

**SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:**

**HPTN 035
DAIDS Document ID 11065**

**Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides
BufferGel and 0.5% PRO 2000/5 Gel (P)
for the Prevention of HIV Infection in Women
Version 2.0 / 2 August 2006**

**THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 3.0 / 12 December 2006**

IND # 62,366

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the HPTN 035 study and must be forwarded to your Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as soon as possible for their information and review. IRB/EC approval is required before implementation of the modifications contained in this amendment.

Issuance of this amendment requires preparation of updated study informed consent forms for the Phase IIb portion of the study. These forms must be used when obtaining informed consent for screening, enrollment, and/or specimen storage after obtaining IRB/EC approval of the amendment and completing protocol registration procedures with the DAIDS Protocol Registration Office. This amendment does not impact previously enrolled study participants; therefore re-consenting of previously enrolled participants is not required as a result of this amendment, unless directed by site IRBs/ECs. All IRB/EC requirements must be followed.

Please file this Summary of Changes, Version 3.0 of the protocol, corresponding site-specific informed consent forms, and all associated IRB/EC correspondence in your essential document files for HPTN 035.

Summary of Revisions

This amendment incorporates two previously approved protocol Letters of Amendment as well as the following additional protocol revisions:

- Updates of the Protocol Team Roster
 - Updates of the study design and timeline to reflect completion of the Phase II portion of the study and ongoing implementation of the Phase IIb portion of the study
 - Modification of the number of Phase IIb participants enrolled at the US site
 - Modification of product use management specification vis-à-vis Pap smear results
 - Modification of adverse event reporting requirements in the Phase IIb portion of the study
 - Other minor editorial and typographical updates and corrections
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Rationale

Throughout the amended protocol (Version 3.0), the description of the study design and timeline have been updated to reflect completion of the Phase II portion of the study and ongoing implementation of the Phase IIb portion of the study.

Eight hundred women were enrolled in Phase II portion of the study, distributed across study sites as follows:

- | | |
|--------------------------------|-----|
| • Blantyre, Malawi | 57 |
| • Chitungwiza-Harare, Zimbabwe | 51 |
| • Durban, South Africa | 194 |
| • Hlabisa, South Africa | 173 |
| • Lilongwe, Malawi | 225 |
| • Philadelphia, PA, USA | 100 |

All Phase II participants from Chitungwiza-Harare and Philadelphia, as well as the first 84 participants enrolled in Durban and the first 66 participants enrolled in Lilongwe comprise the “colposcopy subset” of the Phase II population. These 301 participants underwent colposcopy at screening and at each of their first three monthly follow-up visits.

The first Phase II enrollment took place in February 2005 and the last took place in April 2006. Phase II participants completed three monthly follow-up visits for assessment of Phase II endpoints; the last Phase II follow-up visit was completed in July 2006. Since that time, the Phase II data have been cleaned, analyzed, and reviewed by the DAIDS Vaccine and Prevention Data and Safety Monitoring Board (DSMB). Accrual and follow-up in the Phase IIb portion of the study are ongoing.

Throughout the amended protocol, the total number of participants planned to be enrolled at the US study site has been updated to 200. Upon completion of the Phase II portion of the study, the Protocol Team utilized available Phase II data to re-evaluate the US sample size and determined that 200 participants would provide adequate statistical power to detect clinically meaningful differences in the rates of primary safety endpoints observed among US participants. For example, the sample size of 200 provides greater than 80 percent power to detect three-fold (and larger) differences in the rate of deep epithelial disruption observed on pelvic exam. Based on this re-evaluation, the Protocol Team has determined that a US sample size of 200 is most appropriate to meet the study objectives.

With regard to product use management, the protocol has been updated to reflect clinical practice at sites performing Pap smears, which typically proscribes sexual activity and use of vaginal products beginning not more than 48 hours prior to clinical evaluation and/or treatment of high grade Pap smear results. The protocol previously required product hold immediately upon identification of a high grade Pap smear result; the updates in the amended protocol continue to adequately protect participant safety while also harmonizing protocol requirements with standard clinical practice and maximizing opportunities for adherence to product use.

