LETTER OF AMENDMENT #01 TO:

MTN-015
DAIDS Document ID: 10529

An Observational Cohort Study of Women following HIV-1 Seroconversion in Microbicide Trials

Version 1.0 / 19 June 2007

Letter of Amendment Date: September 16, 2010

Instructions to Study Sites from the Division of AIDS

The following information impacts the MTN-015 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation.

The following information will also impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should implement the LoA immediately. Sites are still required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. An LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

Summary of Revisions and Rationale

This LoA does not impact the overall design and study visit schedule for MTN-015. In addition to incorporating the five previously issued Clarification Memos, this LoA includes the following items:

1. Updates to the protocol to indicate that HIV resistance results will not routinely be provided to study clinicians or participants. Resistance results will be provided to study clinicians upon request. The *Sample Informed Consent (Screening and Enrollment)* document is also updated to reflect that resistance results will not be provided to participants as soon as they become available

2. Updates to Section 8, *Assessment of Safety*, to reflect the revised Manual for Expedited Reporting of Adverse Events to DAIDS (dated January 2010)

3. Updates to Section 13.2, *Protocol Registration and Study Activation,* to reflect new DAIDS Protocol Registration template language

4. Updates to the Protocol Team Roster

5. Updates to the *List of Abbreviations and Acronyms*

Implementation

This LoA is official MTN-015 protocol documentation. Prior to implementing the revisions listed below, the MTN-015 study sites will submit this LoA to all relevant regulatory authorities and the IRB/EC. Upon receipt of all required regulatory and IRB/EC approvals, the protocol revisions listed below will be implemented. With the exception of protocol roster changes, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions Included in Clarification Memo #01, Dated 03 April 2008

1. The following new listings have been added to the Protocol Team Roster:

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2. The following listing has been updated in the Protocol Team Roster:

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3. In Section 7.2 Follow-Up Visits, the 1st and 2nd bullets and the last paragraph have been modified to further clarify the schedule of follow-up visits.

1st Bullet, last sentence: Following the **Screening and** ~~e~~**E**nrollment visit, ~~the~~ subsequent **follow-up** visits will be scheduled according to the seroconversion date. ~~(~~**F**or example, a participant who enrolls ~~4~~ **3** months after seroconversion would **miss her Month 1 and Month 3 Post-Seroconversion Visits, and would complete her Month 6 Post-Seroconversion Visit as her first follow-up visit. She would** ~~have a second visit at 6 months after seroconversion (2 months after enrollment) and~~ then **complete follow-up visits** every 6 months~~)~~ **thereafter.**

2nd Bullet, end of paragraph: **For example, a participant who enrolls 3 months after initiation of ART would miss her Week 2, Month 1, Month 3 post-ART follow-up visits and would complete her Month 6 post-ART visit as her first follow-up visit. She would then complete follow-up visits every 6 months thereafter.**

Last paragraph, 3rd sentence: For example, the Month 24 visit window ~~extends from Month 21 through Month 27~~ **begins mid-way between the Month 18 and Month 24 target dates and ends mid-way between the Month 24 and Month 30 target dates.**

4. Throughout the protocol, all references to PBMC have been modified to indicate that these will be collected at sites with capacity.

5. In Section 7.5.1 Local Laboratory Specimens, the section on Blood Samples now includes further guidance on HSV-2 serology.

~~Study site staff will collect blood samples for the following testing at the local laboratory:~~ **The following blood tests will be performed locally:** CD4+ T-cell counts, plasma HIV-1 RNA, complete blood count **(see Appendix VI)**, liver and renal function tests **(see Appendix VI)**, and syphilis serology. **Blood also will be processed for plasma archive. PBMCs will also be archived at sites with capacity.**

At sites designated and certified by the MTN NL, HSV-2 serology may be performed locally. If the participant has a documented positive result from a parent study, testing does not need to be repeated for MTN-015. If the participant has a documented negative result from the parent study which is performed after the participant is enrolled in MTN-015, this result will be used for MTN-015.

