SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:

MTN-003B

DAIDS Protocol #:10709

Bone Mineral Density Substudy
Ancillary Study to MTN-003 (VOICE)

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine-Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 2.0/ 29 August 2011

IND#: 55,690

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-003B study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. IRB approval is required before implementation of the modifications contained in this amendment. All IRB requirements must be followed.

Please file this Summary of Changes, Version 2.0 of the protocol and all associated IRB correspondence in your essential documents files for MTN-003B.

Summary of Revisions

This amendment incorporates a previously issued Clarification Memo #01, #02, LoA #01 in addition to the revisions listed below.

- The Protocol Team Roster is updated to reflect current members.
- Throughout the protocol modifications have been made to allow for the continuation of VOICE-B follow-up visits beyond the VOICE Product Use End Visit (PUEV). Including the addition of a secondary objective, modification to the length of time a participant may be enrolled in the study, addition of a rationale justifying this continuation, updates to the schedule of study visits and clinical management, updates to the statistical analysis section and revisions to the consent forms, etc.
- The Protocol Summary and Section 2.1, *Vaginal and Oral Interventions to Control the Epidemic (VOICE)*, second and third paragraphs and Section 4.3, *Description of Study Population*, have been updated to describe the updated VOICE accrual information, study population age, as well as the length of time a participant may be followed.
- Section 8.1, *Safety Monitoring*, a new second paragraph was added to describe how the study will be monitored following the completion of VOICE
- Section 8.2, *Adverse Events Definitions and Reporting Requirements*, a sentence was added modify the reportable AEs for VOICE-B following participant completion of the VOICE PUEV
- The protocol has been updated with the publication policy
- The version number, date, and grant number are updated throughout the protocol document
- Correction of minor editorial, formatting, typographical edits and updates are made throughout the protocol document

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Rationale

The primary rationale for the modifications included in this protocol amendment is to extend the period of observation for participants in the bone mineral density substudy of VOICE. The participants will be followed after the end of study product use in VOICE for a period of approximately 12 months. This will allow for the continued follow-up of VOICE-B participants off study product.

Additionally, changes to standard language across recent MTN protocols have resulted in minor updates, corrections, and clarifications to the protocol.

Implementation

This amendment is now official MTN-003B protocol documentation. Prior to implementing the revisions listed below, MTN-003B study sites will submit this Summary of Changes and protocol Version 2.0 to all relevant regulatory authorities and IRBs/ECs.

Upon receipt of all regulatory and IRB approvals and completion of protocol registration procedures, the protocol modifications listed below will be implemented. With exceptions to modifications to the Protocol Team Roster, detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** (for additions).

Detailed Listing of Revisions from CM #01 (26 January 2009) and CM #02 (16 September 2009)

1. The following modifications have been made to the Protocol Team Roster:

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

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The following individuals have been removed from the Protocol Team Roster: Nomapondo Barnabas, Missy Cianciola, David Humiston, Corey Kelly, Morenike Ukpong.

2. In Section 5.3, Exclusion Criteria, text is edited as follows:
   2. Has a medical condition known to affect bone (e.g., hyperparathyroidism, bone cancer) or taking any medication known to affect bone (e.g., glucocorticoids, heparin, warfarin, cyclosporine, ~~medroxyprogesterone acetate,~~ cancer drugs, and thyroid hormone).

   3. The following sections have been updated to allow height and weight measured at VOICE Study Visits to be used at MTN-003B Study Visits.

Section 7.1, Schedule of Study Visits, Table 1: Schedule of BMD Substudy Visits and Evaluations

Nutrition Assessment – Anthropometric (height and weight)****	X	X	X

***** *Height and weight measurements performed and documented for VOICE within 14 days (inclusive) of an MTN-003B visit may be used for MTN-003B***

Section 7.2.2, Anthropometric and Clinical Procedures, third bullet:

- Nutrition assessment - anthropometric (height and weight) ***Note: Height and weight measurements performed and documented for VOICE within 14 days (inclusive) of an MTN-003B visit may be used for MTN-003B***

Section 7.3.2, Anthropometric and Clinical Procedures, second bullet:

- Nutrition assessment - anthropometric (height and weight) ***Note: Height and weight measurements performed and documented for VOICE within 14 days (inclusive) of an MTN-003B visit may be used for MTN-003B***

4. The timing of the DXA scan is further clarified in Section 7.1, Schedule of Study Visits, end of first paragraph:

As indicated in the SSP Manual, all MTN-003B visits may be conducted as split visits.