With regard to adverse event (AE) reporting, the protocol has been updated to limit reporting in the Phase IIb portion of the study to the following:

- All genital, genitourinary, and reproductive system AEs
- All serious AEs
- All AEs of severity grade 3 or higher
- All AEs that result in permanent discontinuation of study product use
- All laboratory test abnormalities not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited reporting requirements

This modification was endorsed by the DAIDS Vaccine and Prevention DSMB following their review of all available Phase II and Phase IIb data in October 2006. The DSMB acknowledged that, at the rate of AE reporting observed through the data cut-off for their review, under prior protocol specifications, over 34,000 AEs would be expected to be reported over the course of HPTN 035. The DSMB also acknowledged that a significant proportion of AEs reported to date had been reported in body systems that are not likely affected by the study products. Taking these observations into account, and given that no safety issues or concerns were evident when AE data were evaluated by treatment group, the DSMB agreed that limiting AE reporting in the Phase IIb portion of the study would appropriately focus ongoing safety reporting and monitoring on those AEs most likely to be associated with the study products and with greatest potential impact on the overall health and well being of study participants.

Implementation

This amendment is official HPTN 035 protocol documentation. Prior to implementing the revisions listed below, HPTN 035 study sites will submit this Summary of Changes, protocol Version 3.0, and updated site-specific informed consent forms to all relevant regulatory authorities and IRBs/ECs. The Division of AIDS Regulatory Affairs Branch will submit this amendment to the United States Food and Drug Administration for inclusion in Investigational New Drug (IND) application #62,366.

Upon receipt of all required regulatory and IRB/EC approvals and completion of protocol registration procedures, the protocol modifications listed below will be implemented. Detailed modifications of the protocol text are indicated by ~~striketrough~~ (for deletions) and **bold** (for additions).

Detailed Listing of Revisions

1. Throughout the amended protocol, the protocol version number and version date are updated to FINAL Version 3.0 and 12 December 2006, respectively. The table of contents is updated to reflect current document pagination.
2. Throughout the amended protocol, verb tenses have been updated to reflect the current status of study implementation. Past tense verbs are used when describing the completed Phase II portion of the study and present and future tense verbs are used when describing ongoing implementation of the Phase IIb portion of the study.
3. The revisions contained in prior Letter of Amendment #1 (dated 14 January 2005) and Letter of Amendment #2 (dated 3 November 2005) have been incorporated into the amended protocol. Because these revisions have been detailed in previous official protocol documentation, they are not also detailed in this Summary of Changes, with one exception. The one exception is contained in item 20 below, in which the revisions specified in item 8 of Letter of Amendment #1 are shown for purposes of clearly identifying prior and current revisions of protocol Section 6.2. Reference copies of the Letters of Amendment are available at the following url:

http://www.hptn.org/research_studies/HPTN035StudyDocuments.htm#Protocol.

4. The Protocol Team Roster has been updated to include the current contact details of current team members from all participating study sites and organizations.
5. On the investigator signature page, first paragraph, fourth sentence: If no marketing application is **to be** filed, or if the application is not approved, the records must be retained ~~for~~ **until** two years after the **investigation is discontinued and** FDA is notified ~~that the IND is discontinued~~.