6. Section 13.4, last paragraph is omitted to permit site specific approaches to the informed consent process.

~~In addition to the informed consent forms, Protocol Team members 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. The process and materials were tested prior to study start-up to ensure cultural appropriateness at each site. The informed consent process covers all elements of informed consent required by research regulations. In addition, the process specifically addresses the following topics of import to this study:~~

- ~~The importance of adherence to the study visit and procedures schedule.~~
- ~~The potential risks of study participation (and what to do if such risks are experienced).~~
- ~~The potential social harms associated with study participation (and what to do if such harms are experienced).~~
- ~~The real yet limited benefits of study participation.~~
- ~~The distinction between research and clinical care.~~
- ~~The right to withdraw from the study at any time.~~

7. Section 13.5 Participant Confidentiality, second paragraph is modified to permit site-specific approaches to confidential storage of study documents.

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. Data collection, process, and administrative forms, laboratory specimens, and other reports will be identified by a coded number only to maintain participant confidentiality. ~~All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number.~~ All local databases will be secured with password-protected access systems. ~~Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an~~

~~area with limited access.~~ Participants' study information will not be released without their written permission, except as necessary for monitoring (see Section 12).

Appendix II: Sites and Site Investigators and Appendix III: Site Laboratories have been updated to accurately reflect the current list of sites, site investigators, and site laboratories. The following has been added to each appendix:
A current list of sites, site investigators, and site laboratories will be available on the MTN website: www.mtnstopshiv.org.

Detailed Listing of Revisions Included in Clarification Memo #02, Dated 21 August 2008

1. The Protocol Team Roster is modified to reflect current Protocol Team members and contact information.

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2. The list of Site Investigators (Appendix II) is removed from the protocol and replaced with content directing the reader to the MTN website for an up-to-date list.

APPENDIX II: SITES AND SITE INVESTIGATORS

For a current list of Site Investigators please go to http://www.mtnstopshiv.org/.

- ~~Lisa Maslankowski, University of Pennsylvania, Philadelphia, Pennsylvania, USA~~
- ~~Bonus Makanani and Newton Kumwenda, Queen Elizabeth Central Hospital, Blantyre, Malawi~~
- ~~Francis Martinson, Lilongwe Central Hospital, Lilongwe, Malawi~~
- ~~Muzala Kapina, Kamwala Health Centre, Lusaka, Zambia~~

- ~~Mike Chirenje, and Tsitsi Magure, University of Zimbabwe Obstetrics and Gynaecology Research Clinic at Spilhaus Zimbabwe~~

- ~~Mike Chirenje and Tsitsi Magure, Seke South Clinic (Chitungwiza), Chitungwiza, Zimbabwe~~

- ~~Gita Ramjee, Medical Research Council-Hlabisa, Hlabisa, South Africa~~

- ~~Gita Ramjee, R.K. Khan Hospital, Chatsworth, South Africa~~

- ~~Smita N. Joshi, Jehangir Hospital - NARI Clinic, Pune, India~~

- ~~Craig Hoesley, University of Alabama at Birmingham, Birmingham, Alabama, USA~~

- ~~Jessica Justman, Bronx-Lebanon Hospital Center, New York, New York, USA~~

- ~~Sharon A. Riddler, University of Pittsburgh, Pittsburgh, Pennsylvania, USA~~

- ~~Michael Lederman, Case Western Reserve University, Cleveland, Ohio, USA~~

- ~~Laura Guay, Makerere University, Kampala, Uganda~~

- ~~David Coetzee, University of Cape Town, Cape Town, South Africa~~

3. The list of Site Laboratories (Appendix III) is removed from the protocol and replaced with content directing the reader to the MTN website for an up-to-date list.

APPENDIX III: SITE LABORATORIES

For a current list of Site Laboratories please go to http://www.mtnstopshiv.org/.

