

**LETTER OF AMENDMENT #01 TO:**

**MTN-004  
DAIDS Document ID 10492**

**Phase 1 Study of the Safety and Acceptability of 3% w/w SPL7013 Gel (VivaGel®)  
Applied Vaginally in Sexually Active Young Women**

**Version 3.0 / 30 June 2008**

**IND # 62,482**

**Letter of Amendment Date: 15 May 2009**

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**Information/Instructions to Study Sites from the Division of AIDS**

The information contained in this Letter of Amendment (LoA) impacts the MTN-004 study and must be forwarded to your Institutional Review Board (IRB) and/or Ethics Committee (EC) as soon as possible for their information and review. IRB/EC approval is required before implementation of the revisions contained in this LoA.

The following information will also impact the sample informed consent. Site IRB/ECs are responsible for assessing whether and how the changes included in this LoA are to be communicated to study participants. All IRB/EC requirements must be followed.

Please file this LoA and all associated IRB/EC correspondence in your essential documents files for MTN-004.

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**Summary of Revisions and Rationale**

This LoA adds an additional study site to the MTN-004 protocol. This LoA also clarifies language regarding specimen collection and archive in the Enrollment and Storage and Future Testing of Specimens Sample Informed Consent documents. Changes previously noted in CM # 02, dated October 3, 2007, and CM #03, dated September 3, 2008, are also included in this LoA.

Changes to the Protocol Team Roster are also noted here.

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**Implementation**

This LoA is official MTN-004 protocol documentation. Prior to implementing the revisions listed below, the MTN-004 study sites will submit this LoA to all relevant regulatory authorities and the IRB/EC. Starpharma Pty Ltd, will submit this LoA to the United States Food and Drug Administration for inclusion in Investigational New Drug (IND) application # 62,482. Upon receipt of all required regulatory and IRB/EC approvals, the protocol revisions listed below will be implemented.

With the exception of modifications to the Protocol Team Roster, detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** for additions.

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## Detailed Listing of Revisions

### 1. **The Protocol Team Roster is updated to reflect updates to the study team.**

*The following protocol team members have been added to the roster:*

**Beatrice Chen, MD, MPH**

**Site Investigator**

Magee-Womens Hospital (MWH) of UPMC  
300 Halket Street, Suite 5414  
Pittsburgh, PA 15213  
(412) 641-5496  
(412) 641-5214 FAX  
[chenba@upmc.edu](mailto:chenba@upmc.edu)

**Missy Cianciola, MS**

**MTN SDMC Senior Project Manager**

Fred Hutchison Cancer Research Center (FHCRC) SCHARP  
1100 Fairview Avenue North, LE-400  
PO Box 19024  
Seattle, WA 98109-1024 USA  
(206) 667-7290  
(206) 667-4812 FAX  
[missy@scharp.org](mailto:missy@scharp.org)

**Yevgeny Grigoriev, MD, PhD**

**Clinical Affairs Safety Associate**

Fred Hutchison Cancer Research Center (FHCRC) SCHARP  
1100 Fairview Avenue North, LE-400  
PO Box 19024  
Seattle, WA 98109-1024 USA  
(206) 667-3440  
(206) 667-4812 FAX  
[ygrigori@scharp.org](mailto:ygrigori@scharp.org)

*The following protocol team members have updated roster information:*

**Katherine Bunge, MD**

**MTN Safety Physician**

MWH of UPMC  
300 Halket Street  
Pittsburgh, PA 15213  
(412) 917-9936  
(412) 641-6170 FAX  
[kbunge@mail.magee.edu](mailto:kbunge@mail.magee.edu)

**Nancy Connolly, MD**

**MTN Safety Physician**

7006 43rd Avenue, NE  
Seattle, WA 98115 USA  
(206) 523-1177  
(412) 641-6170 FAX  
[nancycsc@gmail.com](mailto:nancycsc@gmail.com)

**Ross D. Cranston MD, FRCP**  
**MTN Safety Physician**  
Division of Infectious Disease, UPMC  
Falk Medical Building, Suite 611  
3601 Fifth Avenue  
Pittsburgh, PA 15213 USA  
(412) 647-4007  
(412) 647-5519 FAX  
[rdc27@pitt.edu](mailto:rdc27@pitt.edu)

**Kailazarid Gomez, MPM**  
**Clinical Research Manager**  
Family Health International  
2224 E NC Highway 54  
Durham, NC 27713  
(919) 544-7040 Ext. 11282  
(919) 544-0207 FAX  
[kqomez@fhi.org](mailto:kqomez@fhi.org)

**Lisa Levy, MPH**  
**Prevention Research Specialist**  
Family Health International  
2224 E. NC Hwy 54  
Durham, NC 27713  
(919) 544-7040 Ext. 11260  
(919) 544-0207 FAX  
[LLevy@fhi.org](mailto:LLevy@fhi.org)