6. In accordance with the detailed text modifications listed below, the Schema, Figures 2 and 3, and Appendix I are updated to reflect a total study sample size of approximately 3100 participants (2900 non-US and 200 US). The Schema and Appendix I also are updated to reflect a study accrual period of approximately 30 months and an overall study duration of 42 months.
7. In Section 1.1, first paragraph: The Joint United Nations Programme on HIV/AIDS (UNAIDS) has estimated that ~~37.8~~ **38.6** million adults and children were living with HIV/AIDS at the end of ~~2003~~ **2005**, and that ~~over 13,000~~ **4.1** million new infections occurred ~~each day in 2003~~ **2005 alone** [1].
8. In Section 2.3.1, fourth and fifth paragraphs: The Phase II portion of the study ~~will be~~ **was** conducted among 800 women — 100 from the US and ~~ideally 100~~ **700** from ~~each of the non-US sites. For each site, accrual will begin after all applicable approvals are obtained and a site-specific study activation notice is issued by the HPTN Coordinating and Operations Center (CORE; see also Section 10.1). Depending on the timing of activation across sites, it is possible that some sites will not take part in the Phase II portion of the study. Activated sites will accrue Phase II participants until a total of 800 (100 US and 700 non-US) are enrolled (see also Section 7.1). For non-US sites, accrual of Phase II participants will be capped at a maximum of 350 per site, to ensure adequate cross-site representation in the Phase II data. At all sites, Phase II participants will completed three monthly follow-up assessments for Phase II study endpoints. For planning purposes, as shown in Appendix I, it is assumed that accrual for the Phase II portion of the study will require approximately six months. The Phase II data then were compiled for review by the DAIDS Vaccine and Prevention DSMB.~~

~~Within two months of completing Phase II follow-up, the Phase II data will be compiled for review by the DAIDS Vaccine and Prevention DSMB. In addition, if enrollment in the Phase II portion of the study takes longer than expected, an interim analysis of all available safety data will be compiled for DSMB review no more than 12 months after study initiation. The DSMB routinely meets approximately every four months and will review the Phase II data at its first meeting after the data have been compiled and analyzed. Statistical considerations for the Phase II portion of the study are presented in Section 7.3.1.~~

9. In Section 2.3.1, sixth paragraph: Concurrent with ~~the follow-up in portion of the Phase II~~ **portion of the** study and the time required to complete the Phase II data analyses and DSMB review, accrual of Phase IIb participants ~~will begin~~ and follow-up of ~~the Phase II all~~ participants for Phase IIb study endpoints ~~will continued~~. That is, accrual ~~will continued~~ uninterrupted during the transition from the Phase II portion of the study into the Phase IIb portion. However, prior to the **Phase II** DSMB review, accrual into the Phase IIb portion of the study ~~will be~~ **was** capped at a maximum of 20 US and 175 non-US participants per month. As described in detail in Section 7.1, this approach of a Phase II “lead-in” to the Phase IIb study ~~provided~~ **s** for continuity of study operations at the study sites while also allowing a thorough review of safety data among target populations prior to full-scale exposure of study participants to the investigational study products.

10. In Section 2.3.1, seventh and eighth paragraphs (now combined): ~~Assuming a favorable DSMB review of the Phase II data, a~~ **Accrual into the Phase IIb portion of the study will continue for approximately nine additional months following the Phase II DSMB review, such that approximately 3220 3100 participants total will be enrolled over approximately 48 30 months total. Follow-up of enrolled participants will continue until a total of 192 incident HIV infections are observed in the study, or for a maximum of 30 months for each participant, whichever occurs first. Based on the participant accrual rate, retention rate, and HIV seroincidence rate assumed for sample size determination (see Section 7.3.2), the targeted number of incident infections is expected to be reached approximately 12 months after the date upon which the last participant enrolls in the study. Thus it is expected that participants will be followed for a minimum of 12 months and a maximum of 30 months, depending on when they enroll in the study and when the targeted number of infections is reached. Additional statistical considerations for the Phase IIb portion of the study are presented in Section 7.3.2.**
11. In Section 2.3.2, first paragraph: Study visits and procedures are nearly identical for Phase II and Phase IIb study participants, with the exception that Phase II participants ~~will undergo~~ **underwent** additional safety evaluations — including pelvic exams and laboratory testing — during each of the first three months of their study participation (see Appendices II and III). In addition, all US Phase II participants (n=100) and ~~at least the first 150~~ **201** Phase II participants ~~enrolled across selected non-US sites will undergo~~ **from Chitungwiza-Harare, Durban, and Lilongwe underwent** colposcopic examination as part of their pelvic exams during each of their first three months in the study. ~~In contributing participants to the colposcopy subset, non-US sites may perform colposcopic exams either among a subset of their Phase II participants or among all of their Phase II participants.~~
12. In Section 2.3.2, fifth paragraph, second sentence: Colposcopic evaluations also ~~will be~~ **were** performed for the 100 US Phase II participants and ~~at least the first 150~~ **for 201 non-US** Phase II participants ~~enrolled across selected non-US sites~~, in accordance with the CONRAD/WHO Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004.
13. In Section 2.3.2, sixth paragraph, fourth sentence: HSV-2 testing will be performed on specimens obtained at enrollment and at study exit, however since information on HSV-2 serostatus is not required for clinical management, this testing will be performed in batches ~~in the final year at the end of the study implementation at each site.~~
14. In Section 3, first paragraph, first sentence: The study will include approximately ~~3220~~ **3100** sexually active women from the study sites listed in the Schema and in Section 2.3.1.
15. In Section 3, second paragraph, first and second (added) sentence: ~~Ideally 415~~ **Approximately 300-800** women will be enrolled at each of the non-US sites. ~~and 320~~ **Two hundred** women will be enrolled at the US site.