MTN-003B, LoA #01

1. The Protocol Team Roster is updated. Note that some of these updates include modifications to some listings included in CM #02:

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

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The following individuals are removed from the Protocol Team Roster: Anne Coletti, Nancy Connolly, and Laura McKinstry.

2. The List of Abbreviations and Acronyms is updated:

DAIDS PRO	DAIDS Protocol Registration Office

3. The sample size has been increased to include all eligible participants in the following sections:

Protocol Summary:

Sample Size: All eligible participants

Section 4.1, Identification of Study Design, second sentence:

All VOICE participants randomized to oral study product at selected sites will be offered participation in the BMD Substudy and will be accrued, ~~using competitive enrollment,~~ until ~~300~~ **all eligible** participants have been enrolled.

Section 10.1, Overview of Study Design, second and third sentences:

A**ll** ~~total of approximately 300~~ **eligible** participants randomized to oral study product will be enrolled via competitive enrollment at selected substudy sites. ~~Accrual will stop once the target enrollment of 300 is reached.~~

Section 10.4, Sample Size and Power Calculations, second paragraph:

For the purpose of sample size determination, we are conservatively assuming that a minimum of 300 women will be enrolled in the study (i.e. 100 women per oral arm). Given that at the selected sites all women enrolled into oral arms will be asked to participate in this study, ultimately approximately 300 to 540 women could be potentially enrolled into this study.

Appendix I: Sample Informed Consent (Bone Mineral Density), PURPOSE OF THE STUDY section, first sentence:

~~About 300 w~~**W**omen **who take oral tablets in the VOICE study** will be ~~in this~~ **offered enrollment into the** BMD Substudy, which will take about 3 years to finish. **Up to 540 women will join this study.**

4. Section 7.4, DXA Scan, second paragraph, first sentence is modified to reflect that the SDMC will calculate the average of both DXA scans.

To reduce measurement error, all DXA scans of the hip (total hip, femoral neck) and PA spine (L1-L4) will be performed in duplicate at each visit, and ~~an average of both measurements~~ **results** will be recorded **on case report forms**. **The SDMC will use this data to calculate the average of the two scans for a given visit.**

5. Section 8.2, Adverse Event Definitions and Reporting Requirements, sixth paragraph, is updated to reflect the revised Manual for Expedited Reporting of Adverse Events to DAIDS:

The relationship of AEs involving bone mineral loss will be assessed based on the Manual for Expedited Reporting of Adverse Events to DAIDS, dated ~~may 6, 2004~~ **January 2010** (DAIDS EAE [expedited adverse event] Manual), the VOICE Study oral product Package Inserts and the clinical judge~~-~~ment of the IoR designee.

6. Section 13.2, Protocol Registration is updated to reflect revised Protocol Registration template language, second paragraph:

Site-specific informed consent forms (ICFs) *WILL* be reviewed and approved by the DAIDS Protocol Registration Office (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.

Listing of Revisions New to Version 1.3
Detailed by Protocol Section

1. The *List of Abbreviations and Acronyms* is updated:

~~RCC Regulatory Compliance Center~~
RSC Regulatory Support Center

Other minor updates include the following: Regulatory Compliance Center (RCC) is now Regulatory Support Center (RSC) and the acronym *FHI* no longer stands for Family Health International. In addition, the name of FHI has been changed to FHI 360, this has been updated throughout the document. Any references to RCC or Family Health International have been removed throughout the protocol.

2. The Protocol Team Roster is updated to reflect current Protocol Team members and contact information:

The following individuals are added to the Protocol Team Roster:

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The following individuals are removed from the protocol: Ross Cranston, Kaila Gomez, Lisa Levy, Lisa Noguchi, Mala Shah.

