lack of communication, they did not understand that the results of some tests were not immediate, which is why drugs could not be prescribed at the time of the visit.

Transportation: In Uganda, confidentiality was also an issue in relation to transportation. Three peer leaders reported concerns that women could be associated with the trial through the vehicles taking them to the clinic. As an example, a peer leader explained that participants:

> used not to go with the vehicle. They would park it at the office and then walk to their homes … because whenever people see vehicles they think that maybe a person has HIV. That is what the community people associate those organization vehicles with.

Other women would refuse to be picked up.

D. Understanding of the Clinical Trial

Community understanding of and attitudes towards the CONRAD Phase III trial of Cellulose Sulfate varied widely across the sites. This variation was likely caused by several factors, including the degree to which BSS activities were conducted in a particular site, pre-existing attitudes toward the local implementing agency, and the political climate within a country.

1. Understanding the Trial's Purpose

BSS activities with community stakeholders, peer leaders, potential participants, and trial participants identified a range in understanding of the overall purpose of the Cellulose Sulfate clinical trial, as well as the benefits and risks associated with the trial.

Adequate understanding of the trial's purpose: A sound understanding of the trial's purpose requires some comprehension of the meaning of and relationships among several trial-related concepts. Local BSS data collectors struggled to clearly explain concepts such as randomization, placebo, equipoise,[3] and the rationale for continued condom use during trial participation. Occasionally, they appeared to have succeeded. For example, a potential participant from Chennai was able to "replay" the researcher's earlier descriptions of the trial, explaining:

> "In this research you will give us a product but you have told us that you do not know whether that this would prevent the HIV infection. You will divide the group into two and you will give two different products that will look very similar but one has the medicine and the other does not have. You say that you do not know who would get which product. You said that we use the tube only once… You have told me every thing very clearly. You are not saying that this medicine is going to protect us from HIV and we are also not going to say this. This is just research."

Similarly, after animated discussion during a Preparedness Phase FGD in Benin, one FGD participant demonstrated her understanding that the effectiveness of the product being tested is unknown by stating:

> What they said was that they were looking for 300 women. They will divide them into two. Some will receive the real and others will receive the false (gel). And, if those who received the one that isn't good get infected? ... There's the HIV sickness – no one's yet found a cure for it that's sure.

A few community members, especially those who helped conduct or had previously participated in clinical research, appeared familiar with trial-related concepts. For example, several opinion leaders in Burkina Faso equated the CS versus placebo comparison to the herpes trial that was currently underway, in which some women were given medicine and others were given vitamins before changing to the other treatment. In Zimbabwe, one community member explained, "*Since it's a research, it's a hypothesis, it can be approved or disapproved*."

Difficult terminology: Certain terminology proved difficult for both community members and BSS data collectors to fully grasp. One of the most difficult terms was

[3] The concept that clinical trial research is only justified when the efficacy of a product relative to the comparator is unknown.

"**trial**" – often translated as "test" in French. Few community opinion leaders associated the word "trial" or "test" with the word "experiment." Most suggested that the trial's purpose was to "test" a product that was already known to work. For example, when one Beninese FGD participant during the preparedness phase suggested she would use both gel and condoms because she wouldn't yet know whether the gel was effective, a second corrected her, insisting that:

> You test it because you are sure that the product will be effective. That's why I say that I can use the gel alone. If you get AIDS, you are going to get it. Also, it's in order NOT to get (AIDS) that you are being asked to use it.

Another in the same group felt certain that the gel was already known to be effective, because *"before testing any product on humans, it must be tested on animals."* The French translation of "trial" was also confusing because "test" was used both for clinical "trial" and for HIV "tests," and the two usages of the same term were interrelated, because HIV testing was necessary to determine whether the trial/test itself succeeded or failed. It was not clear whether similar linguistic difficulties existed in other languages, because data from India, Uganda, and Zimbabwe were analyzed in their English translations for this report.

An essential component of a Phase III clinical trial is the comparison of an experimental to a control product or procedure based on the random assignment of participants to different study arms. However, the terms "**randomization**" and "**chance"** were problematic. "Chance" was commonly conflated with the idea of "fate" or "luck". For example, in Burkina Faso, a potential participant explained, *"It's a question of chance. You are going to join. If you are lucky, you are going to have the real (gel) and if you aren't lucky, you'll get the false…"* Similarly, a Beninese FGD participant in the preparatory phase stated, *"I see it as a question of risk. Either you die or you remain living."*

The concept of **"blinding"** was also difficult for some participants to grasp. A Burkinabe potential participant in the Preparedness Phase thought it was good that they would be divided into two groups, *"because there are two doctors. If they divide them into two groups; one will take one group and the other, the other group."*

Finally, the word "**placebo**" was also conceptualized in different ways. Some data collectors and participants described the CS gel as the *"true," "real"* (vrai), or *"good"* gel, while the placebo was the *"false," "unreal"* (faux), or *"bad"* one. In Burkina Faso, the researchers began to describe the two products as "twins" (des jumeaux) in order to avoid suggesting that assignment to one kind of gel was inherently better than the other. Some described the CS gel as the one with "medicine" and the placebo as without medicine. In Chennai, a woman said the following when asked about receiving either a product with the microbicide or one without the microbicide*:*

> About whether you have given us the right medicine? We would be waiting for the tenth month to know whether you have given us the gel which contains microbicide, or the other gel. We would have a chance to tell others about the medicine if we were using it. … women need this medicine.

Difficulty with fundamental concepts: Many community members had difficulty grasping even more fundamental concepts than trial-related terminology. These

included whether the trial was intended to prevent, treat or cure HIV/AIDS and why participants were counseled to use condoms during the trial.

***Trial recruitment*:** Across the different trial sites, community members wondered why the trial recruited HIV-negative instead of HIV-positive women or sex workers instead of discordant couples; why the trial recruited women, but did not include men; or why *"the lowly women"* were targeted instead of *"the middle class, grassroots women, professors, doctors, and their partners"* – that is, those *"who can actually ask questions, who would want certain things to be clear."* The numerous questions about who should be recruited into the CS study revealed a misconception about whether the product being tested was supposed to prevent or treat HIV. For example, a potential participant in Benin suggested that:

> It's those women who are seronegative who can do the study, but for me – if you really want to test the effectiveness of the gel, you must test it on those who are seropositive. That's what I believe.

Focusing on HIV prevention for men, a Burkinabe potential participant believed that an HIV prevention study should provide gel to seropositive women so that seronegative men would not get infected. A community opinion leader in Chennai expressed confusion about the purpose of the trial. She asked:

> I am not clear … whether this prevents HIV or AIDS? What is your objective? Is it to reduce the HIV infection or to bring any changes in the last stage? Now you are going to give this to the sex worker. You can prevent HIV infection, but how will this medicine prevent AIDS?

Similarly, a peer leader in Uganda said that women who were screened out because of HIV asked why – if the gel was to kill the virus – they were only testing in HIV-negative women.

In the African sites, community members asked why men were not included in the study. Community members in Zimbabwe and several peer leaders in Uganda reported being approached by men who wanted to join the study. One Ugandan peer leader said she handled questions about male participation by saying that they would eventually come for them. A staff member from Burkina Faso felt that the study should be conducted with serodiscordant couples, so that NGOs would be more involved. Also in Burkina Faso, some association members felt that microbicides might prevent women from being "reinfected" and could reduce problems within couples.

Gel prevents HIV: Others clearly understood that the study was about prevention rather than treatment. But, as suggested in several community FGDs and interviews in Zimbabwe, Benin, and Burkina Faso, most people were "desperate" for solutions, did not really understand the meaning of research, and would assume instead that the microbicide definitely worked. This kind of thinking made it difficult to accept the possibility of being given a placebo gel.

Why condom use? On the other hand, some community members who understood that the study was to evaluate the effectiveness of the CS gel in preventing HIV had difficulty understanding the condom use message. They wondered how the trial could

determine gel effectiveness if people were using condoms. One community member in Chennai asked:

> You said that you would collect their feedback after using the gel. You suggest to them to use condoms and gel. If they use the condom, it will become safe sex. How will we come to a conclusion? Suppose you tell them to use the gel alone you will also have a problem. If they get the infection after using the gel, they will blame you.

One community member in Burkina Faso asked whether the condom itself is infected, because *"If you are not infected and the person used a condom and the condom is not infected, you cannot be infected."* Another thought it was a waste of resources to use gel and condoms together (she was already HIV-positive and not happy that only negative women could participate). In some cases, it appeared that community members' lack of understanding led them to deduce that women were not supposed to use condoms during the trial. For example, two community members in Bagalkot said women were not ready to join the trial because they did not want to rely on gel for protection. *"If we women only use gel and have sex, our skin will come into contact with men's and we will get that disease."*

2. Community Perceptions of Trial Risks and Benefits

In general, community members identified the same benefits from trial participation that were discussed in the recruitment section (page 10). Community stakeholders in Burkina Faso and Chennai appreciated the medical care provided by the study, as there were "no health facilities available to women in this profession." Perhaps more than potential participants themselves, community stakeholders recognized the value of collecting information to inform HIV/AIDS health policies and strategies. In five of the Zimbabwe discussions, stakeholders reflected on the importance of continuing research to improve people's lives, particularly to protect women who might not be able to protect themselves. Nevertheless, community members raised a number of concerns about the trial.

***HIV testing and treatment**:* Community stakeholders, potential participants, and clinical trial staff members raised several concerns related to the referral and treatment of women who screened out of the trial because of a positive HIV test, or seroconverted during the trial. First, having a good referral system in place was critical not only for the well-being of participants but also for clinical trial staff members. An outreach worker in Bagalkot described her sense of guilt whenever someone she had recruited was found to be HIV-positive. She reported:

> Once I had taken a woman here. She was positive. After getting her result I felt very bad, I could not make out when it was day and when it was night. Since I had taken her to the clinic, I felt like it was my fault. What to do if she commits suicide?

She added that the local trial administrators helped "convince" her of the importance of knowing one's HIV status and obtaining appropriate care. She explained:

> Then I recognized the importance of the test, what would have happened if she had not undergone the test. I showed her many people going to Jeevan Jyoti *[an NGO for*

> *HIV-positive people]*. She also recognized the importance of her life, as she has two children. Later she even thanked me that we saved her life.

However, it appears that HIV-related stigma prevented some women from following through with referrals for further care. In Uganda, a peer leader reported that three women who had tested HIV-positive during screening and were subsequently referred to different hospitals had died. She suggested that their fear of confronting their HIV status prevented them from obtaining the care they needed.

Community stakeholders in Zimbabwe raised concerns about access to, quality and continuity of HIV referral services. One FGD participant suggested that money would affect former trial participants' continuing access to care. She asked:

> Are you going to put her on free ART *[antiretroviral therapy]*. I think you should start considering that, because when we had our discussions, it was said that they are not put on anything. They are just referred … but ART is expensive, it is expensive. What happens to this woman who has seroconverted.

In another FGD, a participant explained:

> We actually have long queues of people that were actually waiting to commence ART. Which meant that the services could not cope with the number of people who require services…I think the research should have enough resources to look after those people and their families other than refer them to other already overstretched institutions that are failing to cope with the population that is already there today."

In Burkina Faso, members of nonprofit HIV-related organizations expressed a similar need to ensure that those who screen out or seroconvert during a trial continue to have access to referral services beyond the end of a clinical trial.

***Gel infects people with the virus*:** Staff, participants, and community stakeholders in Burkina Faso (4), Uganda (9), Benin (1), and Chennai (1) reported others' suspicions that the gel was somehow infected with HIV. For example, a community participant in Chennai heard from friends that *"They would put the virus in the gel boxes and send these to the participants."* Peer leaders in Uganda said women had many worries about the gel at the beginning of the study, and some thought *"we wanted to kill them, the CSW."* Similarly, a former trial participant explained:

> When they approached us, we went, but we had reservations that maybe us, who do not have husbands and are going out with many men, that we have the sickness so they want to reduce our number … the CSWs, … by giving us medicine to die. That is what we thought, but when we were trained, we were told that this is not true!

She further explained that staff's suggestions that they keep gel use a secret made them wonder:

> Why do they want us to keep it our secret? We would have asked (our parents, our elders) for advice, but why do the doctors want us to keep the truth to themselves – what does it mean? We used it *[the gel]*, but with fear.

Study selling body parts: Concerns that staff were involved in "selling kidneys" or "blood" were raised in Bagalkot (1), Chennai (2), and Zimbabwe (4). However, one

community participant in Chennai reportedly countered such rumors by stating, *"By taking one bottle (of blood) we can save one's life. The blood drawn is a few milliliters only for this research purpose and to check the body's condition."* Community stakeholders in Zimbabwe also gave little credence to such rumors, explaining *that "they always say that these people are Satanists because they are drawing blood. … There is nothing specific to CS that was being said in the community."*

Rumors were usually attributed to seroconverters or to "non-participants," especially those who were screened out of the trial. For example, a peer leader in Uganda described the situation of one woman she recruited.

> I was insisting that she go *[join the study]* because I thought she was fine. But, when she tested … she was found HIV-positive, and I think they gave her some drugs. I don't remember, but she told her friends, and she was advised to go to TASO. She spent like only one week in TASO and she died, but people started saying that they gave her some drugs and it is the one that killed her. Her mother was staying around and she came and asked me, "What did they do to my daughter?"

She added that the woman hadn't been given the gel because she was already sick. Staff or former participants in Chennai (1), Benin (2), and Uganda (9) suggested that women who seroconvert during the trial spread rumors, saying the product contains AIDS, because they are upset. Outreach workers in Bagalkot described being followed in the community by members of an HIV/AIDS organization who would then discourage women from enrolling in the study. In Zimbabwe, a community stakeholder attributed the rumors to the District AIDS Action Committee meetings and support groups. In one exit FGD in Chennai, rumors spread when research was stopped halfway through.

Addressing rumors: Former participants in Chennai and Uganda suggested that trials should rely more on their participants to dispel such rumors, saying, *"People who have used the gel and has no side effects should talk about their experience and ask them to seek medical help if they have any such problems,"* or, *"We women who have been examined we are the ones to be mobilized to tell others the good things that are in getting examined."* In Burkina Faso and Zimbabwe, community stakeholders discussed the need to involve associations throughout trial. These associations, community groups, or CABs (community advisory boards) should be involved in setting the groundwork BEFORE any trial organizations enter a community. They should be taught about the protocol; if they accept it, then the launch can be done. *"So they are in a position to explain about the study and dispel the myths on behalf of the study."* One Zimbabwean stakeholder emphasized the need to avoid medical jargon when talking with the community. Other suggestions included using the media better and taking care to address people privately who were perceived as starting rumors, so that the rumors could be quickly dispelled.

Political context: Political undertones clearly influenced staff and community perceptions of the clinical trial. However, these undertones worked in several ways. Especially in Burkina Faso, Zimbabwe, and Benin, allusions to the trial's affiliation with *"whites," "westerners,"* or the United States appeared to indicate a basic mistrust of the clinical trial on the part of community stakeholders. For example, several community stakeholders who participated in a FGD in Burkina Faso described their interaction with a white woman from the Agence Nationale de Recherche sur le SIDA

(ANRS) during a meeting in Paris. One participant reported that this woman asked questions and *"clearly said that it is not a good thing. In France, they opposed it and didn't want it to start. They shouldn't flatter women to put them in trouble."* Though the FGD participant had initially liked the idea of a microbicide gel as a prevention method, the white woman's words made her understand that there was a risk. Later she heard that *"the Whites refused to fund the trial because they refuse to accept it (the gel*?)." A second participant in the same group implied that *"They want to finish (us) because there are too many of us,"* a sentiment also raised by a Ugandan participant (see page 13). In Benin, a staff member explained that some brothel owners didn't want women to participate because they had the idea that *"Whites always come to dupe/mystify us."* Similarly, a community stakeholder in Zimbabwe suggested that Western organizations lack transparency. She remarked that her group had seconded someone to UZ-UCSF:

> I don't know if you are still working with her. But there is no feedback. Basically we are an advocacy organization which looks at women's rights, and by this study I see a lot of women's rights being violated … and I don't know how we can work closely with you. You could share what you will be doing in your research with us, because initially we were pushing that this study be done.

She felt they were never really given results about N-9 (nonoxynol-9, a microbicide gel found to be potentially harmful). In another Zimbabwean group, a community member suggested that studies coming from Western countries were not safe and that most people think that most of the work has been done by Western countries, but *"We have got our own studies and the results that we can use for our own treatment plans. It would be safer (to rely on our own studies?)."*

Less commonly – but perhaps equally problematic – was the feeling that the trial's affiliation with the West made it infallible. For example, a community stakeholder in Chennai reassured community members who were worried about rumors such as YRG Care selling kidneys:

> I told them there are no issues related to this, since this gel has been introduced to protect our health and moreover this research was mainly based from the U.S. Government so there is no need to fear.