16. In Section 3.3, fourth paragraph, third sentence: Those who test negative will undergo a physical exam and pelvic exam with pH assessment, assessment for homogenous discharge, and wet mount testing for BV, candidiasis, and trichomoniasis; colposcopy will be **additionally was** performed for ~~at least the first 250~~ **301 Phase II** participants enrolled at selected sites.
17. In Section 4.6, third paragraph: ~~Participants at selected sites performing Pap smears will be discontinued from product use if they are found to have a high grade squamous intraepithelial lesion or more severe abnormality, however such participants may resume product use after treatment and resolution of the abnormality. For participants at sites where local standards of care require clinical colposcopy and biopsy to assess lower grade abnormalities, product use will be discontinued during the three week period beginning one week before the required procedure and ending two weeks after the required procedure (assuming no further intervention or treatment is needed). If further intervention or treatment is needed, the period of product discontinuation will be extended until after treatment and resolution of the abnormality.~~ **At selected sites performing Pap smears, product use will be held for participants who are found to have a high-grade squamous intraepithelial lesion or more severe abnormality; product use also may be held in response to lower grade abnormalities, if local standards of care require clinical colposcopy and/or biopsy to assess lower grade abnormalities. In all cases, the period of product hold will begin on the day of the clinical evaluation, biopsy, and/or treatment of the abnormality. Alternatively, the hold may be initiated one to two days prior to the day of clinical evaluation, biopsy, and/or treatment, if per local standards of care the participant is advised to avoid sexual intercourse on these days. The period of product hold will continue for a minimum of two weeks after biopsy and/or treatment of the abnormality. Study staff will obtain medical records documenting the evaluation, biopsy, and/or treatment of the abnormality and, assuming adequate treatment is confirmed, will perform a pelvic exam at least two weeks after the evaluation/biopsy/treatment date to confirm healing of the cervix. Thereafter, assuming no contraindications are identified on pelvic exam, product use will be resumed.**
18. In Sections 5.3.3 and 5.4.3, italicized notes below plasma archive: HSV-2 testing will be performed on plasma archived at enrollment and at study exit in batches ~~during the final year~~ **at the end of the study implementation at each site.**