**Lisa Noguchi, CNM, MSN**  
**MTN Director of Operations**  
Microbicide Trials Network  
Magee-Womens Research Institute  
204 Craft Avenue  
Pittsburgh, PA 15213  
(412) 641-8945  
(412) 641-6170 FAX  
[lnoguchi@mail.magee.edu](mailto:lnoguchi@mail.magee.edu)

**Mala Shah, MPH**  
**MTN Protocol Development Manager**  
Microbicide Trials Network  
Magee-Womens Research Institute  
204 Craft Avenue  
Pittsburgh, PA 15213  
(412) 641-3859  
(412) 641-6170 FAX  
[shahms@mail.magee.edu](mailto:shahms@mail.magee.edu)

**Rhonda R. White, RHEd, BS**  
**Community Program Manager**  
Family Health International  
P.O. Box 13950  
Research Triangle Park, NC 27709  
(919) 544-7040 Ext. 11515  
(919) 544-0207 FAX  
[rwhite@fhi.org](mailto:rwhite@fhi.org)

*The following listings are deleted from the Protocol Team Roster: Pat Farrell, Pamina Gorbach, Corey Kelly and Karen Patterson.*

**2. As previously noted in CM #03, Sections 6.2.6, 7.6.3, and 8.3.1 are updated.**

*In Section 6.2.6, Retrieval of Unused Study Products, third and fourth sentences are updated:*

All unused study products must be returned **by the participant** to the site, **placed in a biohazard container** and then **destroyed at the site**. **Unused study product remaining in the pharmacy must be** forwarded to the MTN CORE **pharmacist for destruction** after the study is completed or terminated unless otherwise instructed by the MTN CORE.

*In Section 7.6.3, Enrollment Visit, Table 13: Enrollment Visit, Study Supplies row, is updated to maintain consistency with Version 3.0 of the protocol:*

<b>Study Supplies</b>	<ul style="list-style-type: none"> <li>• Dispense two cartons (20 applicators) of study gel, male condoms and panty liners, and/or pads, <del>and resealable plastic bags</del></li> <li>• Participant to insert first dose in study clinic</li> </ul>
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*In Section 8.3.1, Adverse Events, fourth paragraph, second sentence is deleted and fourth sentence modified to omit AE reporting for male partners:*

Second sentence

~~Participants will be encouraged to report to the study clinician any problems experienced by their male partners that might be potentially related to study product.~~

Fourth sentence

~~Study site staff will document on study CRFs all AEs reported by or observed in enrolled study participants or their partners from the time of their first dose of study gel through the Three-Week Clinic Visit or early termination, regardless of severity and presumed relationship to study gel or applicators.~~

**3. Throughout the protocol, text is updated to reflect the addition of a new study site.**

*In the Schema, participating sites, study design, and study duration are updated:*

Participating Sites:

- University of South Florida, Tampa, Florida
- University of Puerto Rico, San Juan, Puerto Rico
- **Pitt CRS, Pittsburgh, Pennsylvania**

Study Design: Phase 1, three arm, ~~two-three~~ site, randomized, double blind, placebo-controlled trial comparing VivaGel<sup>®</sup>, VivaGel<sup>®</sup> placebo, or HEC placebo gel (HEC Gel) applied vaginally twice daily for 14 days

Study Duration: Approximately 21 days per participant, ~~nine~~ **fourteen** calendar months of accrual, and ~~ten~~ **fifteen** months total planned study duration

*In Section 1.4, Study Investigators is updated:*

Site Investigator: Beatrice Chen, MD MPH  
Site Investigator  
Magee-Womens Hospital of UPMC  
300 Halket Street, Suite 5414  
Pittsburgh, PA 15213 USA

*In Section 4.1, Identification of Study Design, first and last sentences are updated:*

MTN-004 is a ~~two~~**three** site, Phase I, double blind, randomized, controlled comparison with 14 days of twice daily exposure to VivaGel<sup>®</sup>, VivaGel<sup>®</sup> placebo, or HEC gel, and follow-up among HIV-uninfected sexually active women. Participants in all three arms will receive male condom counseling and free male condoms on an ongoing basis. The study will be conducted at ~~two~~**three** sites: University of South Florida, ~~and~~ University of Puerto Rico, **and the Pitt CRS.**

*In Section 4.4, Time to Complete Enrollment is updated:*

The approximate time to complete study enrollment is expected to be ~~nine~~**fourteen** months.