In Benin, a nurse felt that slightly illiterate women who participated in the trial believed that *"if the Whites have put in all these resources, this cannot help but work."*

3. Staff Perceptions of Trial

Staff members were confronted with contradictory perspectives on the clinical trial when deciding on their own involvement. Several staff in Bagalkot, India (3), and Burkina Faso (3) described a process of sorting through community rumors about the failure of earlier microbicide trials or the possibility that the gel would lead to cancer. Mirroring the sentiments of others, one clinical trial staff member in Bagalkot said, *"When we had joined in this project, many people had suggested to us not to do this work."* In Burkina Faso, several staff recognized the need to detach themselves emotionally and approach the trial scientifically, reasoning that the product goes through stages and there is no reason not to try and get involved. Ultimately, there was a sense among staff in most sites that the trial would benefit not only the participants but also the wider community. They also emphasized both the

challenges and the satisfaction they derived from striving to achieve the required level of scientific rigor – good clinical practice, research ethics, and program planning, stressed during site initiation training. In Benin, Uganda, Bagalkot, and even in Burkina Faso, where the clinical trial was not initiated, staff reported benefiting from their participation in training. As explained by a clinic staff person in Bagalkot:

> To tell about the CS gel, there are "programmatic levels" and "research levels". It was good and different in all the aspects of research, program, and data collection. It was challenging to all of us. We were thinking of how to motivate the women. The CS gel was as new to us as it was to the women.

E. HIV Referral Systems

The second Investigators' Meeting in October 2005 recommended that the BSS teams document the types of services and women's experiences using these services at HIV referral sites. To meet this new objective, a range of activities was proposed, including informal visits to HIV referral sites, discussions with service providers and administrators, and formal in-depth interviews with women who seroconverted or screened out of the trial because of HIV. Although the protocol was amended to include this new objective and approved by FHI's PHSC, the South African and Ugandan sites did not feel it was appropriate to include in their on-going protocols informal visits to HIV referral sites or discussions with service providers and administrators, an objective that might be construed as an evaluation of existing HIV services. Additionally, the South African site had already engaged in a thorough process to determine the HIV referral system before initiation of the CONRAD CS trial. While the South Africa BSS team planned to conduct interviews with seroconverters, the local IRB in Uganda did not approve such interviews out of concerns about confidentiality. Furthermore, neither site obtained approval of its on-going protocol before the trial was prematurely closed. While the other sites (Chennai, Benin, and Bagalkot) did obtain approval, only a few activities were conducted before trial closure. In Chennai, in-depth interviews were conducted with three women who were screened out of the trial because of HIV. In addition, field notes provided some information related to the trial sites' HIV referral system in Chennai, Bagalkot, Benin, and South Africa.

Several themes emerged from the transcripts and field notes. First was a concern about how to ensure that women who tested positive for HIV actually used the services to which they were referred. During staff interviews in South Africa, one nurse felt that women who were screened out of the trial were following up on their referrals, while another felt that this was not always the case. She cited an example of a participant who seroconverted during the study, could not accept her HIV-positive status and would not go to the referral site. The site undertook efforts to determine whether such referrals were taking place, attempting to contact six women screened out of the trial because of HIV. In a later report it was noted that three of these women indicated that they had not used the HIV services to which they were referred. A fourth woman had passed away since her referral was made, and clinic staff were unable to contact two other women. Staff in Bagalkot, India, noted that concerns about confidentiality hampered their efforts to ensure that women used HIV referral services. Women who tested positive at screening were encouraged to disclose to at least one outreach worker, who could then accompany them to the referral center. However, women tended to come for screening and return to their villages after

screening in groups. After screening visits, as outreach workers accompanied the groups of women back to the villages, there was little privacy to discuss results of screening tests, enrollment in the trial, or the need for HIV referral. Such linkages did not appear to be a problem in Chennai, perhaps because YRG Care itself was an established site for HIV treatment and care, including provision of ART.

A second theme emerging from transcripts and field notes was the cost of HIV referral services. In Chennai, the plan was to refer all women who screened out or seroconverted to YRG Care. Women who screened out would receive free consultations and drugs on a sliding scale. If they could not afford the drugs, they would be referred to a government facility. Women who seroconverted during the trial would be provided free drugs through YRG Care. The Benin site identified five public HIV care sites in Cotonou mainly funded by the Global Fund. While other NGOs and organizations provided care for HIV-positive people, these private services tended to be less permanent, hence only public referral sites were chosen. The majority of services at the HIV referral sites were free unless hospitalization was involved.

Finally, the three interview transcripts in Chennai provided some information on the quality of HIV referral services. Two of the three women complained about long wait times, insufficient number of beds, or poor quality food at their current referral site. Despite these shortcomings, these women cited positive experiences overall in terms of counseling and support they received from providers. For example, a screened-out woman said that the doctor and even the laboratory technicians took good care of her, spoke kindly to her, and treated her with affection and care. A second screened-out woman who had been to two other referral sites came to the current site at YRG Care because they patiently answered all her questions, treated her well, and were concerned about her well-being. Also, the wait time was shorter at the current site than at the other sites. She said she used to be really scared of her HIV-positive status, but because she was now healthier and received answers to her questions, she felt her quality of life had improved and was continuing with her monthly visits. She also found the current site clean and that the providers used universal precautions. A third woman noted that the counseling she had received gave her hope and provided emotional support. Now she was optimistic about her own life and was providing emotional support for the other patients at the site. She felt that the staff treated her kindly and with respect. She also noted that the financial assistance they provided, including transportation, helped a lot.

F. Gel Acceptability and Adherence

One objective of the BSS Exit Phase was to better understand how well women were adhering to study gel use during the trial. Microbicide literature suggests that adherence (or consistent and correct use) is likely to be influenced by participants' perceptions of the study gel's effectiveness, their attitudes toward gel attributes, and factors related to their sexual and social contexts. In addition, investigators also wondered whether women generally understood that they might have been assigned to an active versus placebo product, and if so, whether they believed they were using one product versus the other. This section presents information related to participants' and clinical trial staff beliefs about study gel effectiveness and which type of gel they might be using, their attitudes toward gel attributes, and various contexts in which study gel was or was not used.

1. Understanding of Study Gel Effectiveness

In general, former trial participants and staff believed that Cellulose Sulfate would prevent HIV transmission. Discussions about study gel effectiveness were noted in Benin, Uganda, and both Indian sites, where from one-quarter to one-half of transcripts included such discussion. There were several explanations as to why participants held such a belief.

The importance of trust: One staff member in Benin suggested that trial participants believed in the study gel's effectiveness as an extension of their confidence in the staff and the clinic. She explained: *"We know that it's a trial, but for them – they had already found a method of protection, because they trust us. They trust the center."* The effect of trust or hope on attitudes toward gel effectiveness is not unique to participants, however. In fact, a number of staff – nurses, counselors, pharmacy or lab technicians, outreach workers, or peer educators – *"felt sure that the gel would work."* As one staff member in Bagalkot, India stated:

> I was very confident that it is going to be very successful throughout the world. When so many people are involved in it, such a huge amount of money is being spent for this and when everything is being done so systematically, I personally had felt that definitely CS gel prevents HIV infection. I had developed a kind of trust and faith in it.

Other staff in Benin and Uganda felt the study would succeed because: CS has already gone through other phases of research; an earlier trial had failed (so this one was bound to be successful); or simply in response to their prayers.

Counseling messages: It is less clear how much this belief or hope in CS effectiveness was incorporated into the messages participants received from trial staff. A peer leader in Uganda said, "…*the explanation we gave the girls about the ability of the gel to prevent someone from contracting HIV/AIDS…even if the condom tears and you applied it, you do not get affected.*" However, two former trial participants in the same country were clear that staff *"told us they were carrying out a study as to whether the gel would be able to help us against STIs and AIDS.*"

Lack of effects from gel use: Several staff in Benin and one participant in Bagalkot cited the absence of sexually transmitted infections or pregnancy as evidence that the gel was effective. For example, an Indian participant echoed the observations of a staff member in Benin when she said:

> When I was using it, I did not have urine problems, there were no rashes in the genitals. Earlier I used to get a burning urination. After using that gel for four months I am not getting that problem."

Two other Beninese staff suggested that participants thought the gel was effective because they used it without condoms and never got pregnant.

CS versus placebo: In general, most participants recognized that they would be assigned a gel that might or might not contain the medicine being tested, and many also understood that they would be assigned one of six different colors. However, at least seven out of ten women in Bagalkot and four in Chennai were confused about the placebo. These women, it seems, believed that a placebo applicator would be empty. For example, a Chennai participant explained, *"as long as there was some gel*

in each of the applicators I used, I think it means there is medicine in it." Similarly, a Bagalkot participant who believed she was using CS said:

> They (staff) said that some tubes will have medicine, some others will not have, and you will get whatever will come to you. There was medicine in the yellow color (tube) which I got. Madam told me earlier that she also did not know whether it has medicine or not, it depends upon what color we get.… But the one I got had medicine.

An eighth participant in Bagalkot deduced that she was using CS in this way:

> Sir showed me a tube and told me that the tube should not be used. Then he showed the tubes I was using. The one I was using had medicine… The one I was using was thick. If it does not have medicine, it will be watery.

There was also some misunderstanding about the six colors. A former participant in Uganda wondered whether they were given different color gels as a way to *"mark"* the participants themselves.

Almost all participants in Benin and Uganda reported that they did not know which type of gel they were using. In fact, six Ugandan participants were adamant that women who claimed to know were *"liars."* This stance did not, however, prevent women in Uganda from trying to figure out what kind of gel they had received. Several women described comparing their color gel with others' colors to see whether they could detect any differences. In contrast, all but two participants in Bagalkot and half of participants in Chennai thought they were using the CS gel. In Bagalkot, this was because of women's misunderstanding about the applicators. In other sites, some women simply had "*belief,*" "*faith,*" or "*trust"* that they were given CS rather than a placebo. Others took the quality of the gel (smell, feel, etc.), its effects, or lack of effects as proof that they were on the active study product. Finally, only two women believed they were on the placebo gel. In Uganda, one woman said she might be on the placebo because *"it was too light. I could see nothing other than small bubbles."* In Benin, another explained that she was probably given the placebo because her "*sister*" (friend/colleague) who was not taken as a participant had used her gel and died from AIDS.

2. Attitudes towards Gel Attributes

Overall, former trial participants found the study gel very acceptable. In particular, trial participants appreciated the lubricating effect of the gel. At exit, most women found the study gel easy to use, and very few reported concerns or experiences with side effects. This section describes women's overall attitudes toward gel, as well as toward attributes, including lubrication, application issues, and experiences with side effects.

Overall attitudes toward gel: At exit, the majority of former participants expressed positive attitudes toward the study gel and disappointment that the trial's closure would prevent its continued use. Women's reasons for liking the gel differed somewhat by site. The most frequent reason, reported by at least half of former participants in Benin and Uganda and several women in Chennai, was because the gel facilitated sex. About a third of participants in both Chennai and Bagalkot liked the gel because they believed that it helped them avoid HIV or other infections. Other

former participants in Bagalkot felt the gel was good because it did not lead to any side effects. This idea was also reflected in the words of a support staff person in Uganda:

> Personally I thought it would help because it is different from family planning methods that may cause problems or condoms that some people may not use. … If it had worked, other people would have also accepted it because it was not bad.

A frequent theme emerging from staff interviews in the four implementing sites as well as Zimbabwe and Burkina Faso was the importance of developing a female-controlled method. For example, a physician in Uganda said:

> Microbicides are very important if you find a very effective one, because you know most of the time ladies don't have an upper hand in love affairs and it is mainly men who dictate what to do most of the time. So if you find some thing which can protect the women it will be very good for them.

In Bagalkot, Benin, Uganda, and Burkina Faso, some staff saw microbicides not just as a product to be used when condoms were not, but also as a supplement to condoms. As a staff person in Benin said:

> If there were condoms and the microbicide, the two actions would give good results because …then there are the two together and the two persons are protected, thus the protection rate would be higher than condoms alone.

Lubrication: High gel acceptability appeared to be linked to lubrication, according to women and staff in Uganda (15), Benin (8), Chennai (6), and Bagalkot (2). Most often, women suggested that this lubrication made sex easier and less painful, thus facilitating sex work and helping them take on more clients. For example, a former participant from Bagalkot said:

> We used to get heat *[a local concept related to imbalance in the body]* from nirodh *[Indian-manufactured condom]* since it is made by rubber... The more sex we had, the more pain we would get. With gel, sex was easy. It was good for us.

Similarly, a staff member explained:

> Earlier they were using condoms and because of that they used to get vaginal itching, white discharge, and severe bleeding. Earlier they used to get tired after satisfying three clients, but after using gel, some of them mentioned that they can enjoy sexual intercourse even up to 10 clients.

There were a few reports of men complaining that the gel was *"sticky"* (in Chennai) or *"cold"* (in Uganda) or *"too loose"* (both countries). More often, lubrication was described as making sex go more quickly, thus reducing sex workers' fatigue, or more slowly, increasing clients' pleasure. In a few instances, gel use was described as making sex more pleasurable for the woman as well as her partner. For example, one Ugandan participant described the following:

> When you have sex with a man, you would feel as if you are having intercourse with your real husband at home. When you use a condom, it doesn't hurt you at all. But when you use the gel, you would feel like you are having live sex *[note: sex without a*

> *condom].* You wouldn't feel pain. Sexual intercourse was even good; you wouldn't even get tired.

A pharmacy/lab worker in the same country reported:

> I thought men would feel uncomfortable because it would be slippery, and that it may cause problems with the family since some of the women were married. From the reports it did not seem to happen.

The gel's lubricating effect was associated with reduced risk of HIV in several ways. Participants in Benin (1), Chennai (2), and Uganda (8) said that the use of gel would prevent condoms from bursting or coming off. Only one former participant, a woman from Uganda, reported that the gel was slippery and could cause the condom to slip off. In addition, one trial participant each from Uganda, Benin, and Chennai suggested that the gel is protective because it lubricates. A Beninese woman thus indicated:

> CSWs are women who don't secrete, and the man has to penetrate, which leads to cuts. With gel use, they don't have problems any more. The gel slides…. It's the cuts that facilitate HIV infection.

One participant in Chennai and another in Uganda suggested that this lubrication was particularly useful when clients were rough or violent.

Application Issues: A few women in Uganda (6) and Chennai (6) and staff in Benin (3) mentioned having some difficulty with gel insertion. Several women from each country said that the applicator or the insertion process made them feel uncomfortable or even fearful. For example, two Ugandan participants felt the "*pump"* was "*scary"* or was "*too long"*; several participants in Chennai found its insertion difficult because it could only be applied *"in certain lying positions."* Often women's concerns about application were related to the amount of gel to be inserted or the unfamiliar feeling of the gel. At least a half-dozen women in Uganda felt the gel quantity was sufficient for two, three, or even four sexual acts. However, as one woman explained, applying only half of the gel *"was not possible because when you press, you couldn't know how much you would have put. You would press and drain all of it."* Another explained that the amount per applicator *"was much for one sex act. … I used to insert a full applicator of gel as instructed. But, I would use it with up to four customers before adding."* Some women in both Uganda and Chennai reported that staff instructions to insert deeply or find a comfortable position for insertion helped them get over their difficulties. Whether or not women reported problems with gel application, some women commented that the clinical staff provided good explanations about gel and how to use it. Such comments arose most often in the two Indian sites, where women were likely to have had the least exposure to vaginal product use.

Side Effects: While women apparently worried about side effects from gel use, very few former participants reported them in BSS interviews. Concerns about side effects arose in two community group discussions in Chennai, in discussions with seven peer leaders and three former participants in Uganda and one former participant in Benin. In Chennai, women were worried that the gel might cause rashes or wounds in the vagina. Women and peer leaders in Uganda worried about cancer or pregnancy-

related side effects. As one Ugandan former participant explained, women were particularly concerned that gel use would *"damage our uterus, or it would damage our reproductive system and we would get bad discharges."* A peer leader in Uganda reported that one woman who experienced a stillbirth attributed this to gel use (although it is not entirely clear she was a trial participant). In contrast, several participants from the same country were convinced that *"The gel makes you conceive"* – in part, because it increased a woman's sexual urge. Only two women actually related gel use to side effects; in Benin, a former participant said that she bled for 21 days the first time she used gel; in Uganda, a woman experienced itching when she first started using the gel *"but it got to some stage and stopped."* More common than discussions about side effects were reports that side effects were NOT experienced – absence of side effects was reported by at least four former participants in Bagalkot, two in Chennai, three in Benin, and six in Uganda.

3. Adherence to Gel and Condoms

Most former trial participants in Benin (6), Uganda (14), and Chennai (9) – but only three in Bagalkot – stated that they always used their study gel while in the trial. However, when the transcripts of these same participants were examined for evidence of contradictory information, claims of gel adherence appeared credible for only one-fifth of BSS participants in Bagalkot and Chennai, a third of BSS participants in Uganda, and two-fifths in Benin.