3. Within the Protocol Summary, the Study Duration and Secondary Objective have been updated to reflect changes that occurred in the parent protocol, VOICE, and new revisions to allow for the continued follow-up of VOICE-B participants:

Study Population: Sexually active, HIV-uninfected women 18 to ~~40~~**45** years old who have been randomized to oral study product in MTN-003 [VOICE (Vaginal and Oral Interventions to Control the Epidemic)], and elect participation in the Bone Mineral Density (BMD) Substudy.

Study Duration: Approximately ~~33~~**48** months total. Accrual will require approximately 21 months. Follow-up will continue **12 months after the VOICE Product Use End Visit (PUEV)**~~until 217 incident HIV infections are observed in VOICE; this is expected to occur approximately 12 months following the end of the VOICE accrual period~~.

Secondary Objectives:

- **To evaluate changes in BMD in the 12 months following the discontinuation of an oral study product in VOICE.**

4. The Protocol Summary and Section 2.1, *Vaginal and Oral Interventions to Control the Epidemic (VOICE)*, second and third paragraphs, have been updated to describe the updated VOICE accrual information, study population age, as well as the length of time a participant may be followed.

VOICE is a Phase 2B, five-arm, multi-site, randomized, placebo-controlled trial that is double-blinded within each mode of administration, but open-label with respect to the randomly assigned mode of administration (vaginal or oral). Approximately ~~4200~~**5000** participants will be randomized to the five study arms in a 1:1:1:1:1 ratio.

While investigators and participants will be aware of randomization to either the oral or vaginal administration of study product, they will be blinded to the specific study products randomly assigned. All participants will complete monthly follow-up visits for a period of 12 to 3~~3~~**6** months, and will receive ongoing HIV risk reduction counseling, condoms, and diagnosis and treatment of sexually transmitted infections (STIs) throughout the course of study participation.

5. Section 2.4, *Rationale for Study Design*, new subsection *Bone Mineral Density Changes Over Time* was added to describe the bone mineral density changes experienced by men who participated in recently completed PrEP studies.

Bone Mineral Density Changes Over Time

Two studies have reported on the changes in bone mineral density in healthy HIV negative adult men. In both the iPrEx and CDC MSM PrEP studies, healthy men taking tenofovir DF 300 mg daily had a statistically significant loss of bone mineral density of approximately 1% after 24 to 48 weeks compared to placebo. In the iPrEx study, 503 geographically diverse (5 countries) men participated in the BMD substudy. The loss of bone mineral density among participants in the FTC/TDF arm of the iPrEx study was not associated with any clinical harm, as the FTC/TDF (247 randomized to FTC/TDF) and placebo (256 randomized to placebo) participants reported comparable rates of bone

fractures. Although these results are reassuring it is important to closely examine the effect of tenofovir in HIV-negative women, who, as previously stated, are exposed to the differential effects on bone density of contraception, breastfeeding, pregnancy, etc., all known to impact bone mineral density.

Limited data suggest that the bone mineral density changes related to tenofovir are reversible after discontinuation of drug in HIV-positive individuals. This has not been studied in HIV-uninfected persons and is critical information for determining the long term effect of a period of oral PrEP, especially for women. MTN-003B is well structured to obtain BMD data after study drug discontinuation, and to compare changes among active drug and placebo participants.

6. Section 3.0, *Objectives,* updated to maintain consistency with the Protocol Summary:

   Secondary Objectives:

   - **To evaluate changes in BMD in the 12 months following the discontinuation of an oral study product in VOICE.**

7. Section 4.1, Identification of Study Design, fourth sentence has been modified to clarify the timing of assessments:

   These assessments will also be completed at the VOICE Product Use End Visit (PUEV) or the BMD Substudy Early Termination Visit (ETV) if either occurs at least ~~90~~**30** days after the last semiannual BMD Substudy visit.

8. Section 4.3, *Description of Study Population* has been updated to describe the updated VOICE study population age, as well as the length of time a participant may be followed

   The study population will be comprised of sexually active, HIV-uninfected women 18 to 4~~0~~**5** years old who have been randomized to oral study product in VOICE, elect participation in the BMD Substudy, and meet criteria outlined in Section 5.

9. Section 4.6, *Expected Duration of Participation,* updated to sustain uniformity throughout the protocol:

   The expected duration of participation in the BMD Substudy is approximately ~~33~~**48** months total. Accrual will require approximately 21 months. ~~, and f~~**F**ollow-up will continue for **12 months after the VOICE PUEV.** ~~until 217 incident HIV infections are observed in the VOICE Study: this is expected to occur approximately 12 months following the end of the VOICE accrual period~~.