*In Section 4.6, Sequence and Duration of Trial Periods, Table 9, Projected Sequence and Duration of Trial Periods for MTN-004, Version 3.0, is updated:*

Enrollment Period	Follow-Up Period	Total Duration
<del>9</del> <b>14</b> months	1 month	<del>10</del> <b>5</b> months

*In Section 4.8, Sites, the number of participating sites is updated:*

~~Two~~**Three** study sites are planned for this trial: University of South Florida, ~~and~~ University of Puerto Rico, **and Pitt CRS.**

*In Section 5.1, Selection of the Study Population, second paragraph, second and third sentences are updated:*

Participants will be recruited from a variety of venues. There are ~~two~~**three** sites: University of South Florida, ~~and~~ University of Puerto Rico, **and Pitt CRS.** ~~Each site will enroll approximately 30 participants.~~ **A total of approximately 61 participants will be enrolled among the three sites.** Additional participants may be enrolled if non-adherent participants need to be replaced. ~~or if enrollment “slots” need to be shifted from one site to another.~~

*In Section 5.1.2, Recruitment, first and third sentences are updated:*

Members of the research teams at ~~both~~**all** study sites will recruit women from various clinical sites at which they are providing direct patient care to potential study participants. Study staff will contact volunteers from previous research studies if those participants have previously signed an authorization permitting this type of contact. Site IRB-approved media advertisements, telephone scripts, and fliers will be used. These materials will be

presented and discussed with the community advisory boards at ~~both~~**all** sites before submission to the local IRBs. Written informed consent will be obtained prior to the initiation of any study-related procedures.

*In Section 6.4.4, Required Medications and Procedures, second paragraph, Male Condoms subsection, first sentence is updated:*

~~Both~~**S**tudy site pharmacies will be provided with a single brand of lubricated male condoms by MTN CORE to distribute to participants in quantities expected to be sufficient according to study-specific procedures when study product is dispensed.

*In Section 6.4.4, Required Medications and Procedures, third paragraph, Panty Liners and Pads subsection, first sentence is updated:*

~~Both~~**S**tudy site pharmacies will be provided with single brands of panty liners and pads by the MTN CORE to distribute to participants in quantities expected by the participant to be sufficient when study product is dispensed.

*Section 7.4.3.1 Quality Control and Quality Assurance Procedures is updated:*

Network Laboratory staff will conduct visits as needed to ~~both~~**all** sites to assess the implementation of on-site laboratory quality control procedures, including the proper maintenance of laboratory testing equipment, etc.

*In Section 7.7, Colposcopy, first sentence is updated:*

Experienced staff at ~~both~~**all three** sites will conduct colposcopic examinations of the study participants. In addition, an MTN Safety Physician will provide specialized training in colposcopy for the evaluation of vaginal products.

*In Section 8.1, Safety Monitoring, first sentence is updated:*

A sub-group of the Protocol Team, including the MTN Safety Physicians, the MTN PI, MTN-004 Protocol Chair, MTN Protocol Specialist, Statistical Data Management Center (SDMC) Clinical Affairs Research Nurse, SDMC Project Manager, ~~both~~**all** Site PIs, FHI Protocol Coordinator, DAIDS and NICHD Medical Officers, and DAIDS Clinical Operations Study Coordinator, will serve as the Protocol Safety Review Team (PSRT).

*In Section 8.3.1, Adverse Events, first paragraph, third sentence is updated:*

This definition will be applied to ~~both~~**all** treatment arms.

*Section 10.1, Overview and General Design, is updated:*

This is a ~~two~~**three** site, Phase I, double blind, randomized, controlled comparison with 14 days of twice daily exposure to VivaGel<sup>®</sup>, VivaGel<sup>®</sup> placebo, or HEC gel, and follow-up among HIV-uninfected sexually active women.

*In Section 10.9, Participant Accrual and Follow-Up, fourth sentence is updated:*

Accrual is anticipated to take approximately 9-14 months. Monthly accrual targets will be available in the SSP.

**4. Throughout the protocol, text is updated for applicability to MTN sites, in addition to ATN sites.**

*Section 1.2, Sponsor and Monitor Identification, is updated to reflect PPD as the monitor for DAIDS sites:*

**Monitor: PPD, Inc.  
929 North Front Street  
Wilmington, NC 28401-3331 USA**

*In Section 12, Clinical Site Monitoring, first paragraph is updated to reflect PPD as the monitor for DAIDS sites:*

Study monitoring **for the Tampa and San Juan sites** will be carried out by Westat (Rockville, MD), **and by PPD, for the Pitt CRS**. On-site study monitoring will be performed in accordance with DAIDS policies. Site monitoring visits will be conducted to assess compliance with Health and Human Services (HHS) Regulations 45 CFR Part 46 and 21 CFR Parts 50, 56, and 312. Study monitors will visit the site to:

*In Section 13.5, Participant Confidentiality, first paragraph, first and second sentences, and second paragraph, first and second sentences are updated:*

Members of the study staff **at all sites** are ~~all~~ trained in patient confidentiality for their participation in ~~the ATN~~**MTN-004**. ~~The only sites at which this study will be performed are both ATN Trials Units (ATU).~~ The log of study participant names and other protected health information will be kept in a double-locked area. All computer information about study volunteers will be kept on a computer with log-on passwords. Laboratory specimens are labeled with study numbers and date, and are delivered or shipped by study staff. The study sites' data management and clinical staff are the only personnel with access to the protected health information of study volunteers. Each member of the staff has log-on identification and password, logs off before leaving a computer screen unattended, and closes their office door when out of the office. All research records will be kept indefinitely following closure of this study.

To further protect the privacy of the study participants, the ATN has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). **The MTN has also obtained a Certificate of Confidentiality which applies to MTN sites.** With this Certificate in place, ~~the ATN~~ researchers cannot be forced to turn over identifying information about a study participant in any Federal, State, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a study participant from volunteering to turn over their research information nor does it prevent researchers from providing research-related information to others when requested by the study participant.

Section 13.2, Protocol Registration is updated to reflect protocol registration for the Pitt CRS.

A subheading is added to the original language in Section 13.2 to clarify the separate protocol registration procedures for the University of South Florida and the University of Puerto Rico:

### **Protocol Registration for the University of South Florida and the University of Puerto Rico**

The text for protocol registration for the University of South Florida and the University of Puerto Rico remains unchanged.

A separate protocol registration subsection is added for Pitt CRS:

#### **Protocol Registration for Pitt CRS**

The study site will complete protocol registration with the DAIDS RCC Protocol Registration Office. For additional information, refer to the protocol registration documents located at <http://rcc.tech-res.com/forms.htm>. Protocol registration must occur as a condition for site-specific study activation; no participants may be screened or enrolled in this study prior to obtaining protocol registration approval and completing all other study activation requirements. MTN CORE (FHI) staff will notify the study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued.

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chairs and the NIAID Medical Officer and NICHD Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s) and the RCC prior to implementing the amendment.

5. The Sample Informed Consent documents are updated to reflect changes to the study sites, anticipated duration of the study, clarify language related to the collection and long-term storage of plasma archive specimens, and to include modifications previously made in CM #02, dated October 3, 2007.

The following changes have been made to Appendix V: Sample Informed Consent document (Screening):

In the Why Are These Screening Exams and Tests Being Done? subsection, fourth paragraph, second, third, and fourth sentences are updated:

A total of approximately 61 women from Florida, ~~and Puerto Rico,~~ **and Pennsylvania** will join this study (~~about 30 in Florida, and about 30 in Puerto Rico~~). ~~About 30 women will be in the study here at [INSERT NAME OF SITE].~~ The whole study will take about ~~ten~~ **fifteen** months to finish.

*The following changes have been made to Appendix VI: Sample Informed Consent document (Enrollment):*

*In the Why is this Study Being Done? subsection, fifth paragraph, second, third, and fourth sentences are updated:*

A total of 61 women from Florida, ~~and Puerto Rico,~~ **and Pennsylvania** will join this study (about 30 in Florida, ~~and about 30 in Puerto Rico~~). ~~About 30 women will be in the study here at [INSERT NAME OF SITE].~~ The whole study will take about ~~ten~~ **fifteen** months to finish.

*In the What Do I Have To Do If I Am In This Study? Enrollment subsection, the second bullet is updated:*

- Give blood for tests to check on the health of your blood cells, liver, and kidneys and to confirm that there is no SPL7013 already in your blood (about 30 mL or about 2 tablespoons). **If you consent to the long-term storage of specimens, a portion of this blood sample will be stored for potential future testing.**

*As previously noted in CM #02, Telephone Call subsection, the first sentence is modified:*

Two **to four** days after you have your Enrollment Visit, you will have a phone call with study staff to talk about any problems you might have with the gel applicator.

*As previously noted in CM #02, One-Week Clinic Visit subsection, the sixth bullet is omitted:*

- ~~Complete a computerized questionnaire about your use of the study gel.~~

*In the How Many Women Will Take Part in this Study? subsection, the second sentence is updated:*

**Approximately** 61 women will take part in this study. ~~About 30 women will be from Florida, and about 30 women will be from Puerto Rico.~~

*In Appendix VII: Sample Informed Consent Document (Storage and Future Testing of Specimens), How Will You Get The Samples From Me? subsection is modified:*

The research doctors want to **collect and** save ~~any extra~~ blood and cervical fluid ~~leftover from your tests~~ during the study. This ~~leftover~~ blood and cervical fluid **(including any leftover specimens)** will be kept and used for future research.