At least one or two participants in all four sites admitted they did not always apply a full applicator of gel. In Chennai, three quarters of women explained that they were sometimes unable to use the entire tube because they were in a rush. A fourth appeared to worry about potential side effects, stating: "*Initially I had been inserting only a little, I was not able to insert it fully. I had fear about how it will be.*" In Benin and Uganda it appeared that women sometimes reduced the amount of gel they applied in an effort to reduce the amount of wetness. For example, one Ugandan former participant stated: "*The reason was that when you use half of the gel you don't get too much fluid, it is not very wet.*" In addition, two participants in Chennai and six in Uganda reported not always reapplying another dose of gel between sex acts. Their explanations were varied, but usually related to a lack of time, clandestine use, or concern about the quantity of gel that would accumulate from multiple applications in a short time.

Secret use of gel: Many participants mentioned that they had to use the gel secretly with their sexual partners. There were many ways of doing this. Participants would go to the bathroom to insert the gel before sex; they would tell their clients that they were going to fetch a condom, at which time they would go to a private place to insert the gel secretly; and they would tell clients that they were being treated for an infection and hence had to insert the gel.

Non-use of gel*:* Most commonly, gel non-use was linked to sex with boyfriends, husbands, steady partners, or clients. Such instances were reported in Chennai (4), Benin (5), and Uganda (7), but not in Bagalkot. In Chennai and Benin it appeared that women were either using the gel or participating in the clinical trial without their primary partner's knowledge. In contrast, more than one-quarter of Ugandan former participants tried using the gel with their primary partners but stopped gel use when their partners told them that they did not like the feel of the gel. In addition,

participants cited several other partner-related reasons for not using gel. For example, one Ugandan participant stopped gel use, as her partner was worried that he would contract an infection from the gel. Another Ugandan participant said that she was not able to use the gel, as her client was worried that she was trying to cheat and hurt him by inserting "chloroform" (which he mistakenly associated with the gel) into her vagina. Four participants from Chennai and two in Uganda reported being unable to use their gel with some clients. This was most frequently reported in Chennai (4), where women might be accosted by *"rowdies"* or *"rogues"* who "*would be in urgency, (and) as soon as they come would finish off their work without any patience. There would be no time to concentrate on the gel.*"

Several other reasons were related to gel non-use. First, participants would not use the gel during menses. Although participants at all sites mentioned this, it was most commonly mentioned in Uganda, where about half the participants specifically stated not using the gel during menses – a time when participants would not engage in sexual relations. In Benin and Chennai, participants also reported that they did not use the gel during menses but would use condoms if they had sex during menses. Interestingly, a Beninese participant preferred to use Vaseline rather than the study gel as lubrication with condoms during menses because she was concerned that the study gel would create problems for her. A second reason was participants ran out of gel and had no time to go to the study clinic to replenish their supply. Third, some participants reported not using condoms when they did not use the gel, as they were counseled to use both the gel and the condom together. Finally, there were two reports from Benin of a participant who temporarily stopped gel use during the first two weeks of study participation because of pain in the lower abdomen. The participant's friend, who was also a study participant, decided to stop using the gel together with her friend. However, they both resumed using the gel a week later.

Condom use: Interviews with former trial participants at three sites (Uganda, Bagalkot, and Chennai) reported that a third to three-quarters of those who were interviewed always used condoms when they used the gel. At all three sites, former trial participants said they liked using condoms and the gel together because the gel provided lubrication and made sexual intercourse less painful. The lubrication provided by the gel, when used with condoms, also prevented condoms from tearing or bursting.

Non-use of condoms: Participants reported that they were not able to use condoms most frequently with their primary partner – a boyfriend, husband or lover. There were several reasons for not using condoms with their primary partners. A participant from Bagalkot said, *"We use condoms with all our clients. But we cannot use condoms with our lovers. … We felt gel was very good to us especially while having sex with our lovers."* Some participants mentioned that it was their choice not to use condoms with their primary partners because they trusted and loved them. As with gel non-use, participants whose primary partners did not know about their trial participation or their commercial sex work reported difficulty using condoms with these partners. A peer leader from Uganda reported that although participants were using condoms and the gel with their husbands as counseled, participants who desired to become pregnant were using only the gel for HIV prevention with no condoms.

Use of gel without condoms: Staff members, peer leaders, and trial participants in all four sites reported that there were times when participants used the gel without

condoms. There were basically two reasons for gel use without condoms. Several participants in Bagalkot and Uganda explained that they complied with customers who asked them not to use condoms because they felt reassured about being protected from HIV. However, a Ugandan participant reported finding out later that she had contracted syphilis. A more frequent response was that participants were able to charge more money in exchange for sex, while also believing that the gel conferred protection from HIV. In Benin, a participant said that her customer would pay her three times the usual price for unprotected sex. A participant in Chennai also said that she would not use condoms with customers who were perceived to be rich and who would pay more for sex without condoms. In Uganda, several peer leaders and participants stated that men were willing to pay more for *"live sex"* – sex without condoms.

Trial's influence on risk reduction behaviors: It's not clear whether participants' non-use of condoms in the situations described above represents a decline in risk reduction behaviors caused by gel availability or whether these women would have failed to use condoms regardless. Despite the trial's potential effect of "disinhibition" on some participants, trial participation appeared to enhance women's risk reduction behavior overall, especially condom use. For example, several participants increased condom use after having tested HIV-negative, while others made sure that they constantly used condoms with every partner so that they could remain HIV-negative. In Uganda, 14 participants explained that they benefited from learning about their HIV-negative status, increasing their resolve to remain HIV-negative by using condoms. As one participant said:

> The advantage is that before, one did not know their HIV status, they would not care for fate of condom whether it is torn, or moved and did not care for their lives but they now care for their lives.

In addition to knowing their HIV status, participants felt that their increased condom use was a result of the risk reduction and condom use counseling that they received as part of the clinical trial. A participant from Bagalkot said:

> Those women who come up to enrollment felt that still they are safe as they are HIV negative, and made their mind that they should continue to be negative. For that they wanted to keep themselves safe…They were eager to know more information. Sex workers as well as devadasi women *[a traditional form of sex work in which young girls are married to the temple]* were not using condoms with their lovers earlier. Actually they are at a higher risk of getting HIV infection. The counseling which they had taken here helped them to understand this.

In Zimbabwe, where the trial was closed before participants could be enrolled, a community member reflected that women who participated in other HIV prevention trials wanted to continue participating in such trials so that their participation would curb their partner's sexual risk behavior. The community member went on to say that in the exit interviews for the MIRA study, some participants:

> tell us that they have been using their participation in studies as a basis for telling their partners that they are being monitored and their partners were now afraid of getting into risky behavior because they feared that their wives are in a study and they are saying now that they are exiting from the study there is no monitoring that is going to be done they might engage in risky behavior.

4. Gel Sharing or Selling

Many women acknowledged that they were counseled not to share their gel with anyone else. More than half of former BSS participants in Uganda (13) and two-thirds of former participants in Chennai (9) explicitly denied sharing. Nevertheless, some reports of gel sharing emerged – especially in Uganda. Several former participants said they had borrowed from a friend who was using the same color. One peer leader explained that some women *"would get so many partners (they) would finish their gel before their scheduled visit*." She didn't think they necessarily borrowed the same color but would borrow from people with whom they shared a room. *"If five people share one room, I don't think they can fail to share the gel."*

Others suggested that sharing was common with non-participants, including friends, peer leaders and homosexual men. One former Ugandan participant was asked by a friend who wasn't in the study to give her some gel *"because she was feeling dry during sex and she had lost the appetite."* She explained, *"I told her that it could affect her if she had not been tested, she feared it… that it could bring blisters, things like that. Everyone has their own color to use and you first get tested."* Five peer leaders in Uganda said they had heard about others who were not in the trial but used the gel. One admitted:

> I was not in the trial. I was a peer leader, but even me – someone gave me some gel. … Some one would lament that today I feel terrible; my private parts are paining. They would have used saliva, so that they get lubricated. So from such conversation, those who had gone for the trials would sympathize and then open up to them and say I have my thing and you use it like this and that; it works well. All I know is they shared it even with me, I was just given – but you had to be friends and it was done in secrecy and they would teach you on how to use it.

Another also talked about secrecy of gel sharing. A former trial participant reported, *"Those homosexuals at Kasanga also used the gel. They also liked it. … They use it behind."*

There were very few reports of selling the gel, mostly because "*Women loved the gel*." However, several peer leaders in Uganda mentioned that women sometimes stole each other's gel. One explained:

> We are many there, like 30, but only nine participated. So all those who didn't attend, used it… they would steal it. Whenever they find it in the handbag, or somewhere under the bed, they pull it out and insert it.

Similarly, a former participant in Benin said that a "*sister*" stole her gel when she was not at home. A friend also asked her for some gel, and she brought her to the clinic to enroll and get her own gel. In Chennai, the BSS team learned about another gel that was being distributed within the same communities who were participating in the trial.

G. Issues Related to Early Closure

1. The Chain of Communication

When the decision was made to prematurely close the CONRAD clinical trial, a chain of communication was quickly initiated – from the U.S. investigators to the country clinical trial staff to trial participants and ultimately to the communities in which the trial was being implemented. At each level, some variations in understanding and acceptance of trial closure were noted.

Informing staff of closure: During Exit Phase interviews, staff in Bagalkot (3), Benin (10), Burkina Faso (7), and Uganda (6) indicated that they were officially informed of closure during a special meeting. While a few staff in each site reported being aware of the possibility of closure from the start, more often staff indicated that closure was sudden and came as a complete surprise (4 in Bagalkot, 4 in Benin, 6 in Burkina Faso, and 3 in Uganda). In fact, a few respondents in Burkina Faso and Uganda did not really believe that the study was stopped and sought confirmation from the interviewer. A Beninese, four Burkinabe, and a Ugandan staff member blamed investigators for failing to make plans regarding what to do, particularly for the staff, in the event of early closure. A Ugandan health visitor said that *"in the training they should have told us that if such a thing happens, abcd … but not just pack your bags and go home."* A Burkinabe staff member suggested that researchers failed to plan for closure because they were overconfident:

> When it reaches phase III, already we are confident about a lot of things. So when it's like this, often we don't take enough precautions. … Everything was well planned. But what had they planned that if it stopped halfway, what do we do? That would surprise me. Even if they had thought about it, it wasn't as good. … I think that these are aspects that we often don't think about too much, because secretly we hope.

Informing participants and the community of trial closure: After trial closure, staff tried to contact participants to tell them the study had been stopped and explain the reasons for closure. Some participants in Bagalkot (7), Benin (2), Chennai (5), and Uganda (6) confirmed during their exit interviews that they had been contacted by staff. Some participants also reported hearing about closure from friends or community members.

Some clinical trial staff in Bagalkot, Uganda, and Burkina Faso noted challenges to informing participants and community members about trial closure. For example, while a Ugandan physician suggested that "*there are very many partners we have involved … all these groups should get very good information and reasons why the study is being closed,"* others suggested that confidentiality should be maintained when holding informational sessions. Therefore, separate meetings were needed for women who enrolled and those who were screened out of the trial. In Bagalkot, several staff FGDs raised the concern that, *"There are many people in the community who do not know anything about this project. If we call and tell them about the study closure it is like creating new problem."* In Burkina Faso, the staff did not tell potential participants why the study was stopped, according to five staff and one woman. Three staff explained that they had not been authorized to talk about closure in an effort to avoid misinterpretations and a subsequent loss of confidence in the clinic:

> Since we were not given the green light, we didn't play that game to say false. … If we had said "ah, what we were going to do there, supposedly the product is not good." In the end, it is going to make a confidence crisis. … at the level of the clinic it was kept a secret.

Ugandan staff talked about the need for accuracy and for confidentiality and therefore they took care not to disseminate information too widely. Clinical trial counselors in Uganda explained that they were able to maintain confidentiality because their clinic seemed like any STD clinic – a fact that led media representatives to go to other places asking about early closure of the CONRAD trial, but not their clinic. As one counselor stated:

> Since the work was done in a confidential manner, the community is not aware of the trial activities. Even some were staying with people in the same house but did not know; even neighbors did not know what we were doing.

Several staff members in Bagalkot and Burkina Faso expressed concern about how to make participants and/or community understand closure and how to respond to their questions. For example, a Bagalkot staff member explained:

> When we first heard of the study's closure, we also felt that what all problems may come from the community, what all questions women may ask. We were thinking how to convince the women and community. But when we worked here at the ground level for one week we did not face any such problems.

Perhaps this was because of to the site's information strategy, which involved three steps: 1) CAB meeting involving *"all the project leaders and NGO leaders working in Bagalkot district"; 2)* second half-day meeting with *"all the outreach workers, PEs, Taluka coordinators ... to understand the 'scientific reason' for the study's closure" and 3)* training for *"our own outreach workers and PEs (on) how to tell women and the community about study closure, reasons for it, and how to answer to their questions."*

Post-closure activities: In Bagalkot, a few staff reported that post-closure activities included the provision of counseling on HIV/AIDS, safe sex, condom use, and STIs. In addition, doctors kept providing STI treatment not only to participants but also to other women after the end of the trial. A staff member thus indicated:

> We told whoever comes here for STI treatment to visit here if they experience any problem. Our outreach workers also do follow-up…It has become an integrated set-up. Positive people can come, general people can come, women with STI symptoms can come, sex workers can come. In total anybody can come here for any problem and can take treatment. … All NGOs are referring women to go to the Arunodaya clinic to get STI treatment or counseling.

In Uganda, all staff (6) indicated that they were doing follow-up with pregnant participants and reviewing files. A doctor explained:

> When we closed the study the participants were not coming to the clinic, so most of the activities went down. The only thing now was to rebuild the binders and filling in the gaps. …That's where we keep the case report forms or all the information about the participants.

2. Community Knowledge of Trial Closure

At exit, there did not appear to be widespread knowledge about the CONRAD trial or its early closure, despite suggestions by staff in some sites that such information be disseminated widely. Unless community members had contact with trial participants – for example, as friends or intimate partners – or had participated in Preparedness Phase activities, they were unlikely to have heard about the gel study. As a former Ugandan participant stated, *"I don't think that a person who was not in this system of ours knew or had seen it (the gel) but those few men who came to us knew it."* In Benin and Burkina Faso, some community representatives who participated in preparedness activities recalled hearing about the study early on, but had heard nothing else until they were again contacted at study exit. In Zimbabwe, many community stakeholders heard about the trial for the first time during the exit phase activities.

Concerns about lack of information on closure: In Zimbabwe, about half of community members were critical of the way the closure was announced. They were concerned that the lack of explanation of why the study stopped would fuel rumors and speculation in the community, particularly through the newspapers. One explained:

> We don't have information, so people will continue lying to each other. Even newspapers, someone may not have correct information, but because they have an opportunity to publish news, they will just publish it like that and people will take it to be the truth.

Several community members felt that the reasons for closure should be clearly explained to stakeholders to correct misconceptions and particularly to reduce confusion between the Cellulose Sulfate trial and other on-going studies:

> People now started spreading rumors because the difference between Buffergel and Pro2000 and Cellulose Sulfate is only known by researchers. But, these other people who are participants, they don't actually know except to read and as you read, you might think you are understanding … but you may not be understanding what you are reading … until somebody comes in like this and then explains.

In Burkina Faso, a staff member similarly feared that people may come with all sorts of explanations for closure:

> In any case people can think there was something terrible behind this story. When there is a lack of information like this, when there is a void like this, well, it makes all possible speculations come together.

In Chennai, a community member regretted that more information was not provided, as closure left everyone *"in a confused state,"* and advocated that participants be invited to an informational meeting to dispel rumors.

Confusion caused by other studies: In some cases, community members confused the CONRAD trial with other research studies that had taken place in their countries. This was especially common in Zimbabwe, where the CONRAD trial had been

planned but never got underway. In 15 of the community interviews or FGDs, participants made references to Buffergel and/or Pro 2000, two microbicide gel products being evaluated in the HPTN035 study currently underway in Zimbabwe. Some of the BSS participants were involved in community outreach activities for that trial. Additionally, it was reported that some CAB and community members were confused about the CS closure and wondered whether it related to the MIRA trial, a recently closed trial to determine the effectiveness of a diaphragm and lubricant in preventing HIV. One community participant explained that people in the community *"might not know the difference between these various studies. So, they actually took the UZ-UCSF studies as failing,"* but they had met with the doctors and clarified things. A Ugandan participant mentioned that some people talked about an injection study but that this wasn't the microbicide study, because it involved couples. Similarly, a peer leader in Uganda didn't hear any rumors about the gel study but did hear something about the *"Walter Reed Project – that they are giving a vaccine. They say that they are injecting us with a dead virus, but how sure are they that the virus is dead?"* In Bagalkot, a few participants related the CONRAD study to an HIV/AIDS prevention project funded through the Indo-Canadian HIV/AIDS Project (ICHAP). In two separate interviews with community stakeholders in Burkina Faso, participants referred to a virucide gel being tested in a Danish laboratory in which many people got infected in several countries, including Togo. Several staff members in the same country reported that earlier rumors related to the nonoxynol 9 study in Cameroun continued to circulate and led people to worry about the CONRAD trial.