~~Site Laboratory:~~ ~~National AIDS Research Institute~~
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~~M.I.D.C. Bhosari~~
~~Pune, Maharashtra 411 026~~
~~India~~

~~Site Laboratory:~~ ~~University of Alabama Hospital Lab~~
~~619 South 19th Street~~
~~Birmingham, Alabama 35233-1924~~
~~USA~~

~~Site Laboratory:~~ ~~UAB Div of Infectious Diseases Lab~~
~~THT 220 1900 University Boulevard~~
~~Birmingham, Alabama 35294~~
~~USA~~

~~Site Laboratory:~~ ~~LabCorp~~
~~Raritan Facility~~
~~69 First Avenue~~
~~Raritan, NJ 08869~~
~~USA~~

~~Site Laboratory:~~ ~~CIDRZ Central Laboratory~~
~~Kalingalinga District Clinic~~
~~Off Alick Nkhata Road~~
~~Kalingalinga~~
~~Post Office Box 34681~~
~~Lusaka~~
~~Zambia~~

~~Site Laboratory:~~ ~~Children's Hospital of Philadelphia~~
~~Abramson Research Center 1204K~~
~~34th Street and Civic Center Boulevard~~
~~Philadelphia, PA 19104~~
~~USA~~

~~Site Laboratory:~~ ~~Queen Elizabeth Central Hospital~~
~~P.O. Box 1131~~
~~Chipatala Avenue~~
~~Blantyre, Malawi~~

~~Site Laboratory:~~ ~~Tidziwe Centre~~
~~Lilongwe Central Hospital~~
~~100 Mzimba Road~~
~~Lilongwe, Malawi~~

~~Site Laboratory:~~ ~~UZ-UCSF Collaborative Research Programme in Women's Health~~
~~15 Phillips Avenue~~
~~Harare, Zimbabwe~~

~~Site Laboratory:~~ ~~Lancet~~
~~102 Lancet Medical Centre~~
~~74 Lorne Street~~
~~Durban, South Africa~~

~~Site Laboratory:~~ ~~Lancet (BARC)~~
~~First Floor, Napier House~~
~~Napier Road, Richmond~~
~~Johannesburg, South Africa~~

~~Site Laboratory:~~ ~~Empangeni Garden Hospital~~
~~Suite 8, 1st Floor~~
~~Consulting Blocks~~
~~Corner of Ukula and Biyela Street~~
~~Empangeni, South Africa~~

~~Site Laboratory:~~ ~~Department of Cytology~~
~~Nkosi Albert Luthuli Central Hospital~~
~~800 Bellair Road~~
~~Mayville, 4091 South Africa~~

~~Site Laboratory:~~ ~~MU-JHU Research Collaboration Lab~~
~~IDIL at New Mulago Hospital Complex~~
~~P.O. Box 22418,~~
~~Kampala, Uganda~~

Detailed Listing of Revisions Included in Clarification Memo #03, Dated 20 February 2009

1. The following update is made to the Protocol Team Roster that appeared in MTN-015, CM #02, dated 21 August 2008:

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2. Reference to wet mount is replaced with **testing** in the following tables and sections:

Table 1: Screening and Enrollment Visit, Pelvic Samples.

Pelvic Samples	Vaginal pH ~~Wet Mount~~ **Testing** for bacterial vaginosis (BV), Candida, and Trichomonas †Pap Smear at Selected Sites

Table 2: Month 1 and Month 3 Post-Seroconversion Visits

Pelvic Samples	*Vaginal pH *~~Wet Mount~~ **Testing** for BV, Candida, and Trichomonas */† Pap Smear at Selected Sites

Table 3: Month 6 and Q6 Months Post-Seroconversion Visits

Pelvic Samples	*/**Vaginal pH */**~~Wet Mount~~ **Testing** for BV, Candida and Trichomonas */† Pap Smear at Selected Sites (annually)

*If indicated; */**Urine SDA for Chlamydia and Gonorrhea, Syphilis Serology, Vaginal pH, and ~~Wet Mount~~ **testing for BV, Candida, and Trichomonas** should be performed at visits annually, with performance of these measures at additional scheduled visits as clinically indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

Table 4: Week 2, Month 1, and Month 3 after Initiation of ART

Pelvic Samples	*Vaginal pH *~~Wet Mount~~ **Testing** for BV, Candida, and Trichomonas */† Pap Smear at Selected Sites

Table 5: Month 6 and Q6 Months Visits After Initiation of ART

Pelvic Samples	*/**Vaginal pH */**~~Wet Mount~~ **Testing** for BV, Candida and Trichomonas */† Pap Smear at Selected Sites