19. In Section 6.1, second and third paragraphs (now combined): ~~As noted in Section 2, and described more fully in Section 7, the DAIDS Vaccine and Prevention DSMB will complete a formal review of the Phase II study data and will continue to monitor participant safety throughout the Phase IIb portion of the study. after the 800 Phase II participants have completed three months of product use and follow-up. In addition, if enrollment in the Phase II portion of the study takes longer than expected, an interim analysis of all available safety data will be prepared for DSMB review no more than 12 months after study initiation. Based on the results of that (these) review(s), the DSMB will advise as to whether the Phase IIb portion of the study should proceed as designed, should proceed with design modifications, or should be discontinued. Assuming continuation of the Phase IIb study, the DSMB will conduct interim reviews of study progress, including rates of participant accrual, retention, and HIV incidence, and product safety. The DSMB routinely meets approximately every four months, and it is expected that reviews will take place approximately every eight months. At the time of these reviews, or at any other time, the DSMB may recommend that the Phase IIb portion of the study proceed as designed, proceed with design modifications, or be discontinued. Formal comparisons of HIV incidence across treatment groups will be made only at final analysis.~~ **has reviewed** of the Phase II study data **and will continue to monitor participant safety throughout the Phase IIb portion of the study.** ~~after the 800 Phase II participants have completed three months of product use and follow-up. In addition, if enrollment in the Phase II portion of the study takes longer than expected, an interim analysis of all available safety data will be prepared for DSMB review no more than 12 months after study initiation. Based on the results of that (these) review(s), the DSMB will advise as to whether the Phase IIb portion of the study should proceed as designed, should proceed with design modifications, or should be discontinued. Assuming continuation of the Phase IIb study, the DSMB will conduct interim reviews of study progress, including rates of participant accrual, retention, and HIV incidence, and product safety. The DSMB routinely meets approximately every four months, and it is expected that reviews will take place approximately every eight months. At the time of these reviews, or at any other time, the DSMB may recommend that the Phase IIb portion of the study proceed as designed, proceed with design modifications, or be discontinued. Formal comparisons of HIV incidence across treatment groups will be made only at final analysis.~~
20. In Section 6.2, third paragraph: ~~Study site staff will document on case report forms in source documents all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. Study staff also will report on case report forms the following subset of AEs reported by or observed in enrolled participants:~~ **source documents** all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. **Study staff also will report on case report forms the following subset of AEs reported by or observed in enrolled participants:**
- **All genital, genitourinary, and reproductive system AEs**
 - **All serious AEs, as defined by the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice**
 - **All AEs of severity grade 3 or higher**
 - **All AEs that result in permanent discontinuation of study product use**
 - **All laboratory test abnormalities not otherwise associated with a reported clinical AE**
 - **AEs that do not meet the above-listed criteria but do meet expedited reporting requirements per Section 6.3 below**

For HPTN 035, Version 3.0, dated 12 December 2006, all AEs except vulvovaginitis and cervicitis will be graded using the DAIDS Table for Grading Adult and Pediatric Adverse Events (also referred to as the “Toxicity Table;” dated December 2004) which is available at the following web site: <http://rcc.tech-res-intl.com>. Vulvovaginitis and cervicitis will be graded as follows:

	Vulvovaginitis	Cervicitis
Grade 1	Vulvar and/or vaginal discomfort (including itching or burning), pelvic exam findings indicative of inflammation, and/or other exam findings* (including findings involving epithelial disruption) that do not require medical therapy and that cause no or minimal interference with usual social and functional activities	Cervical inflammation or other findings on exam (including erythema, mucopurulent discharge, and/or friability) that do not require medical therapy and that cause no or minimal interference with usual social and functional activities
Grade 2	Vulvar and/or vaginal discomfort (including itching or burning), pelvic exam findings indicative of inflammation, and/or other exam findings* (including findings involving epithelial disruption) that require minimal medical therapy (such as a course of topical or oral antibiotics or antifungals) or cause greater than minimal interference with usual social and functional activities	Cervical inflammation or other findings on exam (including erythema, mucopurulent discharge, and/or friability) that require minimal medical therapy (such as a course of oral antibiotics) or that cause greater than minimal interference with usual social and functional activities
Grade 3	Vulvar and/or vaginal discomfort (including itching or burning), pelvic exam findings indicative of inflammation, and/or other exam findings* (including findings involving epithelial disruption) that result in inability to perform usual social and functional activities and/or require significant medical intervention such as a surgical procedure or hospitalization	Cervicitis or other findings on exam (including erythema, mucopurulent discharge, and/or friability) that require significant medical intervention (such as intravenous antibiotics) or that cause inability to perform usual social and functional activities
Grade 4	Life threatening — vulvovaginitis with perforation	Life threatening

*Findings include erythema, edema, grossly white finding, petechiae, ecchymosis, peeling, ulceration, abrasion, laceration.