10. Section 7.0, *Study Procedures* was updated to include two procedures to more accurately assess bone density and bone turnover/metabolism:

    - **Collection of medical history (if not done in VOICE or other study)**
    - **Collection of concomitant medications (if not done in VOICE or other study)**

11. Section 7.1, *Schedule of Study Visits*, Table 1: *Schedule of BMD Substudy Visits and Evaluations* updated to clarify the VOICE-B follow-up period:

Procedure	Screening and Enrollment Visit	Semiannual Follow-up Visit (every 6 mo **during VOICE participation and for 12 months after the VOICE PUEV)**	VOICE PUEV / BMD Substudy ETV*
Informed Consent for BMD Substudy	X		
Eligibility Determination	X		
Reimbursement	X	X	▲
Schedule Next Visit	X	▲	▲
Collect Contraception History	X		
Collect/Update Lactation History	X	▲	▲
Collection of medical history (if not done in VOICE or other study)		▲	▲
Collect concomitant medications (if not done in VOICE or other study)		▲	▲
Nutrition Assessment – Anthropometric (height and weight)**	X	X	X
Nutrition Assessment – Clinical (physical signs of malnutrition)	X	X	X
Nutrition Assessment – Dietary (food frequency questionnaire)	X	X	X
Collect/Update Physical Activity History	X	X	X
Urine Collection for Pregnancy Test (may be omitted if already performed as part of VOICE procedures on same day	▲	▲	▲
Urine Collection and Storage for Exploratory Objective Testing of Excreted Phosphorus and Creatinine	X	X	X
DXA of Spine and Hip	X	X	X
Blood Collection and Serum Storage for Exploratory Objective Testing of Markers of Bone Turnover and Bone Mineral Metabolism	X	X	X

X required

▲ *if indicated*

**These procedures are performed at the VOICE PUEV or BMD Substudy ETV if either occurs at least ~~93~~30 days after the last semiannual BMD Substudy follow-up visit*

***** ***Height and weight measurements performed and documented for VOICE within 14 days (inclusive) of an MTN-003B visit may be used for MTN-003B***

12. Section 7.3, *Follow-up Visits*, has been modified to describe those semi-annual visits that will occur after VOICE PUEV:

    Follow-up visits will occur on a semiannual basis (approximately every 6 months) and may be completed on the same day as VOICE Study visits. **The follow-up visits will occur at 6 months and 12 months following the VOICE PUEV.** The semiannual follow-up visit procedures listed below will also be completed at either the VOICE PUEV or the BMD Substudy ETV if at least ~~93~~30 days have passed since the last semiannual follow-up visit.

13. Section 7.3.2, *Anthropometric and Clinical Procedures* was updated to include two procedures to more accurately assess bone density and bone turnover/metabolism:

    - Update lactation history, if indicated

- Nutrition assessment - anthropometric (height and weight) *Note:* ***Height and weight measurements performed and documented for VOICE within 14 days (inclusive) of an MTN-003B visit may be used for MTN-003B***
- Nutrition assessment – clinical (physical signs of malnutrition)
- Nutrition assessment – dietary (food frequency questionnaire)
- **Collection of medical history (if not done in VOICE or other study)**
- **Collection of concomitant medications (if not done in VOICE or other study)**
- Physical activity history
- Urine collection
- Blood collection

14. Section 7.6.1, *Participants Who Become Pregnant*, second paragraph was updated to remove information regarding study product use to allow for the instruction for study product use resumption to be at the direction of the parent protocol:

    These procedures may be resumed according to original schedule following completion of the pregnancy ~~and associated resumption of VOICE Study oral product use~~.

15. Section 8.1, *Safety Monitoring*, a new second paragraph was added to describe how the study will be monitored following the completion of VOICE:

    Following the completion of VOICE, the site IoRs will notify the MTN-003B Protocol Team with any unexpected safety concerns. No DSMB oversight or MTN Study Monitoring Review is planned for this study following completion of VOICE. The protocol team will conduct periodic internal reviews of study progress including rates of participant retention. These reviews will take place every 3 months.