Media after closure: A number of participants and community members did not see any information on trial closure in any type of media in Bagalkot (8), Benin (19), and Chennai (15). In Uganda, several participants and staff said they or some friends heard about closure on TV (2) or the radio (12), or read information about it in the newspapers (7). Seven respondents indicated that radio messages reported that the gel was faulty, did not work, or caused AIDS. A pharmacy lab assistant further confirmed that participants were suspicious that something was wrong with the gel because of the way closure was announced on the radio. The nature of newspaper reports is less clear, but one health visitor mentioned two separate articles:

> Initially they reported the official position that WHO/UNAIDS had halted the CS microbicide trial. Then later after some days I saw a media report that South Africa in particular had had many seroconversions. That is actually what created the spark.

In Burkina Faso, three respondents heard on Radio France Internationale that the trial had stopped at other sites. Three others indicated that they read about the closure on the Internet, and two referred to the press, although they did not give any specifics. Most people (18), however, did not see any information relating to closure in the media, although several of them admitted that they may have missed the reports because they did not consult the media regularly. In Zimbabwe, community members also mentioned information on trial closure on TV (2), on the radio (1), and in at least two newspapers (6). Reports of the contents of newspaper articles varied across respondents, who indicated reading that the gel *"enhances sexual feelings,"* that the gel had been banned *"because it has been discovered that a lot of women in South Africa who were participants in this project succumbed to the virus HIV and AIDS,"* or that the trial had been stopped *"because the results of the participants in this study were negative instead of being positive as required by the study protocol."* In addition, a respondent remembered *"a press statement where the Ministry of*

Health and Child Welfare were saying of all the studies being done, nothing bad has been found as it has been recorded in other countries."

3. Reasons for Early Closure

This section discusses participant, staff, and community comprehension of the reasons for early trial closure. Some respondents from these three groups in Benin (9), Burkina Faso (17), Chennai (1), Uganda (4), and Zimbabwe (2) admitted that they didn't know why the study had stopped. In general, others provided varied explanations for trial closure, but it was not always apparent that respondents had a clear idea of why the study was stopped, as several BSS respondents in each site could not elaborate on the reasons they provided for closure.

Gel is not effective and may even be dangerous: Participants, staff, and community members in Bagalkot (11), Benin (19), Burkina Faso (9), Uganda (9), and Zimbabwe (4) attributed closure to the fact that the gel was found not to prevent HIV. Although many of them didn't elaborate further, a clinic staff member in Bagalkot explained: *"When it is known that the gel is not going to show any 'light' to our women, there is no meaning in continuing its trial."* Participants and staff in Bagalkot (11), Benin (10), Burkina Faso (7), and Uganda (4), and community members in Zimbabwe (3) also emphasized that the gel was exposing women to increased risk of acquiring HIV, although whether this was caused by the gel specifically or to reduced condom use was not always clear. A Beninese staff member may have been alluding to the failed nonoxynol-9 trials when s/he stated, *"It seems that the product is again causing the transmission of HIV. To preserve the health of the population and of target groups, they took the responsibility to stop."* Furthermore, a participant in Bagalkot, one in Benin, and two community members in Zimbabwe thought that the gel could cause other types of health problems for women, for instance *"scouring"* or damage to the womb. In Uganda, four peer leaders and a participant heard that the gel was faulty or didn't work, while another three peer leaders, a counselor, and a participant specifically heard that the gel caused people to get HIV. Not all women, however, believed these rumors, according to two participants and a peer leader. One participant explained:

> I never thought about anything like "It is going to destroy my ovary or it might transmit HIV" … because I personally liked the gel. Even if you could ask your friend you could not know because you might have got gel without the medication and yet the other friend got the gel with medication … the health worker told us that they saw that the gel could not protect people from HIV. That is why they withdrew it from people.

In Burkina Faso, a client, a potential participant, and a staff member thought that the gel contaminated women. Several participants in two community focus group discussions in Zimbabwe and an association member in Burkina Faso were even more exaggerated in their theories. A Zimbabwean respondent said that s/he read in the press that *"most of those people who were in the research have AIDS."*

Problems not with the gel, but with how it is being used: In Chennai, all community members (5) and all but one participant (18) heard that the study was stopped because participants in foreign countries failed to use condoms with the gel and were infected with HIV/AIDS. One participant explained:

> in some of the foreign countries (they) have not followed these instructions properly. … If both (gels and condoms) had been used, then the outcome would have been successful. If either one had been used (alone), there are chances of getting infected with HIV/AIDS.

One participant further heard that *"the gel was used in the wrong method"* by having anal and oral sex. Failure to follow instructions is seen as a "mistake," which two community members indicated can be caused by external pressures: *"We cannot blame others for an individual's mistake. We cannot blame all since some of the clients would not be interested to use the gel."* One staff and one participant in Bagalkot, two staff in Benin, one association member in Burkina Faso, and four community members in Zimbabwe similarly refused to believe that there was anything wrong with the gel and attributed the increased rate of infection to lack of adherence to condom use. One Beninese staff member stated:

> We were told that the rate of infection was increasing a little too much. Me in my head I think that all women would not have used condoms well, for me it is the only reason that can explain the infection rate.

A participant and two staff in Benin, and a potential participant in Burkina Faso blamed the increase in HIV/AIDS cases not on the failure to use condoms but on improper use of the gel, suggesting either that participants did not stick to their assigned gel color, or that they didn't apply the right amount of gel. In Zimbabwe, a community member took the argument one step further to blame poor adherence in South Africa on local organizations. S/he stated:

> We have never encountered a study that was said to be bad here in Chitungwiza – one that was rejected. It all depends on how you lay your foundation, how you start community mobilization and sensitization. …

***Trial stopped for ethical problems*:** In Zimbabwe, two community members heard that the study was stopped because subjects were put at risk by participating in the study: *"exposing (negative people) to the virus to see if they don't turn negative. If they turn negative, we dump them … they are not part of the program anymore."*

***Gel supply**:* A few community members in Benin (2) and Burkina Faso (1) heard that the study was stopped because the gel had expired. Another Beninese community member reported that some women asked if the trial ended because there wasn't enough gel. A community member and a participant in Chennai expressed similar suspicions, although they also both thought that closure was caused by lack of adherence to condoms in foreign countries.

The case of Burkina Faso: Before intermediary results showed that CS gel could potentially increase the risk of HIV infection among participants, Burkina Faso was discontinued from the study out of concern that HIV incidence was too low. The distinction between the reasons for closure in Burkina Faso and at other sites, however, was not always clear to participants, staff, and community. Three community members and eight staff correctly attributed closure to low seroincidence. A staff member explained:

> Considering that the incidence was not high. That with a population like this, they had calculated the size of their samples, about 5 or 4 percent. And we had something of 1%. It didn't suit them. Scientifically, it is like this. It had to stop.

Most other participants, staff, and community members either didn't know why the study stopped (15) or solely evoked problems with the gel (7), as described above. An association member explained that she felt bad that the Burkinabe were afraid and didn't have the courage to try the gel so that a medication could be found to cure the disease in the world.

In addition, administrative difficulties were cited as the cause of closure either in conjunction with low seroincidence (4) or alone (2). A community respondent thus reported that potential participants thought that the trial did not take place because the clinic officials didn't do things on time, an indication of their lack of interest in the trial. A staff member similarly stated:

> We were not able to start when the funders wanted. It dragged on for so long that they decided to stop… It dragged on, they thought it was at our level. The gels were delayed at the airport. All of it counted a little. And when we had the gels, the lab papers were missing too, that hadn't arrived.

Two staff and a potential participant reported that some women thought the clinic was going bankrupt because the project was not starting and the follow-ups had stopped. A community member thought that there was a checklist to go through to make sure that a site fulfilled specific conditions (social, sanitary, and technical) before it was selected for the trial. She felt sure that Burkina Faso met these conditions, and hence suspected that the study did not start either because of a financing issue (an idea echoed by two other community respondents) or because some of the initial selection criteria had markedly changed. In a similar vein, a staff member suggested that the Burkinabe site was not retained because the majority of women worked with condoms while researchers wanted to try the gel on participants who did not use condoms. Lastly, two staff members indicated that some potential participants from the clinic cohort did not believe that the study was closed, but thought that other women were recruited instead of them. One of them suggested that women thought that the staff suspected they were seropositive: "*They have people who are here for how long. It's worth 8 years. But we don't want to take them. Or else it is because we mean that they are positive.*"

4. How Justified Was Trial Closure?

In general, participants, staff, and community members in Bagalkot (14), Benin (23), Chennai (8), and Zimbabwe (10) thought that closure was justified on the basis of the intermediary results. Their rationale varied slightly according to their specific understanding of the reasons for closure (as described above), but most agreed that closure was needed to protect women from getting infected by HIV/AIDS. Two Beninese staff and a Zimbabwean community member further pointed out that the larger community would be exposed through the women if the trial was not closed. One staff member in Benin explained:

> If the women don't get infected it means that the community also won't get infected because these are women to whom our husbands, our sons, our fathers, our brothers go. They are the ones who link the community to STI/HIV/AIDS.

Nevertheless, some respondents in Bagalkot (4), Benin (10), Chennai (4), Uganda (7), and Zimbabwe (8) refused to endorse closure, were skeptical about the reasons explained to them, or felt that the decision was premature, even though in some cases they still agreed that closure was overall good. Some respondents based their opinions on their lack of direct proof that the gel was harmful. For instance, three participants in Bagalkot and one in Uganda understood that the study was stopped because of an increase in HIV/AIDS cases but were adamant that in their site, the gel was *"good for everybody."* In Benin, two community members similarly had trouble accepting that the gel *"did not work"* based on their impressions of the gel. One of them used the gel and felt it protected him, and the other saw that the gel was white, while s/he would have expected it to be brown if it was defective. In Uganda, respondents in three staff focus group discussions were shocked that the gel could increase the risk of HIV infection because they had very few seroconversions on their site. A pharmacy lab assistant said:

> Honestly, the five seroconverters we had out of 300 participants would not make the gel ineffective. Maybe they considered other sites but then, they told us that the other sites were just beginning.

In Chennai, two community members and two participants felt that closure was unacceptable, perhaps because of a loss of faith.

> Participants had faith that we can prevent HIV/AIDS. If they had been able to finish this research, the result would have been successful and we could have used the gel instead of condoms in the future.

One staff member in Benin, one in Uganda, and four community members in Zimbabwe similarly suggested that the results that came out in South Africa may have been at least partly imputable to behavioral factors (improper use of gel and condoms). As a result, they felt that closure was not justified at all sites because behaviors differ from one country to the next. A behavioral scientist respondent in Zimbabwe said:

> I actually don't think that there is something wrong with the gel, I think in the other countries, you know if you are told that this sweet is nice without a wrap you will definitely eat it like that and maybe they didn't use other components like condoms because they just wanted to use the gel on its own. So obviously I would be more sexually active if there is a gel that can possibly stop me from having HIV. So the thing is why then all these countries and then in Zimbabwe it's dangerous? ... Though Zimbabwe has the second-highest of HIV prevalence the people are becoming more cautious and their behavior has been adjusted with the conscience that there is HIV, so there is some mishaps when it comes to taking data from other countries relating to research.

Another Zimbabwean community member expressed similar feelings, suggesting that cultural taboos in sex practices could have affected the behaviors of participants. In a related but different argument, one community member in Benin and one in Zimbabwe did not feel that the South African results were sufficient proof that the gel

was not effective because different people may react differently. According to a Zimbabwean community participant: *"We all react to different medicines … I mean that's why some diseases are more prevalent in other races, and they are rare in other races."*

Perceptions of reasons for trial closure in Burkina Faso: In Burkina Faso, 25 respondents thought that closure was not justified on the basis of an argument of low seroincidence, while nine felt that this decision was acceptable. Only one association member, however, seemed to understand that low seroincidence would cause difficulties at the research level. Others primarily focused on the fact that seroincidence was low, rather than on why this would be a problem for the study. A client said:

> They brushed Burkina aside to give the opportunity to another country, I think it is a really positive gesture. Since Burkina, we are not really under pressure. So it is better to target the countries that risk being annihilated by this pandemic.

Among those who found closure unjustified, nine persons were shocked to hear that seroincidence had reportedly decreased because they felt that many people were still infected. A community member wondered if the sample used for the calculations was biased:

> What proves that they didn't choose these women? We see girls wandering around town. The women who cross the town, that, that can't in any case prove that Burkina should not do the study.

Four respondents suggested that researchers could still have assembled a group to meet selection criteria. A staff member thus stated: *"We could find a sub-population in our cohort that would be exposed a lot and whose HIV incidence goes beyond the 1% that was given."* [on pouvait trouver une sous population dans notre cohorte qui serait beaucoup exposée et dont l'incidence du VIH va au-delà des 1% qui ont été donnés.] An association member had trouble understanding why low seroincidence was a problem, because the study targeted seronegative women. After receiving some explanations, she was shocked that a high rate of conversions could in fact be desirable: "*I feel like they (the researchers) are sorry that there aren't any conversions. Whereas, the goal of this thing, it is to limit the transmission. And so this thing revolts me."*

Four clients were also specifically concerned that seroincidence could go up again and that by not doing the study, they were in fact wasting a chance to eradicate HIV/AIDS completely. One of them explained: *"If they stop like this, what proves that [the seroincidence] is not going to increase? It was better to continue to bring this rate down to 0*%." In fact, two community members, two potential participants and two staff believed that there were untold reasons for closure. A community respondent pointed out that calculations of seroincidence were only estimates and that an estimate over a one-year interval could not alone justify closure, hence she suspected that there were other motives.

5. Implications of Trial Closure

This section addresses the loss of benefits from the trial for participants, staff, and community members. In general, participants were disappointed because closure signaled the end of the benefits associated with the trial. For the most part, they lamented the benefits that drew them to the trial in the first place (see section on recruitment) but also indicated that they would miss the gel itself for various reasons. Participants, community members, and staff also reported frustration at the loss of an opportunity to prevent HIV/AIDS. In addition, staff members were upset that their employment ended earlier than expected.

Loss of access to care: Participants and staff in Bagalkot (4), Benin (3), Chennai (7), and Uganda (13) indicated that women would miss the care they had been receiving through the trial. A Ugandan doctor explained that the care provided to participants was better than the norm:

> The health setting in our countries is kind of poor. People don't have good access to health facilities. So, our participants were used to free medical check-ups, continuous counseling, free medication for STDs and other medical conditions.

Similarly, two participants in Chennai stated that getting tested elsewhere was not affordable. A witness in Bagalkot described her feelings by comparing the suspension of care to mourning:

> …how to come for minor problems like fever, cough and cold? ... When we were using gel, all facilities were there. They were giving us the most care and all the respect – the way we respect some important guests in our house. … Now it has stopped. Who will ask us? We feel very bad like with the death of a minister.

In Uganda, participants and peer leaders further noted that the suspension of care penalized not only women, but also their entire families because their children would get free treatment (3) and because some women shared the drugs they were prescribed with others at home (3). Three potential participants in Burkina also indicated being upset at losing access to care and medication.

In Benin, seven staff members reported that visits to the clinic had significantly decreased after closure. A staff member estimated that three out of 20 women came, another suggested three out of ten. The Beninese staff offered three explanations: the absence of gel, free condoms, and money (3), that women believed that the center was closed (1), or that women no longer trusted the staff (2). One staff member in particular reported: *"When we ask women to go to the center to be treated, they ask us what we will give them."* In Bagalkot, on the other hand, three participants suggested that women continued to get treatment at the clinic after closure.

Loss of other benefits: According to participants and staff in Benin (8) and Uganda (9), women lamented the loss of the money they were receiving for participating in the study. Participants and staff in Benin (7), Burkina Faso (2), and Uganda (7) further reported that women were upset because they could no longer collect free condoms and had to buy them. Of the two Indian sites, only one participant, in Chennai, voiced similar complaints, explaining: *"Now we are like birds in a cage. We don't have any income, gel, condom, or any doctor to see us. That's why we are feeling bad."*

Staff in Bagalkot (3), Benin (9), Burkina Faso (11), and Uganda (5) were upset because they suddenly found themselves without jobs. They expected to be employed until the end of the trial and had planned their lives accordingly. A Beninese staff member described his reaction when he learned of closure:

> When one sees a man or a woman, there's a whole load of people behind them. And the family, and the children, how are they going to live? There is nothing social about this study. Before stopping it, one had to see all it can cause socially. We are the victims of this closure.