The investigator or designee will assess the relationship of all AEs **reported on case report forms** to the study product based on the Manual for Expedited Reporting of Adverse Events to DAIDS (**dated 6 May 2004**), the Investigator's Brochures, and his/her clinical judgment. The expedited reporting manual is provided in Appendix VI. ~~The Toxicity Table is available at the following web sites:~~

http://www.hptn.org/network_information/regulatory_resources.htm

<http://rec.tech-res-intl.com>

21. In Section 7.1, first paragraph: As noted in Section 1.3, the design of this study follows several of the current recommendations of the International Working Group on Microbicides. In particular, a multi-site Phase II study among 800 participants will “lead in” to the Phase IIb study which will include the Phase II study participants plus approximately ~~2420~~ **2300** additional women. By capping, rather than stopping, enrollment during the transition between Phase II and Phase IIb, continuity of study operations is maintained without exposing more women than necessary to the candidate microbicide products. **Monthly accrual rates during the first 19 months of study implementation ranged from 2 to 33 at the US site (average = 10.7) and from 10 to 114 across non-US sites (average 63.7).** Specifically, with a cap at the accrual rates ~~As shown in Appendix I, (10 US participants and 70 non-US participants in Month 1, 15 US participants and 105 non-US participants in Month 2, etc) and three months of Phase II follow-up, plus two additional months for Phase II data cleaning, analysis, and DSMB review, approximately 372~~ **385** women ~~will be~~ **were** exposed to each candidate microbicide prior to the ~~data cut-off for the Phase II DSMB safety review. This includes (including~~ the 200 Phase II participants assigned to each of these products). These ~~745~~ **770** participants constitute ~~less than~~ half of the total number of participants planned to be exposed to a candidate microbicide during the full Phase II/IIb study.

22. In Section 7.3.1, first (added), second, and third paragraphs: **Participants are assigned at random to the four study treatment groups in a 1:1:1:1 ratio.**

A total of 800 women (700 non-US and 100 US) ~~will be~~ **were** enrolled in the Phase II portion of the study over a ~~period of approximately six~~ **15** months, ~~and each woman will be~~ **Each of these women was** followed monthly for three months in the Phase II portion of the study. Thus, the total duration of the Phase II portion is ~~was~~ approximately ~~nine~~ **18** months, ~~and~~ **47.5 person-years (p-y) of follow-up were accumulated in each treatment group.** ~~After completing~~ **Having completed** their three months of Phase II follow-up, Phase II participants will complete ~~up to~~ another ~~24-27~~ months of follow-up for the Phase IIb portion of the study.

~~Participants will be assigned at random to the four study treatment groups in a 1:1:1:1 ratio. Assuming a five percent significance level for a two-sided test (i.e., a 2.5 percent false-positive error rate) and five percent loss to follow-up over the Phase II study period, 47.5 person-years (p-y) of follow-up will be accumulated in each treatment group during the Phase II portion of the study.~~

23. In Section 7.3.2, first paragraph: The Phase IIb study will enroll a total of approximately ~~3220~~ **3100** women, with enrollment ending approximately nine months after the DSMB review of the Phase II data, resulting in a total enrollment period of approximately ~~18~~ **30** months for the Phase II/IIb study.

24. In Section 7.3.2, second paragraph: The US site will enroll a ~~total of 320~~ **200** women. Non-US sites are expected to enroll ~~at least 200~~ **approximately 300-800** women each, ~~and ideally will enroll approximately 415 women each,~~ to achieve the total non-US sample size of approximately 2900.