16. Section 8.2, *Adverse Events Definitions and Reporting Requirements,* a new paragraph added immediately following the table entitled, *Protocol-specific Grading Table for Bone Mineral Loss* to modify the reportable AEs for VOICE-B following participant completion of the VOICE PUEV:

    Following participant completion of the VOICE PUEV, any AEs identified during an MTN-003B visit, including bone mineral loss of any grade, will not be a reportable (unless the participant is co-enrolled in another MTN trial, in which case the other trial's AE reporting guidelines apply).

17. Section 9.2, BMD Status: During Follow-up, last paragraph has been removed; sites no longer need to consult the PSRT regarding temporary holds or permanent discontinuation of study product.

    ~~Consult the PSRT regarding a possible temporary hold or permanent discontinuation of study product~~

18. A new Section 9.3, *BMD Status: Following Completion of VOICE* was added to describe the procedures to be performed after the participant has completed VOICE PUEV:

    For participants with more than a 1 SD reduction in BMD compared to baseline, the IoR/designee should repeat the DXA scan, if not previously done.

    For participants with Z-scores (ages 18-29) or T-scores (age ≥30) less than -2.0 SD compared to baseline, the IoR/designee will be required to do the following:

    - **Discuss options for treatment or prevention of osteoporosis with the study participant. The study will provide calcium supplementation if recommended by the IoR/designee.**

19. Section 9.5, *Clinical Management of Pregnancy*, was updated to remove information regarding study product use to allow for the instruction for study product use resumption to be at the direction of the parent protocol:

    Participants who become pregnant will discontinue DXA scans and collection and storage of urine and serum, but will resume these procedures per their original substudy follow-up schedule after completion of the pregnancy ~~and resumption of VOICE Study oral product use.~~

20. Section 10.1, *Overview and Summary of Design*, first and second sentence, the competitive enrollment condition was removed and the timing of the BMD Substudy ETV was modified:

    All eligible participants randomized to oral study product will be enrolled ~~via competitive enrollment~~ at selected substudy sites. Follow-up assessments will occur semiannually throughout participation; follow-up assessments will also be completed at the VOICE PUEV or the BMD Substudy ETV if at least ~~90~~**30** days have passed since the last BMD Substudy semiannual follow-up visit.

21. Section 10.2, Study Endpoints, a new second paragraph was added to note that the total hip and lumbar spine bone density via DXA will be used as an endpoint for the new secondary objective:

    Note that these endpoints will be used also for the secondary objective to explore changes in BMD among VOICE participants using oral study products after discontinuation of product use.

22. Section 10.3 Primary Study Hypotheses, Primary endpoints subheading, clarifying language was added to the second sentence:

    Therefore, the null hypothesis is that there will be no difference in the safety profile between daily regimens of oral active products and oral placebo after one year **of product use**.

23. Section 10.4, Sample Size and Power Calculations, second paragraph, previously modified language was clarified:

    For the purpose of sample size determination, we are conservatively assuming that a minimum of 300 women will enrolled in the study (i.e. 100 women per oral arm). Given that at the selected sites all women enrolled into oral arms will be asked to participate in this study, **the total enrollment will be between** ~~ultimately approximately~~ 300 **and** ~~to~~ 540 women~~ could be potentially enrolled into this study~~.

24. Section 10.4, Sample Size and Power Calculations, clarifying language added to the new third paragraph, first sentence:

    At each assessment time point **during the expected product use period**, the arithmetic mean of the duplicate measurements will be used for the following primary analysis.

25. Section 10.4, Sample Size and Power Calculations, new third paragraph, fifth sentence typo corrected:

    Note that this is a conservative estimate of power since the duplication of measurements at each time point will reduce the SD and thus provide power to detect lower differences (i.e., <2.~~2~~**1**%).

26. Section 10.4, Sample Size and Power Calculations, new fourth paragraph added:

    Similarly, the percentage change in BMD between the TDF active arm, FTC/TDF active arm, and placebo arm observed during the year after product use was discontinued will be compared. Based on similar assumptions as above, 100 women per oral arms will allow the detection of a difference as small as 2.1% with 90% power with a type one error rate of 5%.