For a few staff in Bagalkot (2) and Uganda (1), the loss of a job was experienced as more than a material loss, as closure also signified the end of the strong relationships that had been built among the members of the team. For this reason, an Indian staff member said, *"We felt bad as our team, which we had built with some dream, has broken. We are feeling like crying, like when a sister gets married and goes out of our home."* The Burkinabe staff were particularly frustrated because they were trained and mentally ready but never had a chance to start. Moreover, four of them indicated that they had worked a year without pay to prepare for the trial and were waiting to be compensated. In addition, three staff members were disappointed because they were expecting to benefit from the study on a professional level as a boost to their career. Four respondents further noted that closure hurt not only individuals, but also the clinic because of the loss of funding and because no other projects were planned. In Benin, four staff members were worried about their ability to find new work, especially on short notice. Three clinic staff expressed similar concerns in Bagalkot, anticipating particular difficulties for outreach workers and peer educators. One of them explained:

> About clinical staff it is different thing. We have come from different places and we can go to other places also. Social workers and clinical staff have experience and we can go to other projects. But for outreach workers and PEs it has become very problematic. Now they have got very good training and their salary was also very high. Now they have to work for low salary and they have to work at lower designation.

Trial-related activities were extended by a few months at all sites to ease the transition after closure. Although they appreciated this effort, a few staff in Benin (2) and Uganda (1) stated that they would have preferred to receive a compensation package without work. One staff member in Bagalkot and two-thirds of the staff in Uganda further reported a loss of satisfaction in post-closure activities. According to a Ugandan pharmacy assistant, *"We just come and do whatever is available. We have no morale. Not knowing what your day will look like feels bad."*

Disappointment about loss of gel: In Benin and Chennai, an equal number of participants were disappointed about having to return their gels versus those who understood the need to return their gels. In Uganda, three times as many participants reported that they or others were very disappointed about being asked to return the gel. A Ugandan pharmacy or lab technician reported: *"Participants are angry. We told them to bring back the gel and they refused. Imagine someone in the 11th month of follow-up being told to bring back the gel."* Nevertheless, very few women admitted to keeping the gels themselves after the study stopped. Among these, a woman in Chennai explained that she kept five to six gels, thinking that

"since the outcome of the research is not known, it is better that they can use the gels … there is no need to return them." A few participants in Benin (3) and Uganda (4) were unable to return to the clinic and finished using their remaining gels. Most participants reported that they didn't have any gel left to return when the trial was closed. However, many of these same women reported that others kept their gels. The most common explanation was because women *"liked"* the gel (in Uganda) or because it was *"useful"* to women (in Chennai). Some suggested that women's decisions to keep or return the gel were based on whether they continued to believe that the gel was effective. For example, a participant in Chennai explained: *"They might think that it will give them protection even if condoms are not used"* and because sex was *"free and easy"* with gel use. According to a Ugandan woman, some participants refused to return their gel because they liked it and *"whenever we went to the clinic and it was found to have no effect on the uterus, she decided to use it until it was finished."* She reported that one of her friends hid three boxes of gel. Another Ugandan participant recognized that the effectiveness of the gel was not known but that she liked it anyway: *"I compare it to money in the way I like it … it doesn't protect, but is helpful to me in some way."* A community member in Benin and a peer leader and a nurse in Uganda similarly reported that women would miss the gel even knowing that it didn't protect against HIV. According to a Ugandan nurse, some participants requested that *"if you found it ineffective you just give it to us because we like it for lubrication."*

A few participants and staff in Bagalkot, Chennai, and Uganda indicated that the loss of gel affected women's work and income because they couldn't have as many customers without the gel. A Ugandan woman stated: *"I used to make seventy but now I stop at fifty because I had got used to the gel. Without the gel I couldn't do it perfectly it had spoiled me."* Staff in Benin (5) and Uganda (2) and one participant in Chennai reported that women got used to the gel and were distressed because they could no longer get it. Five Beninese participants and a Ugandan woman expressed their intention to buy lubricants in pharmacies but complained that it was expensive. According to staff, other women turned to Vaseline as a substitute (one in Benin) or were simply not using any alternatives to the gel (one in Benin and one in Uganda). In addition to the loss of lubrication, a few women in Bagalkot and Chennai feared having unprotected sex now that they no longer had access to the gel, as they believed it protected them. A trial participant from Chennai said, *"This gel was useful to have sex now only, condoms are the methods and sometimes some may not have the condoms so we feel uncomfortable."*

Loss of opportunity to prevent HIV: According to participants and staff in Bagalkot (2), Benin (7), and Uganda (5), women were hoping, and in some cases confident, that the trial would be successful and that the CS gel would provide a new protection method against HIV. As a result, closure was a disappointment to participants. A Beninese staff member explained: *"It is like a baby drinking from its bottle and suddenly it is taken from him, he won't be happy."* Community members in Burkina Faso (1), Chennai (2), and Zimbabwe (9) similarly perceived closure as *"a setback for the community in the search for a solution to HIV/AIDS."* Staff members in Bagalkot (3), Benin (6), Burkina Faso (5), and Uganda (3) also reported feeling discouraged because they really wanted a solution to be found. The sadness was compounded by the feeling that a solution to HIV was now even further delayed, as captured by the comments of this Beninese staff member:

> Our desire to have a protective product for these women failed and because of this failure, we can't even know when there will be another gel available for these women any more. We are still in nothingness, we are back to zero.

Loss of confidence in gel products: Trial closure raised concerns regarding the harmfulness of the CS gel, according to some participants and staff in Bagalkot (4), Benin (2), Chennai (5), and Uganda (4). The early and sudden withdrawal of the gel created doubts that something was wrong with it, and some women feared developing HIV infection or other long-term side effects. A participant in Chennai explained that women were fearful when they returned the gel:

> They would think that for the past six to eight months they have used (the gel) and definitely will return (it) with fear…the participants will have doubts about the gel and whether by using the gel the body has affected.

Similarly, two staff members in Bagalkot and one in Benin were concerned that women might attribute future health problems to the gel even though they were healthy at the end of the trial. A staff member in Bagalkot said:

> Human nature is if anything happens in future, we blame others. It may happen in the next month or after a year. They will definitely say "as I had gone to the trial I have got HIV."

A couple of staff members in Bagalkot, Benin, Burkina Faso, and Uganda, and six community members in Zimbabwe perceived closure as a sign that the gel had not been developed thoroughly enough before the trial. A staff member in Bagalkot said: *"When it has passed through the first two phases, how can it be so defective to lead to higher risk of getting infection in the third phase? ... I have lost hope in all clinical trials."* Not all women, however, appeared to be worried. At least two participants in Bagalkot, one in Chennai, and three in Uganda stated that they or others didn't experience any problems, particularly HIV infection, from using the gel.

Concerns about the CS gel, however, did not necessarily lead to the rejection of the idea of microbicides as a way to prevent the transmission of HIV/AIDS. Staff in Benin (2), Burkina Faso (10), and Uganda (4) stated that their opinion of microbicides had not changed in spite of the trial closure and that research on microbicides should continue. One Burkinabe staff member specifically emphasized that failures were part of the research process, as he/she explained: *"We are not always on the right track, we don't always knock on the right door, I think that these are risks we take, and these risks, we must keep taking them."* In Zimbabwe, six community members expressed similar feelings as they suggested that researchers modify the CS gel and bring it back:

> The major objective of a study is to find ways of maybe reducing the prevalence of HIV in Zimbabwe. So if ways could be found on how to sort out what went wrong in this study so that it continues just like any other study I think that would be helpful.

Trust in clinical studies: Some participants, staff, and community members in Bagalkot (9), Benin (13), Burkina Faso (15), Chennai (3), Uganda (5), and Zimbabwe (11) indicated that some people, and more specifically former CS trial participants, would be reluctant to participate in future trials because they had lost faith in research. Two staff members in Benin, one in Burkina Faso, and two community

members in Zimbabwe thus indicated that the cumulative failures of microbicide trials (referring explicitly in one case to nonoxynol-9) put the credibility of microbicide research at stake. A Beninese staff member stated:

> This trial has just shaken the African soil one more time, shaken the human resource that we are. This failure puts our credibility at stake, credibility of the center, credibility of microbicide research, if only because here we do not have the degree of civilization that Westerners do. A first time it didn't work, a second time halfway, a third time what will women say?

In Benin, Burkina Faso, and Zimbabwe, closure in particular created feelings that women were exploited. One Zimbabwean community respondent mentioned that closure *"might affect recruitment for other studies because people still have the feeling that they are being used in these research studies, they are no longer safe."* In Bagalkot, participants' trust in research and staff was affected because they felt that they had been "dropped in-between" after they were told that the gel was good and that the study would last for 12 months. One participant explained that she would consider participating in future studies but indicated *"before that I put a condition. You should not do as you did earlier with gel. If you want to give continuously, you give, otherwise do not give it to us … then only we will come."* Three staff in Benin and one in Uganda similarly feared that they would lose their credibility among women. A Ugandan pharmacy assistant explained, *"We had built relationships and trust with the participants. They may have lost this trust because the gel did not work."* Trust issues were also identified as a potential obstacle to recruitment for future studies by four staff and community members in Burkina Faso, because women were mobilized and then told that the study would not take place.

Despite these misgivings, two-thirds or more of former participants in Bagalkot, Benin, Chennai, and Uganda said they would be ready to join another trial. In general, staff and community members were also favorable to the idea of new studies (7 in Bagalkot, 18 in Benin, 35 in Burkina Faso, 5 in Chennai, 5 in Uganda, and 15 in Zimbabwe). Many believed that women would still be amenable to joining future studies but indicated that prior sensitization work would be necessary to dispel negative information on the CS trial or explain the new study to motivate participants and ensure they were making an informed decision. There were also reports that the early closure of the CS trial could increase trust in clinical trials. For example, two Burkinabe staff and five Zimbabwean community members acknowledged that closure showed that researchers were responsible and cared about participants and their safety. A staff member in Bagalkot and two community members in Zimbabwe indicated that closure would generate similar feelings among women and the community: *"They know that if anything goes wrong, their safety is a key concern for the investigators."*

H. Recommendations for Future Trials

In light of the premature closure of the CONRAD CS trial, community members, staff, and former participants made numerous recommendations for improving the planning and implementation of future trials. Recommendations included strategies for improved recruitment of trial participants, increased adherence to study products, confidentiality, and access to care and treatment of seroconverters.

1. Future Recruitment Efforts

Staff and community members in each site emphasized the importance of sensitization to motivate people to join new studies, make informed decisions about participation, and minimize resistance in the community (and thus pressures on women not to participate). In this section, we describe the various strategies proposed by respondents. These strategies range from suggestions to directly approach women, to increasing community involvement in the research process, for instance by involving women's partners or community associations.

Directly approaching women: Participants, staff, and community members identified some of the challenges and best practices involved in directly approaching women. A few respondents in Benin, Burkina Faso, and Zimbabwe indicated that illiteracy could sometimes be a challenge in recruiting women and emphasized the need to provide clear explanations using simple terms and appropriate language. In Burkina Faso, two potential participants recommended organizing meetings of 10 to 12 women at their work sites or in their neighborhoods to introduce the study and make them understand its benefits. One of them explained that group talks were more likely to provide women with the courage to enroll than if they were approached individually. Two outreach workers in Bagalkot, a community member in Benin, and a participant in Chennai further stressed the importance of establishing a rapport with participants and introducing the study gradually. An Indian outreach worker in Bagalkot said:

> To convince them fully we need at least one month. First time when we go they won't give us any respect. We have to go to their house in the same way as their sister. We ask about their daily routine casually; ask about their family history, about their food, children, parents, etc. By that we try to understand them. After going to them many times like that, we start talking to them about HIV/AIDS and STI. Initially they won't reveal that they do sex work even if they do it. … If they come close to us they will tell everything to us. On the other hand if we behave as if we are doing our duty they will not talk to us.

To launch the study in the community, some Zimbabwean community respondents suggested broadcasting information on television or, because not everyone has access to the media, distributing literature through the clinics, explaining the study to women at the clinic, or putting up posters in schools and churches. A respondent explained: *"If people see it also coming out on TV, they would be more receptive to the study. Even if some people may want to distort the information later, still very few people would be fooled."*

Increasing grassroots participation: Two community members in Burkina Faso and ten in Zimbabwe advocated increasing grassroots involvement in future studies. In Zimbabwe, respondents specifically explained that people would be more likely to support future trials or to participate in them if they received regular feedback on their progress and were informed of the results. One of them said:

> (Receiving) no feedback is not good, that is why you end up with people saying, "These people want to use us. Once they get what they want, they go and leave us." But this feedback is what should happen and people get motivated through that. Even if I did not go to school, it feels good to know that I participated in this study and these are the results. I would be in a position to encourage others to participate in new

> research that comes because we would have been involved with other research and this is what we came out with.

Moreover, feedback allows people to make informed choices and be partners, rather than "guinea pigs":

> We really want…. when we involve them to be meaningful involvement where we actually give them a chance to speak their minds without them feeling that they have just said something that has no weight.

Two respondents emphasized the importance of being approachable to develop open channels of communication with residents. One of them suggested:

> You are known that you drive around in cars but when you get to the community people, you should leave your cars, and as for the Outreach workers they should mingle with the people all the time. … If they get used to the people the community will not be afraid of them.

Networking with community leaders and associations: Several community members in Burkina Faso (3) and Zimbabwe (11) and two staff in Uganda suggested that investigators should network with community leaders and associations because these actors have local knowledge and could help them explain the study and recruit participants. According to a Zimbabwean community member, local organizations were also more likely to get feedback from participants on adherence:

> [Participants] will tell us how they are using it and they will also be free to come and tell you how they are using it and this is important for you to know how they are using it … the leaders and stakeholders can explain fully about the study when it comes because the people in the community confide more in the stakeholders than in the researchers because researchers come and go.

In fact, a few staff in Bagalkot (3) and Uganda (1) and two community members in Zimbabwe argued that involving community leaders and groups was essential because people tended to follow leaders, and if leaders disapproved of the study, recruitment could be very difficult. Thus, according to a Zimbabwean respondent:

> When we introduce a study we don't just come and pitch camp in the community and start. We should go through the gate keepers. Those are the people who will see to it that this is permitted or this is not permitted, they are what we might term the voice of the community.

Moreover, involving local groups could limit opposition at later stages, as suggested by two Zimbabweans:

> They [investigators] need to deal with all interested parties in the local community so that people can openly discuss on the merits and demerits of their trials so that once the people are agreed on a position, it will be easy to implement such a trial and also if there are any shortcomings people would look at it positively because they would have been involved in the discussions.

Respondents in Zimbabwe suggested that the following people or groups be involved: school heads, women's organizations, AIDS service organizations, CABs, clinics, and support groups. In Bagalkot, a staff member cited *"key informants like anganwadi*

teachers, Gharwalis, pan shop owners, auto drivers, gram panchayat members, opinion leaders, NGO/CBO."

Involving women's partners and families: In Zimbabwe, about half of community members (9) advocated men's involvement in future research as a way both to facilitate women's participation and to increase adherence to study requirements and retention. One of them explained:

> … men are actually more powerful than females when it comes to the control of a family. So if the male counterparts are more involved, the more they will understand about this research, the more they will allow their families, their children and so on to come and participate.

In Burkina Faso, an association member similarly mentioned that women needed the approval of their husband or partner to participate, and a staff member further suggested potential obstacles from women's employers. Another staff member advocated involving parents in the recruitment process because familial education matters a lot in Burkina Faso. A Burkinabe client and a Zimbabwean community respondent also indicated that religious beliefs might hinder participation, the former suggesting that integrist parents in the Muslim community may not allow their daughters to participate, and the latter referring to *"some religious and cultural beliefs, like you know we have this apostolic faith church which doesn't allow people to go the clinic to seek any medical advice."*

Enrolling for the wrong reasons: In Zimbabwe, several community members (4) worried that the current economic climate would lead women to enroll in future studies for financial reasons without fully understanding their role in the research process. One of them explained:

> As the economy goes on like this, so you are also going to have a situation where a client is here for all the wrong reasons but they know they will come out of it with some money for their family.

In addition to ethical problems, such behavior may attract the "wrong type" of participants. A Zimbabwean community member predicted that seropositive people, drawn by compensation, would come to be screened even though they know they are not eligible:

> There are many associations for people living with HIV in this community, those people from these groups may come just for the benefits and at the end of the day our resources and our nurses get exhausted from screening many people who know that they are HIV positive.

Even among seronegative people, a few community members in Zimbabwe (3) and a Ugandan doctor indicated that women who joined studies only for the money were more likely to drop out or to fail to adhere to the study requirements. In the words of a Zimbabwean respondent:

> Take for instance that I want to be getting the fifty thousand dollars every month, I may go there and lie and tell you what I think you want to hear but in reality that is not what I would be doing.

Furthermore, three community members suggested that the current economic crisis in Zimbabwe would make it more difficult to retain participants because of increased mobility and reluctance to miss work:

> because of the economic climate in Zimbabwe today, you may not find women who will be able to pursue the study to the end because she can be there today, and tomorrow she is in Botswana and the following day she is in South Africa. The same may also apply to the working women if you are going to be doing your study during the week when they are at work.

Multiple trials: In Zimbabwe, three community members suggested that other on-going trials may affect recruitment for future studies. The first hinted at competition across studies, suggesting that *"this community is over-researched; any new study is going to depend on how we are going to sell the new study."* The other two, however, were more concerned about participants co-enrolling to maximize benefits and the problems it may cause. One of them recounted experience in the MIRA trial, where people borrowed IDs from others to be able to enroll, thus providing false addresses, which made it hard for the staff to locate them.