25. In Section 7.3.2, third paragraph, first sentence: Approximately every three months during the accrual period, and/or additionally at the recommendation of **Protocol Team members**, the HPTN SMC, or **the DSMB**, the Protocol Team will review performance data from each study site — including accrual rates, retention rates, protocol adherence measures, data quality measures, and HIV incidence rates — to determine whether enrollment slots should be shifted across sites to achieve the study objectives most efficiently and to determine when to discontinue accrual.
26. In Section 7.6, third paragraph: **Three DSMB reviews of study safety data will have been conducted to date. Additional reviews are expected to take place after the Phase II portion of the study is completed, and approximately every eight months during the Phase IIb portion of the study. If enrollment into the Phase II portion of the study takes longer than expected, an interim analysis of all available safety data will be compiled for DSMB review no more than 12 months after study initiation. O'Brien-Fleming methods for interim analyses will be used in this case.** In addition to safety data presentations, analyses will be performed for these reviews to assess the assumptions used to determine sample size (i.e., accrual, retention, and HIV incidence rates at each site) and alterations will be made to the overall sample size if recommended by the DSMB.
27. In Section 8.1, first paragraph: This protocol and the template informed consent forms contained in Appendices VII-XIII ~~—and any subsequent modifications—~~ **will be** reviewed and approved by the HPTN Protocol Review Committee and DAIDS Prevention Science Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations. **When required by HPTN and DAIDS policies, these committees also will review and approve subsequent protocol modifications.**
28. In Section 8.2, third paragraph: In addition to the informed consent forms, Protocol Team members ~~will have worked~~ **will have worked** with study staff and community representatives to develop locally-appropriate information materials about the study and a standardized approach to the informed consent process to be implemented at all study sites, **which is detailed in the study-specific procedures manual.** ~~Written educational materials as well as other more innovative approaches will be considered.~~ The process and materials ~~will be~~ **were** pilot tested prior to study start-up to ensure cultural appropriateness at each site.
29. In Section 8.2, fifth paragraph: The informed consent process ~~will~~ **includes** an assessment of each potential participant's understanding prior to enrollment and randomization of concepts identified by the Protocol Team as essential to the informed consent decision. ~~Based on input from study site staff and community representatives, this assessment may take the form of a self-administered "quiz," interviewer-administered instrument (qualitative and/or quantitative) or other method. Regardless of method, p~~ **Participants** who are not able to demonstrate adequate understanding of key concepts after exhaustive educational efforts will not be enrolled in the study. For quality assurance purposes, similar assessments of participant understanding will be undertaken among a sub-sample of participants ~~throughout the accrual period~~ **during** follow-up; results will be used to provide feedback and recommendations to the Protocol Team and relevant study site staff to optimize the informed consent process.

30. In Section 8.5.1, first paragraph, second sentence: Counseling ~~will be~~ **is** provided in accordance with a standard **HIV counseling policies and methods at each site and additionally** ~~study counseling manual, and will~~ emphasizes the unknown efficacy of the candidate microbicides in preventing HIV infection.
31. In Section 8.8, second sentence: Site-specific reimbursement amounts ~~will be specified in the local study informed consent forms and~~ **must be** approved by all responsible IRBs/ECs.
32. In Section 10.1, first paragraph, first sentence: Following IRB/EC review and approval, study sites will submit required administrative documentation — ~~as listed in the study-specific procedures manual~~ — to the HPTN CORE.
33. In Section 10.1, second paragraph, first sentence: Pending successful protocol registration, ~~and~~ submission of all other required study activation documents, **and DAIDS approval**, HPTN CORE staff will “activate” the site to begin study operations.
34. In Section 10.2, second paragraph: Study implementation ~~will be~~ **is** directed by this protocol as well as a common study-specific procedures manual. This manual — which ~~will~~ contains reference copies of the protocol, DAIDS SOPs for Source Documentation and Essential Documents, and DAIDS Toxicity Tables — ~~will~~ outlines procedures for conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. The manual ~~will be available upon request to the FDA, other government and regulatory authorities, and site IRBs/ECs~~ **is available at the following web site:**
- http://www.hptn.org/research_studies/HPTN035StudyDocuments.htm#SSP**
35. In Section 10.5, third sentence: If no marketing application is **to be** filed, or if the application is not approved, the records must be retained ~~for~~ **until** two years after the **investigation is discontinued and** FDA is notified ~~that the IND is discontinued~~.
36. In Section 11, Reference 1: Joint United Nations Programme on HIV/AIDS (~~July 2004~~ **2006**). ~~2004~~ **2006** Report on the Global AIDS Epidemic: **A UNAIDS 10th Anniversary Special Edition**.
37. In Appendices X, XI, and XII, under Purpose of the Study, third paragraph, second sentence: About ~~3200~~ **3100** women from Africa and the United States will be in the study.