*If indicated; */**Urine SDA for Chlamydia and Gonorrhea, Syphilis Serology, Vaginal pH, and ~~Wet Mount~~ **testing for BV, Candida, and Trichomonas** should be performed at visits annually, with performance of these measures at other scheduled visits as clinically indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

Table 6: Final Visit

Pelvic Samples	Vaginal pH ~~Wet Mount~~ **Testing** for BV, Candida and Trichomonas */† Pap Smear at Selected Sites

Section 7.5.1, Local Laboratory Specimens, Pelvic Samples, first paragraph:

Vaginal pH testing and ~~wet mount~~ testing for bacterial vaginosis, candidiasis and trichomoniasis will be conducted at the sites by clinical and/or laboratory staff who have established proficiency in these procedures per MTN policies and procedures.

Appendix I: Schedule of Study Visits and Evaluations

~~Wet Mount~~ **Testing** for BV, Candida, Trichomonas	X	▲	▲	▲ (Annual)	▲	▲ (Annual)	X

Detailed Listing of Revisions Included in Clarification Memo #04, Dated 07 July 2009

1. The following updates are made to the Protocol Team Roster:

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Detailed Listing of Revisions Included in Clarification Memo #05, Dated 02 March 2010

1. The following updates are made to the Protocol Team Roster:

The following individuals have been added to the Protocol Team Roster:

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The following listings have updated contact information:

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The following individual is removed from the Protocol Team Roster: Nancy Connolly

2. The following updates to testing for BV and Candida are included in the following tables. Note that changes to these tables were originally included in MTN-015, CM #03, dated 20 February 2009, and are currently in this section to facilitate comprehension of new modifications:

Table 1: Screening and Enrollment Visit, Pelvic Samples.

Pelvic Samples	Vaginal pH ***Testing for bacterial vaginosis (BV)~~,~~ **and** Candida~~, and Trichomonas~~ **Testing for Trichomonas** †Pap Smear at Selected Sites

*If indicated, **If not previously confirmed in a Network Laboratory, † PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

Table 2: Month 1 and Month 3 Post-Seroconversion Visits

Pelvic Samples	*Vaginal pH *Testing for BV~~,~~ **and** Candida~~, and Trichomonas~~ ***Testing for Trichomonas** */† Pap Smear at Selected Sites

*If indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

Table 3: Month 6 and Q6 Months Post-Seroconversion Visits

Pelvic Samples	*/**Vaginal pH *~~/**~~Testing for BV~~,~~ **and** Candida ~~and Trichomonas~~ ***/** Testing for Trichomonas** */† Pap Smear at Selected Sites (annually)

*If indicated; */**Urine SDA for Chlamydia and Gonorrhea, Syphilis Serology, Vaginal pH, and testing for ~~BV, Candida, and~~ Trichomonas should be performed at visits annually, with performance of these measures at additional scheduled visits as clinically indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

Table 4: Week 2, Month 1, and Month 3 after Initiation of ART

Pelvic Samples	*Vaginal pH *Testing for BV~~,~~ **and** Candida~~, and Trichomonas~~ ***Testing for Trichomonas** */† Pap Smear at Selected Sites

*If indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

Table 5: Month 6 and Q6 Months Visits After Initiation of ART

Pelvic Samples	*/**Vaginal pH *~~/**~~Testing for BV~~,~~ **and** Candida ~~and Trichomonas~~ ***/** Testing for Trichomonas** */† Pap Smear at Selected Sites

*If indicated; */**Urine SDA for Chlamydia and Gonorrhea, Syphilis Serology, Vaginal pH, and testing for ~~BV, Candida, and~~ Trichomonas should be performed at visits annually, with performance of these measures at other scheduled visits as clinically indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

Table 6: Final Visit

Pelvic Samples	Vaginal pH *****Testing for BV~~,~~ **and** Candida ~~and Trichomonas~~ **Testing for Trichomonas** */† Pap Smear at Selected Sites

*If indicated; †PAP smears should be done at 6 month intervals in the first year after seroconversion, and then annually if the initial tests are negative.