2. Recommendations on Other Aspects of Trial

In addition to the recruitment phase, participants, staff, and community members further discussed a few other aspects of trial procedures in relation to future studies. This section summarizes their recommendations regarding ways to check on product use, confidentiality, the care and support of seroconverted women, and the usefulness of the BSS team.

Find ways to check on product use: Several staff and community members in Benin (3) and Uganda (2) who thought that participants did not use the CS gel or did not use it well recommended finding ways to check on participants' adherence (more specifically on gel use in the event of another microbicide study). A Ugandan health visitor explained:

> If they are going to use a microbicide again, I would encourage them to get or design a way to verify that the participants actually use the product, not to just depend on the word of the participant. We may get wrong results relying on the people. Say they get a method using lab a test or doctor to check… What if they connive and tell you lies? … what if they are using one product - ten people - and you think (there) is only one using it?.. There should be a scientific way to know that these people actually use the product not only depend on their word.

Two community members in Zimbabwe similarly advocated continuing education throughout the trial to remind participants of the importance of adhering to study rules. According to one of them:

> The fact that they are using the gels or they are using the condom doesn't mean that they are fully protected … people need continuous education. People will relax, and when they relax things will go wrong and they will come back and say I was using your gel and this is what has happened so we need to continuously work with them.

Confidentiality: A few respondents re-emphasized the need to maintain confidentiality in future trials. A community member in Chennai, a participant and a

counselor in Uganda, and a community member in Zimbabwe insisted on keeping information related to participants confidential. The Ugandan counselor said:

> Some information should remain confidential and should not be given to the community. Like the recruitment criteria – they should not know that we are targeting sex workers. For example, in the past trial, they did not know and the media did not mention sex workers in their articles. It would not be nice because sex work is illegal.

A staff member in Bagalkot and a counselor in Uganda mentioned confidentiality in the context of women's visits to the clinic. The former suggested that women felt embarrassed visiting clinics in their own village, and recommended using clinics in other places so that women could use them independently or on their way to the market. The latter praised the system used in the CS trial in Uganda, whereby the CS clinic *"was like any other normal clinic and some people thought it was part of the STD clinic, maybe because we had multiple offices with several activities happening in different places."* A Ugandan health visitor stressed confidentiality in the context of the clinic vehicles. S/he recommended that transportation should be made available to participants at all times, but was adamant that the vehicles should not have any labels on them or distinctive license plates that could link them to the clinic.

Care and support of seroconverted participants: Staff in Bagalkot (2) and Uganda (2) and Zimbabwean community members (2) emphasized the need to provide adequate care and support to women who seroconverted as part of research trials. The two Ugandan staff members were particularly concerned that support be extended beyond the end of the study. A Zimbabwean community member also suggested that "serious compensation" be provided to seroconverters. S/he explained:

> If they seroconvert during the study, besides just referring them to these institutions, they are likely to meet problems when they get to those institutions. One of them is transport from Chitungwiza to whereever they would be going to have that. … There is also going to be … in terms of time, you know. When they go out there and sit in a long queue and they are followed, certain things that should have happened at home are not happening and this is a person who is possibly ill.

Maintaining a behavioral and social science component in future trials: A staff member in Burkina and a doctor in Uganda recommended that future studies include a behavioral and social science component from the beginning. The Burkinabe staff thought that the BSS team could provide independent feedback on participants' reactions and concerns, thereby helping the staff make adjustments to improve their work. The Ugandan doctor indicated that *"the participants sometimes they tend to fear people who are putting on gowns and they open up for other people who associate with them in the community"* and thus proposed having the BSS team do counterchecks on what participants reported to doctors. In Bagalkot, however, a staff member expressed concerns at exit that women would not speak openly to the BSS team, as they were strangers and might have felt that their confidentiality had not been maintained. Instead s/he suggested that outreach workers be trained to collect information on participants' feelings and experiences. However, unlike other sites, the BSS team was not an integral part of the clinical trial in Bagalkot, but was identified shortly after trial initiation and abrupt closure.

IV. Discussion and Conclusions

The BSS activities described in this report were undertaken to enhance implementation of the CONRAD phase III clinical trial of Cellulose Sulfate, rather than as independent social science research. While local BSS teams were trained and encouraged to use qualitative methods to collect, record, and analyze data that could inform the trial, they were also expected to regularly feed such information back to their site's clinical trial staff. In an effort to balance these competing demands (timeliness versus methodological rigor), BSS teams in some sites, or during some phases, relied on verbal feedback or quick field notes to relay information, rather than more formal and time-consuming documentation approaches. It's possible, therefore, that some important insights from BSS activities have not been fully captured in this report. Nevertheless, several important themes emerged from this aggregate analysis.

Promoting understanding of the clinical trial: Certain concepts seemed particularly difficult to understand. For example, questions about the recruitment of HIV-negative, but not HIV-positive participants suggested that some community members and participants believed the trial to be for treatment rather than prevention of HIV. Numerous participants understood that the CS gel was meant to "kill" the virus – an action they may have associated with other therapeutic treatments. It's likely that the language used to describe the potential effect of CS on HIV contributed to this misunderstanding about the ultimate goal of the product being tested. A number of participants struggled with the idea that the efficacy of the gel was truly unknown (a fundamental requirement for implementation of a phase III trial to be ethical.) During the Preparedness Phase, and even at exit, some participants and community members insisted that the gel was being tested on humans because it was **known** to be effective in preventing HIV. At times, outreach workers and other staff appeared to reinforce misperceptions about the effectiveness of CS gel. Without an understanding of the concept of equipoise, other trial-related concepts, such as randomization and use of a placebo comparator gel, also become difficult to accept. While former participants in the two Indian sites appeared to understand the general concept of a placebo, a number of women misunderstood the form that a placebo gel would take, incorrectly concluding that placebo gel tubes would be empty rather than filled with the white substance found in their own tubes.

Perceptions of trial-associated risks and benefits varied across sites and within participant groups. Some community participants in Zimbabwe and Burkina Faso had prior experiences with clinical trials. They appeared to more easily understand the general concept of research versus treatment and the rationale for randomization and use of placebo gel in order to determine the effectiveness of the CS gel. However, some participants in these same sites raised strong concerns about aspects of the

clinical trial, including the adequacy of arrangements for HIV treatment and care for those screened out of the trial and the ultimate and potentially negative role of foreigners or whites. Within sites the biggest detractors of the CS clinical trial seemed to be individuals or groups who were not brought into the trial process. For example, during the trial, rumors that the gel infected people with HIV or that staff were selling people's blood were thought to be circulated by those who were screened out of the trial or who seroconverted. Indeed, neither Zimbabwe nor Burkina Faso initiated the CS study in their sites; their lack of experience implementing the CS trial may have contributed to the strong concerns emanating from some community groups. The unique role of YRG Care in Chennai, India, may have buffered it from some of the rumors and concerns expressed in other sites. In this site, for example, few concerns were expressed about access to HIV treatment and care, the role of foreigners, or the inadequacy of other trial-related procedures. And at exit, fewer BSS participants expressed a loss of faith in clinical trial research than in other sites. Instead, BSS participants conveyed their trust in YRG Care – an NGO with many years of experience providing HIV and related education, treatment, and care to the surrounding communities.

During the Exit Phase, numerous recommendations were made by staff and community participants to better involve local community leaders and their organizations in planning and implementation of future trials. It was suggested that their involvement could facilitate recruitment, enhance trial-related compliance, and remove community opposition. In some sites the list of such community stakeholders was long and varied, including teachers, brothel and other business owners, men or other family members, as well as local politicians and NGO representatives. There was, however, little discussion about how the underlying power/political structures of these various groups might affect the autonomy and confidentiality of future trial participants. For example, the more widespread the knowledge about specific aspects of the clinical trial (eligibility criteria, visit procedures, or product information), the more difficult it might be for women to make independent decisions about participation or to maintain confidentiality should they not be able to participate.

Future trials should consider ways to increase the community's research literacy, while balancing the potentially beneficial and coercive effects of greater involvement of different community stakeholders in trial planning and implementation. In addition to developing community-level strategies for communicating the fundamental principles of clinical trial research, new trials should also carefully pre-test informed consent and counseling information – and train staff to provide this information – to ensure that trial participants correctly understand the content. Community and participant-oriented communication strategies could make use of information from reports such as this one by incorporating participants' perspectives (on trial-related risks and benefits, for example) into scenarios with guided discussion.

Recruitment and retention of trial participants: Preparedness activities highlight the challenge and complexity of identifying and recruiting high risk women into HIV prevention trials. First, our labels and related eligibility criteria do not necessarily fit local perceptions of risk. Some women, particularly self-identified sex workers, might engage in more sex with a greater number of partners, but be better able to use condoms consistently. Women in other professions – bar and hotel workers, hairdressers – and even housewives were also at high risk of HIV according to many participants. However, these women would likely be harder to recruit, especially if

recruitment criteria were based largely on sexual behavior criteria. A second recruitment challenge relates to identifying the most effective models for recruitment. Most sites relied in part on peer referrals to identify and recruit women into the trial. Outreach workers in Bagalkot emphasized the need to spend time in the community, to get to know potential participants personally, before trying to recruit them into the trial. In Burkina Faso, it was suggested that a group approach to recruitment would likely work better than trying to recruit women one-on-one. A final recruitment challenge is that trial participation itself is likely to change women's risk behavior, enabling some to better negotiate condom use and other risk reduction behaviors while perhaps encouraging others to abandon condom use out of belief that the gel itself conferred protection.

Several aspects of the trial that reportedly influenced retention in some sites included long wait times, insufficient compensation, fear of pelvic exams and blood draws, and treatment by clinic staff. In terms of enhancing retention of trial participants, the BSS teams in Benin, Uganda, Bagalkot, and Chennai found the provision of food, drinks, and – in some sites – videos to be helpful in alleviating the long clinic waits. Some sites adapted their communication strategies or clinic procedures to accommodate participants. For example, staff in Benin began to show participants the vials used in blood collection before blood draws to ease participants' worries about the procedure. The Ugandan site increased travel reimbursement and sometimes sent transportation to pick up participants for their study visits in order to mitigate transportation difficulties. These adjustments were not without their own problems, however. It seemed that some Ugandan participants who completed the trial before the increase in transportation allowance believed that staff had simply retained some of their reimbursement, while others refused to take clinic-provided transportation out of concerns they would be associated with the trial. Few former participants reported mistreatment by clinic staff. However, several such reports were associated with missed visits. In fact, during Exit Phase interviews, many participants praised the care they received at the study clinic. Future trials should emphasize the important link between clinic staff's treatment of participants and retention rates. Furthermore, trials might consider strategies to identify and rapidly address participant concerns, through the type of BSS activities conducted in this study or perhaps through the appointment of a special clinic staff position to ensure client/participant care.

Gel acceptability and adherence: Although potential participants and community members worried initially about possible side effects from the study gel and its ease of use, Exit Phase data indicate the gel's widespread appeal. Particularly in Uganda, Benin, and Chennai, women liked the gel's lubrication; it made sex less painful and enabled sex workers to take on more clients. About a third of Ugandan participants emphasized that the lubricating effect of the gel reduced their risk of HIV by preventing condoms from bursting or coming off. Others in all sites had faith that the gel was conferring some protection from HIV even when they were unable to use condoms. The high acceptability of the vaginal gel led some participants to refuse to return unused gels at study closure and prompted the Benin and Burkina Faso sites to investigate ways to make other lubricants available in the site.

Despite high acceptability, there was evidence that women did not always use the study gel correctly or consistently. Some participants described inserting only a partial dose, and others failed to reapply the gel between rounds of sex. Partial use was usually ascribed to the need to act quickly or secretly, the desire to reduce

messiness, or possible side effects. In addition, participants described several scenarios when gel use was not possible. The most common reason was the difficulty of using gel with husbands, boyfriends, or primary partners – especially if this partner was not aware of their participation in the clinical trial or in sex work more generally. Some women also described being unable to use condoms with these same intimate partners.

In fact, the ability of the CS gel to prevent HIV transmission can only be tested during sex acts when women use their study gel but not condoms. Regardless of gel use, when condoms are correctly used, women are not likely to be exposed to HIV. When study gel is not used, lack of transmission cannot be attributed to the gel. Therefore, better understanding the circumstances in which women are likely to use the gel but not condoms could provide useful information. In this study it appeared that exclusive gel use was more likely with "certain" clients or customers – for example, those who could pay more. However, it was not clear from this study whether trial participants would forgo condom use with such clients even outside a clinical trial setting, or only because they believed themselves to be protected from their study gel.

Future trials should recognize that gel and condom use behaviors are likely to differ by partner type, and trials should help women develop appropriate strategies for negotiating use with these different types of partners. In this study, some women described different ways to use the study gel clandestinely or to negotiate its use overtly with some sex partners. However, this study was able to interview former participants only after the study had closed. Examining gel adherence behavior prospectively is likely to lead to better insights about how and with whom participants can negotiate gel use, and when they cannot.

Finally, it is somewhat troubling that the lubricating effect of gel use led some women to conclude that gel use would enable them to take on more clients, earning more income. Although it is not clear that these women actually substituted use of an unproven gel for highly effective condoms, the possibility of gel-for-condom substitution remains. Should a future microbicide product prove to be partially effective – that is, less effective than condoms, product introduction messages will require careful tailoring to discourage such substitution.

Planning for early closure: Once the decision to prematurely close the CONRAD CS trial was made, the international and local study staff made concerted efforts to control the announcement: first notifying local IRBs and trial participants, and then disseminating the information more broadly. Still, community members in several sites felt that information about trial closure was not disseminated widely enough. In general, BSS participants suggested that the less information available, the more rumors circulated. While intensive activity was required, dissemination efforts in the Benin, Uganda, Chennai, and Bagalkot sites seemed to proceed without many problems. In general, participants felt that closure of the trial was justified and undertaken to protect women's well-being. The Durban, South Africa, site faced difficulties with trial closure, in large part because of inaccurate reports in the media that a lot of South African women participating in the trial had contracted HIV. This negative media attention was also noticed by some Ugandan and Zimbabwean community participants. In both sites, the fact that other microbicide trials were also underway caused some confusion.

Even when considered justified, trial closure was a serious disappointment to participants and staff in most sites. Participants lamented their loss of access to high-quality healthcare, to the gel, condoms, and other trial benefits. Staff worried about their loss of jobs and the dissolution of a project in which they had invested much hope and professional pride. Some staff expressed real shock about the decision to close the trial early and suggested that future trials plant the possibility of early closure at the beginning of trial.

Nevertheless, the early closure of the CS clinical trial did not seem to have the long-term negative impact of the earlier trial of nonoxynol-9, which was fully implemented and showed an increased harmful effect of N-9 as compared to placebo. In part, the CS study may have avoided greater associations with the N-9 study because of its increased attention to media and the careful work of local sites to inform trial participants and other community groups. Finally, most former participants indicated they would participate in a future trial; staff and community members also favored the idea of new studies, and some indicated that the CS study's concern for the safety and well-being of participants was apparent.

V. Appendices

A. IRBs ASSOCIATED WITH BSS ACTIVITIES IN EACH SITE

Site	Institutional Review Board
Benin	• Ethics Committee of the Faculty of Health Sciences of the Université D'Abomey-Calavi (Benin) • Research Ethics Review Board of the Centre Hospitalier affilié universitaire de Québec (CHA) at Hôspital du St-Sacrement (Canada)
Burkina Faso	• Ethics Committee of Centre Muraz • Ministry of Health
India – Bagalkot	• Research Ethics Board of the University of Manitoba, Bannatyne Capus (Canada) • Institutional Ethics Review Board of St. John's Medical College and Hospital (Bangalore, India)
India – Chennai	• IRB of YRG Care (India)
Uganda	• Uganda National Council for Science and Technology (UNCST) • The HIV/AIDS Research Committee of the UNCST
South Africa	• University of Kwazulu-Natal, Biomedical Research Ethics Administration
Zimbabwe	• Medical Research Council of Zimbabwe
US – FHI	• Protection of Human Subjects Committee
US - CONRAD	• Eastern Virginia Medical School

B. Interview Guides

The following are examples of interview guides used for each site during the three phases of the study. Due to the nature of qualitative studies such as this one, guides varied slightly by site. An iterative approach was used to maintain the topic domains but allow flexibility to more accurately represent a site's situation as it became known.

Preparedness Phase:
- Potential Participant / Trial Surrogates Guide
- Community Opinion Leader Guide

On-Going Phase:
- Staff Topic Guide
- Missed Visit Topic Guide
- Community Stakeholders On-Going Guide
- HIV Screened Out Referral Interview

Exit Phase:
- Staff Topic Guide
- In-depth Interview with Former Trial Participants
- Discussions with Community Stakeholder Guide
- Discussions with Community Stakeholder Guide (Burkina Faso)

Trial Surrogates

Thank you for agreeing to meet with me/us today.