27. Section 10.5, Data and Safety Monitoring and Analysis, new fifth paragraph added to describe how bone mineral density will be analyzed after product use has been discontinued:

    For evaluating changes in BMD after product use was discontinued, two Student t-tests will be used to compare the percentage change over the year of follow-up without product use in BMD between each of the following: (1) the TDF active arm and placebo oral arm; and, (2) FTC/TDF active arm and placebo oral arm. Analysis for hip and lumbar spine measurements will be done separately. Note that this analysis is more relevant in the case where at least one effect from the use the active oral products on BMD is observed. In that case, it would be worthwhile to investigate if the effect on the BMD is waning after product use is discontinued and eventually returns to its baseline values (i.e. prior to initiation of product use).

28. Section 10.5.1, Data and Safety Monitoring Board (DSMB), new third paragraph added to provide additional information regarding DSMB after VOICE completion:

    No DSMB oversight or MTN Study Monitoring Review is planned for this study following completion of VOICE as there will be no further product exposure, thus no deleterious effect of study participation is anticipated.

29. Section 14.0, Publication Policy, has been updated to specifically state the publication policy for this protocol.

    ~~Section 14 of the VOICE protocol provides information on the publication policy applicable to the BMD Substudy.~~ **DAIDS/NIAID and MTN policies and Clinical Trial Agreements between CONRAD and NIAID, and between Gilead Sciences, Inc. and NIAID will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee, DAIDS, NICHD, NIMH, CONRAD, and Gilead Sciences, Inc., for review prior to submission.**

30. Appendix 1: Sample Informed Consent (Bone Mineral Density), PURPOSE OF THE STUDY section, second paragraph, previously modified text (see LoA #1) has been updated to allow for the continued follow-up of VOICE-B participants:

    Women who take oral tablets in the VOICE study will be offered enrollment into the BMD Substudy ~~which will take about 3 years to finish~~. Up to 540 women will join this study. Each woman will be in the BMD Substudy for up to ~~3~~**4** years; **this substudy will continue for about 1 year longer than the VOICE study**. Results and other medical information collected during your participation in the VOICE Study may be used to help researchers understand the results of this BMD Substudy.

31. Appendix 1: Sample Informed Consent (Bone Mineral Density), STUDY PROCEDURES section, second full paragraph, updated to allow for the continued follow-up of VOICE participants:

    After today you will be in the BMD Substudy for up to ~~3~~**4** years~~, depending on when you join~~. You will have the procedures listed above today and every 6 months while you are in this BMD Substudy. ~~You~~ **If needed, you** will also have ~~these~~**a visit when you stop taking the oral product for VOICE. These** procedures ~~when you are finished~~**will continue for approximately 12 months after you finish** taking your VOICE Study tablets~~, if it has been 90 days or more since the last time these procedures were done.~~. These procedures will take about 60 to 90 minutes. These procedures may be done on the same day as your regular VOICE Study visits, when possible. [BMD Substudy site to insert if applicable: A BMD Substudy staff member will take you to a different clinic for the DXA test]

32. Appendix 1: Sample Informed Consent (Bone Mineral Density), Risks of DXA Test, Pregnancy subsection, second and third pagraphs:

    All VOICE Study participants should use effective contraception. Effective contraception includes hormonal methods (such as the birth control pill or shot), intrauterine contraceptive device (IUCD);

and sterilization of you or your partner. You should not use spermicides as a method of contraception while participating in the VOICE Study. **After completion of the VOICE study, contraception will not be required but the study staff will ask whether or not you are using contraception and will discuss contraceptive options with you if you wish.**

If you become pregnant during the BMD Substudy, the study staff will refer you to available sources of medical care and other services you or your baby may need. You will stop having DXA tests and giving blood and urine samples, but keep coming here for substudy visits as originally planned. Depending on when you become pregnant, ~~and if you start taking VOICE Study tablets again after pregnancy,~~ you may be able to have the DXA tests again after your pregnancy. The BMD Substudy staff will talk more with you about this after your pregnancy.

33. The version number, date and grant number are updated throughout the protocol document

34. Correction of minor editorial, formatting, URLs have been updated throughout, typographical edits, updated references and updates are made throughout the protocol document.