Appendix I: Schedule of Study Visits and Evaluations

	Screening and Enrollment	Month 1 Post-Seroconversion	Month 3 Post-Seroconversion	Mo. 6/Q6 Mo. Post-Seroconversion	Week 2, Month 1, Month 3 Post-ART Initiation	Month 6 and Q6 Months Visits After Initiation of ART	Final Visit
Testing for ~~BV, Candida,~~ Trichomonas	X	▲	▲	▲ (Annual)	▲	▲ (Annual)	X
Testing for BV and Candida	▲	▲	▲	▲	▲	▲	▲

X=protocol-defined procedure; ▲=performed as indicated; *If ART is begun more than 24 months after identification of seroconversion, then the Follow-Up Behavioral Questionnaire is omitted at post-ART visits.

Detailed Listing of Revisions New to LoA #01

1. The following changes are made to Section 9.4, Provision of Test Results and Appendix VII: Sample Informed Consent (Screening and Enrollment) to indicate that HIV resistance results will only be available to the study clinician upon an approved request during an ongoing parent randomized trial and that accordingly, resistance test results will not be provided to the participants as soon as they become available:

Section 9.4 Provision of Test Results:

Because laboratory testing will be performed at all scheduled study visits, a post-visit contact is required after each visit to provide participants with their test results, clinically relevant post-test counseling, and/or clinically indicated treatment. Study staff may complete these contacts at the

study site or at community-based locations, depending on site capacities and site and participant preferences. **To maintain blinding of product assignments, HIV resistance test results will not be routinely available during ongoing parent randomized trials. The site clinician will determine if resistance test results are needed for an individual participant's ongoing medical care and can therefore request that these results be provided.** All contacts will be documented in participant study records and written documentation of test results will be provided upon request to participants and/or their primary HIV-1 care providers.

The following changes are made to Appendix VII: *Sample Informed Consent (Screening and Enrollment)* to modify language requiring the systematic provision of resistance test results to study participants.

Appendix VII: Sample Informed Consent (Screening and Enrollment), Screening/Enrollment Visit:

Second paragraph:

Some of your test results will be available during the visit, and will be given to you at that time. Most other tests will take about two weeks. The tests for herpes ~~and for resistance to HIV medications~~ will take 2-3 months. Study staff will make arrangements to give your results to you when they are ready.

Fourth paragraph:

This study does not provide treatment for HIV, but study staff will refer you to available sources of medical care, counseling, and other services you may need. Study staff also will be available to talk with other doctors that you see for your medical care. Because the results of study tests may help other doctors make the best medical choices for you, study staff will give the results of your study tests to your other doctors, if you wish and with your permission. **The resistance test results will be made available to a study doctor at your study site if the main study has been completed. If the main study is still ongoing, results will only be provided to the study doctor if he/she requests the results for your medical care.**

2. The following changes are made to Section 8, Assessment of Safety to reflect the revised DAIDS EAE Manual, Version 2.0 (January 2010):

Relationship to study participation or procedures will be assessed based on the following definitions:

- ~~Possibly r~~**Related**: ~~unanticipated problem and study participation/procedures are reasonably related in time, and the unanticipated problem could be explained equally well by causes other than study participation/procedures.~~ **There is a reasonable possibility that the AE may be related to the study agent(s)**

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

- ~~Definitely related: unanticipated problem and study participation/procedures are related in time, and a direct association can be demonstrated with study participation/procedures.~~
- **Not Related: There is not a reasonable possibility that the AE is related to the study agent(s)**

3. The following changes are made to Section 13.2 Protocol Registration and Study Activation, to reflect new DAIDS Protocol Registration template language:

~~Each study site will complete protocol registration with the DAIDS Regulatory Compliance Center (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 staff will notify each study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued.~~

~~The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and NIAID Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRBs/ECs and the RCC prior to implementing the amendment.~~

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) *WILL* be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

4. The following updates are made to the Protocol Team Roster:

Added:

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Removed: David Burns, Anne Coletti, Smita N. Joshi and Jeanna Piper

5. The List of Abbreviations and Acronyms is updated:

~~RCC~~	~~Regulatory Compliance Center~~
RE	**regulatory entity**
RSC	**Regulatory Support Center**

The above information will be incorporated into the next version of the protocol at a later time if it is amended.