A new research study will soon begin in <u>*Cotonou.*</u> The study will be conducted by *the Project Sida-3*. I/we are working with Sida-3 and Family Health International in the United States. We will advise the clinical team on how best to set up the study. I/we are not the persons who will be conducting the clinical research study.

The purpose of the clinical study is to test a new kind of product. The product may prevent HIV, the virus that causes AIDS, and some sexually transmitted infections. The product is called a microbicide gel. The gel being tested in this study is called "Cellulose Sulphate."

There are many things that the clinical researchers haven't yet decided about the study. That is why we wanted to talk with you today. We recognize that you have some experience and knowledge that will be helpful to us in making plans for the study. We want to make sure that this study is as good as it can be.

Today, I want to spend about 45 minutes to an hour with you to ask some questions about your knowledge about issues surrounding women at risk of getting HIV. I will be talking about the community in general and women in particular, sources for HIV and STI treatment and care, and your thoughts on how we might recruit women to join the clinical study. However, if there are any questions you don't want to answer, we can skip those. Just let me know. All of your answers will be treated with confidentiality, and we won't link what you tell us with your name. I am providing this agreement of confidentiality to everyone we speak with

We believe your insights into these topics will help us to design a better clinical trial. If this study is successful, it will inform the development of a new product that women can use to protect against STDs and HIV infection. You may not personally benefit from participating in this study. However, if microbicides are proven to work, this will benefit many in your community. In appreciation, we would like to give you *<u>(x[4])</u>* to reimburse you for the time you took to talk with us today.

We do want to write down/record[5] your thoughts to make sure that we get what you have to say. Again, we will not put your name on any of our notes. We will destroy the tape recording after we have written up the notes from the tape.

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[4] Amount of reimbursement will be informed by suggestions from previous discussions with community stakeholders.

[5] Information will be recorded in either hand-written notes or tape recorded transcripts, depending on site preferences. The decision for tape-recorded will be informed by discussions with clinical trial staff, and initial meetings with community stakeholders, who will advise on the use of recordings with both stakeholders and trial surrogates.

- During our talk please feel free to ask any questions you may have about the work we are doing to prepare for the study, or the study itself. I'll give you the name of a contact person working with our team, in case you have any questions after we finish talking. (Name of clinical investigator) could also be asked.

HIV/AIDS Knowledge and Attitudes

- What have you heard about HIV? What are the ways a person can become infected with HIV?
- How big a problem is HIV in Cotonou?
- How do people usually find out they are HIV-positive?
- Where do people go to get tested for HIV? Are free testing services available? How much does it cost to get an HIV test?
- What kinds of treatment or services are available for people with HIV?
- How do others treat people with HIV?

Perception of Risk

- How much are you personally concerned about getting infected? Why?
- Is there anything you do to protect yourself from HIV or other sexually transmitted disease?
- What have you heard about condoms? How effective do you think condoms are to prevent pregnancy? How effective do you think condoms are to prevent STIs or HIV?
- How available are condoms (price and availability).
- In what circumstances are you not able to use a condom? Which kind of partners do not like using condoms?
- (Other measures taken to protect themselves) Is there anything else you do to protect yourself from STIs or HIV? If yes, what? Can you explain in detail?

Attitudes towards Microbicide Attributes

As I mentioned, a research study will soon begin to test a product called Cellulose Sulfate. This is a gel – that looks and feels a little like (insert a similar product.) To use the gel, a woman will fill an applicator (if possible, show a sample) and insert the product in her vagina. Researchers hope this product will help protect a woman from getting HIV if she uses it before having sex with someone who is already infected. However, we do not yet know whether or not this product will actually work. That is why they must study whether the gel works.

- (General level of interest) How interested would you be in something like this (in various formulations – gel, woman-controlled method)? Why?
- What worries might you have about using this product? How easy or difficult do you think it would be to insert the gel before having sex?
- What, if anything, would you tell a partner about the gel? Who would you tell about it?

- How do you feel a partner would react to your gel use? (intimate partner or boyfriend, a casual partner etc.)
- Are there any other people who would object to your participation in a study? (if formal sex worker, how would "madame" or pimps react to study participation?)

Knowledge of Clinical Trial Research

Before new drugs can be sold in stores or markets, they must be tested – first in laboratories and then in people. These tests find out whether the drugs are safe and effective. During these tests, the new drug is usually compared to a similar product that doesn't have the same medicine in it. Some people in the study are given the new drug. Some are given the other product. Neither the researcher nor the participants know who has received which product until after the tests are finished.

- Have you ever heard about any research that was testing a new drug or other kind of product? What have you heard?
- What does it mean to you when we say that participants will be given either the product being tested or the other product "at random"?
- Have you ever participated in research before? Tell me about your experience. (What was the purpose of the research? What were you asked to do? What was good or bad about your experiences?)

Attitudes towards Clinical Trial Participation

Earlier I said that a new product was going to be tested to find out whether it prevented HIV transmission. This study is going to happen in six different countries. In Cotonou, researchers hope to recruit 300 women who are HIV-negative. About half of the women will be given the new product to use and half will get the other product – the one that doesn't have any microbicide ingredient in it. Both of the products will look alike. They will be asked to use the gel every time before they have sex. They will be asked to participate in the study for 12 months. During that time, they will need to come for monthly check-ups to make sure they are doing well, and to give them more gel. They will also be tested for HIV (once every three months?) During the study, some women will probably become HIV-positive. Researchers will compare HIV rates differ between the two groups.

- What do you think about the process I have just described?
- Do you think you might be willing to participate in a trial like this? (Remind them that saying yes does not mean they are agreeing to participate.) Why or why not?
- What kinds of questions do you have about the study?
- What would you want to know before deciding whether or not to participate in a trial like this?

Researchers do not know whether the new product will actually prevent HIV transmission. For that reason, all participants will be given condoms and asked to use them along with the gel before sex.

- How easy or difficult do you think it would be to use both gel and condoms?
- Can you imagine circumstances when a participant might only use condoms – but not the gel?
- Are there circumstances when she might use just the gel, but not condoms?
- When might she not be able to use either gel or condom?

Women who participate in the study will receive free gel and condoms, free HIV tests, free treatment for any sexually transmitted diseases or any health problems that might arise from using the gel. They will also receive some money to reimburse them for their time and travel costs.

- What parts of the trial would make you want to participate? What parts would make you not want to participate? Why?
- You would be requested to return to the DIST or the Clinic Aliou Diop once a month for follow-up. How easy or difficult would it be to come to one of these clinics on a monthly basis?
- If you missed a visit, the clinic staff would need to contact you. How could they best get in touch with you? Do you have any concerns about being contacted in your home or place of work? Can you suggest other ways for the staff to follow up women?
- What do you think would be a woman's reaction if she became HIV+ during the trial? What would she expect from the clinical trial staff? Do you think she might blame the trial? How could this be avoided?

Clinical Trial Recruitment

Women must have certain characteristics in order to participate in this study. For example, they must be sexually active- having sex at least three times per week - and have had at least three different male partners in the last three months.

- What should researchers do in order to recruit women who meet these criteria? Where should they go to recruit them?
- How will women react to being asked about their sexual practices?

Women should not have anal intercourse while participating in the research.

- What do you think about this requirement?
- How common is this kind of sex in Cotonou?

In addition, women should not douche with anything except water while in the study. Also, they should not insert anything else in the vagina except the gel.

- How common is it for women to douche?
- What other things do women insert in their vaginas to enhance sexual pleasure?

Before we finish today, what questions do you have about the microbicide or about the research? (Once you have addressed any of the participants' questions, thank them and reimburse them for their transportation.)

Opinion Leader Guide

I'd like to start by asking you some general questions about research.

Knowledge and Perceptions related to Previous Research

- What does the word "research" mean to you?
- Are you familiar with any research that has been conducted in or around Cotonou in the past? What kind of study was it? (If the participant doesn't describe a clinical trial or drug test, as specifically about clinical trial.)
- Are you aware of any reactions – either positive or negative – from different community groups about this research? What types of reactions arose? From which groups (media, NGOs, etc.)?

General Attitudes towards CS Study

Earlier I said that a new product was going to be tested to find out whether it prevented HIV transmission. This study is going to happen in six different countries. In Cotonou, researchers hope to recruit 300 women who are HIV-negative. About half of the women will be given the new product to use and half will get the other product – the one that doesn't have any microbicide ingredient in it. Both of the products will look alike. They will be asked to use the gel every time before they have sex. Because we do not know whether the microbicide gel actually works, women will also be counseled to use condoms along with the gel every time they have sex. They will be asked to participate in the study for 12 months. During that time, they will need to come for monthly check-ups to make sure they are doing well, and to give them more gel and condoms. They will be tested for HIV (once every three months?) During the study, some women will probably become HIV-positive. Researchers will compare HIV rates differ between the two groups to find out whether the microbicide gel works.

- In general, what is your reaction to the study I just described?
- How much of a problem is HIV/AIDS considered to be in this area?
- What is the general level of interest in microbicides (or new HIV prevention methods, or a woman-controlled HIV-prevention method)?
- What specific concerns do you have about the trial?
    - For example, what is your reaction to the fact that some women will receive a product with a microbicide ingredient, while others will receive a similar product without the microbicide?
    - What other concerns do you have?
    - How should these best be addressed?
- What stakeholder groups will be concerned with this trial and its results? Which groups will be supportive and which may not? Why? Any suggestions for dealing with this?
- How should trial information be shared with various stakeholder groups? When, and in what form?
- What sort of things does the research team need to address/do before, during and after the trial to ensure community support?

Recruitment
Women must have certain characteristics in order to participate in this study. For example, they must be HIV-negative, sexually active- having sex at least three times per week - and have had at least three different male partners in the last three months.

- How common are the sexual behaviors that I have described?
- What kinds of women might be willing to participate in trial? What might prevent them?
- Would women with multiple partners be considered sex workers in this community?
- How are sex workers thought of in this area? Stigmatization?
- How do we recruit high risk women without stigmatizing them as sex workers and/or possibly HIV+?
- What form of recruitment would work best – group meetings? Written literature (what kind? What languages?)? Person to person?
- Who should actually conduct the recruitment? (Does sex matter? Need to be already known within the community?)
- What information should be included in the recruitment messages? Anything that we should avoid? Why?
- *Women will receive an HIV test, before joining the trial. If she is found to be HIV-positive, she will be referred to a government health facility for treatment and care. She will not be able to join the study, however.* What kinds of provisions do you think should be made in such cases? What HIV/AIDS facilities are available in and around Cotonou?

Retention
Women who participate in the study will receive free gel and condoms, free HIV tests, free treatment for any sexually transmitted diseases or any health problems that might arise from using the gel. They will also receive some money to reimburse them for their time and travel costs.

- How appropriate do you feel these reimbursements are?
- What would be the women's motivations for staying in/completing the trial?
- What factors might account cause a woman to withdraw before completing the study? How can these be addressed?
- Logistics – how far will women be willing to travel to trial sites? How often? What form of transportation? What should be done in terms of reimbursing for transportation (ok to do after the fact?) Any stigma associated with going to these sites?
- What might make adherence to trial protocol, in terms of consistent microbicide and condom use, difficult?
- How much of a problem might the selling or sharing of trial products (microbicides, condoms) be? How can this be addressed?

Provision of Care

- Could participating in the trial potentially expose the women to any violence or other negative ramifications (from their partners, madames, other SWs, etc.). Please explain. How can we address this?
- What services are available for victims of partner violence? What is their reputation? How can they be accessed? Will women actually use these services?
- What might be other opinions with regard to provision of healthcare during and after the trial? What has been done in the past?
- What healthcare are participants likely to expect during and after the trial?
- What type of care and support should the trial provide for women who seroconvert during the trial? For how long? Is this likely to be a contentious issue? Please discuss.
- Are anti-retroviral therapies available to HIV-positive people in this area? How can people obtain ARTs? What is the cost – through government programs or in pharmacies? If access to ART is limited, how should this influence the trials policies in terms of women who either screen as HIV-positive or seroconvert during the trial? How will this influence the community's attitudes towards the trial?

Topics and Activities: CT Staff Interactions

Review of Enrollment Log (on a weekly basis BSS staff will review the enrollment log and identify missed visits)

- Generate list of participant IDs who missed their scheduled visit during the previous week.
- Identify patterns among participants who have missed visits. (Is this their first missed visit? Do they always come late for visits? Do they come to visits with other participants?)
- Work with CT to plan missed visit contacts for within a few days of the missed visit. (When should they go, who should go?)
- Generate list participant IDs who are scheduled for a visit in the upcoming week.
- Flag any participant IDs due for a visit who have been irregular in the past and decide if they should receive reminder phone calls or visits.

Review of Screening Logs: yes; see site-specific protocol

Missed Visit Follow-up Topics

BSS staff note: Please be very responsive to the participant and in following-up on her comments. The topic guide was designed to be very open-ended, to allow the BSS staff room to probe and develop a rich understanding of the woman's reasons for missing study visits and/or discontinuing the study. Explain to the participant that we are trying to make sure that study participants have a chance to ask any questions or tell us any concerns they have related to the trial, and that we also want to understand what might make it difficult to attend all the study visits.

Specific missed visit
Based on our records, you missed a clinic visit scheduled for (date). I/we wanted to talk to you about your reasons for missing this visit.

- What were the main reasons that you missed this visit?
  - How often does this type of problem(s) occur?
  - What can we do to help?
  - Probe for other factors that play into the stated reason for missed visit (*ex: she says she couldn't get off work; more probing could reveal that she hasn't told her boss about her research participation b/c of associated stigma*)

- Are there any other things that have made it difficult to visit the clinic as scheduled?
  - *Some possibilities; not an inclusive list; listen to the woman and follow-up on clues she gives you.*
    - *Factors mentioned by other participants (learned from meetings with CT staff)*
    - *Unsatisfactory interactions/treatment with clinic/study staff*
    - *Want/expect more money*
    - *Can make more money doing something else in that time*
    - *Change in home life/marital status since starting study*
    - *Change in job since starting study*
    - *Childcare*
    - *Illness (own or family)*
    - *Unplanned travel*
    - *Transportation*
    - *Not allowed to by others/can't tell others (family, job)*
    - *Rumors about the gel or study*
    - *Stigma of HIV research participation*
    - *Inconsistent gel or condom use → ashamed or thought will be found out*

- If not first missed visit, ask about similarities and differences between reasons for missed visits.

Overall study experience (*includes the travel, time spent, interaction with staff, community/family/peer reactions, etc.*)

- How different from what expected?
- What parts liked, or thought were good?
- What parts difficult, or caused problems?
- Feelings about the study gel (*how did it feel, easy/difficult, side effects, etc.*)

Study continuation plans

- Plans for continuing in study
- If decided not to return: Main reason decided to stop? Anything study could do to help?
  If returning: When plan to return? What might stop you from returning?
- Plans to travel in the next xx months?

Anything else you would like to tell us?

Community Stakeholders
On-Going Meetings

Note: This question guide would be used during formal meetings with community groups.

Review Clinical Trial Progress

Note: At the beginning of the meeting, provide the group with an update of how the clinical trial is proceeding in that site and, when possible, overall. You may review the following types of information:

- Total numbers of people recruited into the trial
- Any issues with retention
- Trial efforts to ensure quality informed consent
- Other aspects of the protocol

Community Awareness of Trial

- Have you heard people in the community talking about the trial? What specifically have you heard?
  - Probe for both positive and negative issues; rumors.
  - (If any concerns or negative rumors) What do you think we can do to address these concerns/rumors?

- Have you heard people from community based organizations, like yourself, talk about the trial? What specifically have you heard?
  - Probe for both positive and negative issues; rumors.
  - (If any concerns or negative rumors) What do you think we can do to address these concerns/rumors?

- Have you seen/heard any mention of the clinical trial in the media such as on the TV, radio, in the newspaper or on the internet? (For each item, probe to find out the specifics such as names of TV or radio shows, name of newspapers, specific information mentioned.)

Issues to Discuss if Recruitment Becomes an Issue –

Describe current recruitment sites. Describe recruitment problem(s). Describe study population (i.e. an overview of eligibility requirements). Then probe:

- What might prevent women from these sites from joining the study?
- Where are other sites/settings in which we could recruit?

Issues to Discuss if Retention Becomes an Issue –

Describe overall study procedures in terms of study visits and overall procedures participants are asked to follow (i.e. use assigned gel and condoms each time they have sex). Describe retention problem(s). Then probe (in addition to probe specifically on the problem):

- What do you think would be reasons that women in your community would not be able to keep their monthly visits? What could the study do to help these participants?

- What would be the women's overall motivations for staying in and completing the trial?
- What factors might account cause a woman to withdraw before completing the study? How can these be addressed?

Interviews with Women Screened Out of the Clinical Trial
About Accessing Referral Sites

Recently, you were screened for a new clinical research study at [name of local study clinic]. The purpose of the study is to test a new kind of vaginal gel to find out if it can prevent HIV and some sexually transmitted infections among women who use it. Because of your HIV-status, you were unable to participate in the clinical research. However, the clinic staff gave you some information about places to obtain treatment for HIV.

I would like to talk with you today about your experiences seeking treatment and care for HIV. We believe this information is very important to the clinical research I just described. That is because other women will also learn they have HIV during screening. In addition, some of the women who participate in this study may develop HIV during the trial. We would like to refer women who are unable to participate or who get HIV during the trial to the best program available. I/we are working with [name of organization] and Family Health International in the United States. *(May need to answer the participant's questions about the research – or perhaps can defer until after the interview.)*

1. After learning you could not participate in the clinical trial, where were you referred for HIV treatment?
   - Did you go to the referral center for care? Why or why not?
   - If not, are you currently obtaining treatment and care for your HIV?
   - If so, where did you go? Why did you choose to go there instead?

2. *(if obtaining care somewhere)* Tell me about your experiences accessing care at this site.
   - How long have you been obtaining HIV services t/here?
   - Who, if anyone, helped you get to the first visit? Do you still receive assistance from this person/group? (NGO or personal contact etc) How important is their assistance in obtaining care t/here?
   - How easy or difficult have you found it to obtain HIV services t/here?

3. In addition to the services you just spoke about, have you obtained any other kinds of treatment or care for your HIV?
   - Where else (or from who else) have you sought treatment?
   - *(If applicable)* What were your earlier experiences with HIV treatment/care? Why did you stop receiving services there?
   - *(If applicable)* What additional services are you obtaining currently?

4. I would like to talk to you in greater detail about the range of services you receive through *(current or most relevant in terms of CT referral)* site.
   - Are you currently receiving medical treatment/ART at this site?

- What are all the other kinds of services do you receive? *(OB/GYN or FP services, HIV or other counseling etc.)*
- How often are you asked to visit the site for a check-up or to obtain a re-supply of HIV or other medication?
- How much time do you typically have to wait at the clinic to obtain *(explore the different kinds of services that they listed – of if all obtained during single visit)* care at this clinic?
- What, if anything, are you asked to pay for services or medicines?
- Who (which staff members) do you meet with when you come for a clinic visit?
- In your opinion, how knowledgeable do they appear to be about their work? *(If more than one staff member, ask about each separately.)*
- How do you feel you're treated by the staff? *(If more than one type of staff person mentioned, ask about each separately.)*
- How satisfied are you with the amount of time they spend with you? Their willingness to answer your questions?
- How well do you feel that staff members protect your privacy?

5. Now I'd like to hear your thoughts about the facility/building and how services are organized.
   - What do you think about the location of this site?
   - How easy or difficult is it to come during the scheduled clinic hours?
   - What is your opinion about the cleanliness of exam rooms? What about the comfort and/or cleanliness of the waiting room *(if one available)*?
   - How well do you feel that staff members practice hygienic practices during exams?
   - Are toilet facilities available for patient use? How well are they maintained? Are they adequate for the number of patients at the clinic?
   - Are there any other aspects of the facilities you'd like to discuss?

6. In a more general way, what have been the biggest challenges you have faced in obtaining treatment and care?

Discussion Guide for Clinical Trial Staff

As you know, the CONRAD phase III microbicide clinical trial has been halted here, as well as all the other sites in which it was being conducted. The BSS team would like to talk with staff involved in the trial, as well as former participants and the larger community in order to document their opinions and concerns about the trials closure in order to ensure that everyone understands this decision. We would also like to explore with you the information or rumors being circulated within the community or among former participants about the study's closure.

During our meeting today, some questions may occur to you. Don't hesitate to ask any questions you might have about this research. As I mentioned before reading the informed consent document, everything we discuss today will remain confidential. Your name will not be included in any notes that we take. Also, you are not obligated to answer any questions. We will not discuss your comments or questions with others. Likewise, we also ask that you maintain the confidentiality of your colleagues' comments or questions.

I. Perception of the Microbicide Clinical Trial

1. Before the announcement of the study's halt, what were your thoughts about the clinical trial here in (name of site)? Please explain.

2. Before this announcement, what were your thoughts about microbicides in general as a potential method for prevention HIV transmission?
   - What expectations did you have about the CS gel?
   - In what ways, if any, have your opinions about microbicides changed since termination of the trial?

3. What do you understand about the reasons that the study was stopped? Please explain all that you have heard or understand about the study's closure.
   - How did you learn about the closure?
   - When did you learn about it?
   - Do you think the study's closure was justified? Why or why not?
   - Do you see any positive effects emerging from the study's closure? Please explain.
   - Do you see any negative effects emerging from the closure? Please explain.

4. What effects has the closure had on:
   - clinic activities?
   - participants?
   - the community?

5. What suggestions do you have for managing the closure of a trial if such a situation occurs again?

HIV Prevention Research

6. What would be your reactions if another HIV prevention clinical trial was announced to begin here in (site name)?
   - What would be the reactions of the community?
   - What about participants' reactions?

7. What obstacles would a new HIV prevention trial face in terms of recruiting participants?
   - Other than recruitment issues, what other kinds of obstacles would a new HIV prevention trial face?
   - What should be done to overcome these obstacles?

……..

Thank you for sharing your time and ideas with us today.

In-depth Interview with Former Trial Participants

As you know, the CONRAD phase III microbicide clinical trial has been halted here, as well as all the other sites in which it was being conducted. The BSS team would like to talk with staff involved in the trial, as well as former participants and the larger community in order to document their opinions and concerns about the trial closure in order to ensure that everyone understands this decision. We would also like to explore with you the information or rumors being circulated within the community or among former participants about the study's closure.

During our meeting today, some questions may occur to you. Don't hesitate to ask any questions you might have about this research. As I mentioned before reading the informed consent document, everything we discuss today will remain confidential. Your name will not be included in any notes that we take. Also, you are not obligated to answer any questions. We will not discuss your comments or questions with others.

Now, if you agree, we would like to begin asking you questions.

I. Perception/Knowledge of the microbicide clinical trial

1. Before the announcement of the study's halt, how did you feel about participating in the clinical trial here in (name of site)? Please explain *(probe both about positive thoughts and negative thoughts)*.

2. What do you understand about the reasons that the study was stopped? Please explain all that you have heard or understand about the study's closure.
   - Do you think that the study closure was justified? Why or why not?
   - Do you see any positive effects from the study closure? Please explain.
   - Do you see any negative effects from the study closure? Please explain.

3. What effects has the study closure had on the participants? What can the study staff do to address these?
   - What effects has the study closure had on the community? What can the study staff do to address these?

4. What have you heard from media, such as television, radio, newspapers, or Internet, concerning the study closure?

5. Have you heard rumors about the study closure? Please explain.
   - How did you hear about these rumors?
   - In which populations are these rumors circulating?
   - What was done to handle these rumors?
   - In your opinion, what should be done to handle these rumors?

II. Experience in Clinical Trial Participation

Now let us talk about your experiences using the study gel.

6. What is your overall impression of the gel? *(probe about the likes and dislikes)*
7. How often did you use the gel during the trial? *(probe: with ever sex act, once a day, etc)*
   - When were you not able to use the gel? What made it difficult?
     - Insertion (including applicator and privacy)
     - Timing
     - Type of sexual behavior
   - Was it easier to use the gel with some partners than with others? Which ones? Why?

8. How did the amount of gel in the applicator affect the way you used it?
   - How often were you able to use the entire applicator of gel?
   - In which circumstances were you able to use only part of an applicator of gel?
   - Did you ever put the gel in another container?

9. Please tell me about your condom use during the trial.
   - How often were you able to use condoms and gel at the same time/
   - When were you not able to use a condom during the trial?
   - When you were not able to use condoms, how often were you able to use the gel by itself?
   - Were there times that you could not use a condom or the gel? Please explain.
   - In your opinion, which method seemed easier to use – vaginal gel or condom? Why?

10. How do you feel about the fact that some women received a gel with the active substance (microbicide) and some women received a gel without the active substance (placebo)?
    - What expectations did you have about the gel you were assigned? Why?

11. Some women have told us that they could figure out which type of gel (placebo or microbicide) they were given. Do you think participants could figure out the type of gel they were given?
    - Did you try to guess? How? If yes, what do you think you were given? Why? *(probe about color of gel or of packaging, consistency, smell)*
    - How did this affect your behavior in the trial? *(probe; used gel or condom more or less frequently)*

12. Have you heard of any instances when participants shared or traded their gels during the study? Please explain.

13. Given the early termination of this study, we are asking women to return all of their study gels. How do you feel about that?

- How willingly do you think former participants will return their study gels? For what reasons would they not want to return their gel?
- Have you heard of any women stockpiling gels to use as a lubricant after the study?

14. In general, how do women in your community feel about the use of vaginal lubricants – as opposed to vaginal gels used to prevent HIV transmission?
    - How common is the use of vaginal lubricants in your community? (users, brands, supplies, price, availability)
    - In your opinion, what need is there for lubricants in your community? Please explain.
    - Would women buy lubricant if it were available at an affordable price?

III. HIV prevention research

15. The CS study was one of several HIV prevention studies currently in process or in development in the world. The research activity called a "clinical trial" isn't very well known in (country name). Before your own participation in a trial, had you heard of clinical trials?
    - What is your opinion about clinical trial research now?
    - Based on your experience, would you want to participate in another study? Why or why not?

16. What obstacles would a new HIV prevention trial face in terms of recruiting women to participate?

Do you have any questions to ask?

Thank you very much for giving your time to participate in this interview today.

Discussions with Community Members

As you know, the CONRAD phase III microbicide clinical trial has been halted here, as well as all the other sites in which it was being conducted. The BSS team would like to talk with the larger community, as well as former participants and staff involved in the trial in order to document their opinions and concerns about the trials closure in order to ensure that everyone understands this decision. We would also like to explore with you the information or rumors being circulated with the community or among former participants about the study's closure.

During our meeting today, some questions may occur to you. Don't hesitate to ask any questions you might have about this research. As I mentioned before reading the informed consent document, everything we discuss today will remain confidential. Your name will not be included in any notes that we take. Also, you are not obligated to answer any questions. We will not discuss your comments or questions with others. *(If conducted in a group setting, ask that they maintain the confidentiality of their colleagues' comments or questions.)*

Now, if you agree, we would like to begin asking you questions.

I. Perception of the microbicide clinical trial

1. Have you heard about the HIV prevention microbicide study that took place in (site name)?
    - Please explain everything you know about the microbicide study that took place in (site name).

2. Before the announcement of the study's halt, what were your thoughts about the clinical trial here in (name of site)? Please explain. *(probe both about positive and negative thoughts)*
    - What did leaders of local associations think of the study? Please explain.
    - What did the participants think about the study? Please explain.
    - And the community in general? What did you hear in the community about this study?

3. Now I would like to talk about reactions to and effects of the study closure. What do you understand about the reasons that the study was stopped? Please explain all that you have heard or understand about the study's closure.
    - What other thoughts do you have about the trial closure?

The interviewer may explain the reason for the closure [Approved explanation to be inserted]

- Do you think that the study closure was justified? Why or why not?
- Do you see any positive effects from the study closure? Please explain.
- Do you see any negative effects from the study closure? Please explain.

4. What effects has the study closure had:
    - on the community?

- on the participants?
- What can the study staff do to address these?

5. Have any participants called on you to explain to them the reasons for the study closure?
    - If yes, how did you handle this situation?
    - What would you suggest to communicate these reasons to the participants?
    - To the community?

6. What have you heard from media, such as television, radio, newspapers, or Internet, concerning the study closure?
    - Have you heard rumors about the study closure? Please explain.
    - How did you hear about these rumors?
    - In which populations are these rumors circulating?
    - What was done to handle these rumors?
    - In your opinion, what should be done to handle these rumors?

II. HIV prevention research

The CS study was one of several HIV prevention studies currently in process or in development in the world. The research activity called a "clinical trial" isn't very well known in (country name). Clinical trials in HIV prevention may look at microbicides or other methods such as vaccines and oral medication.

7. In general, how do women in your community feel about the use of vaginal lubricants – as opposed to vaginal gels used to prevent HIV transmission?
    - How common is the use of vaginal lubricants in your community? (users, brands, supplies, price, availability)
    - In your opinion, what need is there for lubricants in your community? Please explain.
    - Would women buy lubricant if it were available at an affordable price?

8. What would be your reaction if another HIV prevention clinical trial were announced in (site name)?
    - What would be the reaction of HIV prevention associations?
    - What would be the reaction of the community?
    - What would be the reaction of former participants to a new trial?

9. Would you like to be involved in such a study? Explain.

10. What obstacles would a new HIV prevention trial face in terms of recruiting women to participate?
    - Other than recruitment issues, what other kinds of obstacles would a new HIV prevention trial face?
    - What can be done to overcome these obstacles?

Do you have any questions to ask?

Discussions with Community Members
Burkina Faso

As you know, the CONRAD phase III microbicide clinical trial has been halted here, as well as all the other sites in which it was being conducted. The BSS team would like to talk with the larger community, as well as former participants and staff involved in the trial in order to document their opinions and concerns about the trials closure in order to ensure that everyone understands this decision. We would also like to explore with you the information or rumors being circulated with the community or among former participants about the study's closure.

During our meeting today, some questions may occur to you. Don't hesitate to ask any questions you might have about this research. As I mentioned before reading the informed consent document, everything we discuss today will remain confidential. Your name will not be included in any notes that we take. Also, you are not obligated to answer any questions. We will not discuss your comments or questions with others. *(If conducted in a group setting, ask that they maintain the confidentiality of their colleagues' comments or questions.)*

Now, if you agree, we would like to begin asking you questions.

I. Perception of the microbicide clinical trial

7. Have you heard about the HIV prevention microbicide study that took place in (site name)?
    - Please explain everything you know about the microbicide study that took place in (site name).

8. Before the announcement of the study's halt, what were your thoughts about the clinical trial here in (name of site)? Please explain. *(probe both about positive and negative thoughts)*
    - What did leaders of local associations think of the study? Please explain.
    - What did the participants think about the study? Please explain.
    - And the community in general? What did you hear in the community about this study?

9. Now I would like to talk about reactions to and effects of the study closure. What do you understand about the reasons that the study was stopped? Please explain all that you have heard or understand about the study's closure.
    - What other thoughts do you have about the trial closure?

The interviewer may explain the reason for the closure

[As I mentioned earlier, the goal of the CONRAD Cellulose Sulfate clinical trial was to find out whether CS gel was effective in protecting women from HIV infection. In order for this kind of HIV prevention study to find out whether a study

gel is effectiveness, the people who participate in the trial must be HIV negative but at high risk of getting HIV. After having selected Bobo Dioulassa as one of the trial sites, it was determined that the level of HIV in this community was not high enough to help the study answer its question about whether the CS gel is effective. For this reason, researchers decided not to conduct the study in Burkina Faso, but to add sites in South Africa and Zimbabwe.]

- Do you think that the study closure was justified in Burkina? Why or why not?
- Do you see any positive effects from the study closure? Please explain.
- Do you see any negative effects from the study closure? Please explain.

10. What effects has the study closure had:
    - on the community?
    - on the participants?
    - What can the study staff do to address these?

11. Have any participants called on you to explain to them the reasons for the study closure?
    - If yes, how did you handle this situation?
    - What would you suggest to communicate these reasons to the participants?
    - To the community?

12. What have you heard from media, such as television, radio, newspapers, or Internet, concerning the study closure?
    - Have you heard rumors about the study closure? Please explain.
    - How did you hear about these rumors?
    - In which populations are these rumors circulating?
    - What was done to handle these rumors?
    - In your opinion, what should be done to handle these rumors?

II. Need for Lubricants

7. In general, how do women in your community feel about the use of vaginal lubricants – as opposed to vaginal gels used to prevent HIV transmission?
    - How common is the use of vaginal lubricants in your community? (users, brands, supplies, price, availability)
    - In your opinion, what need is there for lubricants in your community? Please explain.
    - Would women buy lubricant if it were available at an affordable price?

III. HIV prevention research

The CS study was one of several HIV prevention studies currently in process or in development in the world. The research activity called a "clinical trial" isn't very well

known in (country name). Clinical trials in HIV prevention may look at microbicides or other methods such as vaccines and oral medication.

8. In general, how do women in your community feel about the use of vaginal lubricants – as opposed to vaginal gels used to prevent HIV transmission?
    - How common is the use of vaginal lubricants in your community? (users, brands, supplies, price, availability)
    - In your opinion, what need is there for lubricants in your community? Please explain.
    - Would women buy lubricant if it were available at an affordable price?

9. What would be your reaction if another HIV prevention clinical trial were announced in (site name)?
    - What would be the reaction of HIV prevention associations?
    - What would be the reaction of the community?
    - What would be the reaction of former participants to a new trial?

10. Would you like to be involved in such a study? Explain.

11. What obstacles would a new HIV prevention trial face in terms of recruiting women to participate?
    - Other than recruitment issues, what other kinds of obstacles would a new HIV prevention trial face?
    - What can be done to overcome these obstacles?

Do you have any questions to ask?

Thank you for giving your time to participate in this interview today.


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Family Health
International