The Procter & Gamble Company
Cincinnati, Ohio USA

A RANDOMIZED CLINICAL STUDY TO ASSESS THE EFFECTS OF VARIOUS DENTIFRICE TECHNOLOGIES ON DENTINAL HYPERSENSITIVITY

23 May 2019
Protocol Number 2019079

Signatures below indicate approval of the Protocol.

Sponsor:	The Procter & Gamble Company Worldwide Clinical Investigations—Oral 8700 Mason-Montgomery Road Mason, OH 45040
PII	

Investigator's Agreement Statement: I have read, I understand, and I will conduct the study according to this Protocol and Good Clinical Practices.	PII

Signatures below indicate approval of the Protocol.

Clinical Scientist/Medical Monitor	PII
Clinical Trial Manager	
Statistician	
Clinical Data Manager	
Associate Director Global Oral Care Clinical Operations	

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE(s)	Adverse Event(s)
B&A	Balance & Assignment
CFR	Code of Federal Regulations
CRF(s)	Case Report Form(s)
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IRB/IEC	Institutional Review Board/Independent Ethics Committee
SOP(s)	Standard Operating Procedure(s)

PROTOCOL BODY

1. Study Objective

The objective of this study is to evaluate the efficacy (changes in dentinal hypersensitivity) and safety (oral soft tissue evaluation) after use of one of four dentifrices in subjects with pre-existing hypersensitivity over an 11-week period.

2. Overall Study Design and Plan

This is a randomized, controlled, single center, double-blind study to assess efficacy (the changes in dentinal hypersensitivity) and safety (oral soft tissue evaluation) of four dentifrices with different desensitizing technologies over 8 weeks of assigned product use, followed by three weeks of washout product use (Colgate Cavity Protection). After informed consent, approximately 150 subjects with a history of tooth sensitivity will be evaluated to enroll a target population of approximately 120 healthy adult volunteers with current dentinal hypersensitivity. Subjects will be randomized to either an experimental potassium oxalate dentifrice, marketed potassium nitrate dentifrice, marketed stannous fluoride dentifrice, or a regular anticavity dentifrice (negative control). Subjects will use assigned product for 8 weeks. After 8 weeks, all subjects will use Colgate Cavity Protection and come back 3 weeks later (Week 11) to have their dentinal hypersensitivity re-evaluated. Dentinal hypersensitivity will be measured by a standard thermal challenge (cold air response measure via Schiff Index) and probing force (calibrated Yeaple probe). Measurements will be taken at Baseline (before any treatment), Day 3, Week 2, Week 4, Week 8 and Week 11. Safety will be assessed from clinical examination of the oral soft tissue. A digital image of the oral soft tissue and hard tissue may be taken, at the discretion of the examiner.

PROCEDURE	VISIT 1 SCREENING/BASELINE	VISIT 2 DAY 3	VISIT 3 WEEK 2 (±2 DAYS)	VISIT 4 WEEK 4 (±2 DAYS)	VISIT 5 WEEK 8 (± 2 DAYS)	VISIT 6 WEEK 11 (± 2 DAYS)
Informed Consent	X					
Medical History Review	X					
Confidentiality Disclosure Agreement (CDA)	X					
Demographics	X					
Questionnaire*	X				X	
Documentary Image (optional)	X	X	X	X	X	X
Inclusion/Exclusion Criteria	X					
Continuance Criteria		X	X	X	X	X
Oral Examination	X	X	X	X	X	X
Tactile Challenge	X	X	X	X	X	X
Cold Air Challenge	X	X	X	X	X	X
Product Distribution	X				X	
Wash-out Product Distribution					X	
Product Usage Instructions	X				X	

Post Treatment Oral Exam	X					
Product Return					X	X
General Comments	X	X	X	X	X	X
AEs	X	X	X	X	X	X
Subject Accountability						X

*Questionnaire will be analyzed outside of the database.

Screening/Baseline Visit 1

Subjects will be asked to read and sign duplicate copies of the informed consent form which will be witnessed by site staff. Subjects will be given one signed copy of the informed consent form and the other signed copy will be maintained as site source documentation. Subjects will be asked to complete a confidentiality disclosure agreement. Personal medical history information will be reviewed and retained as site source documentation. Subjects will be asked to complete a questionnaire regarding their tooth sensitivity. All screening data collected will be recorded on site source documentation. Demographic information and entrance criteria will be assessed. A comprehensive oral examination will then be conducted to evaluate the oral and perioral region, including hard and soft tissues. Tactile sensitivity will be assessed using a standard calibrated Yeaple probe beginning at 10 g probing force. Approximately 5 minutes later, thermal sensitivity will be assessed using a standard cold air challenge (Schiff Index). For each subject, 2 test teeth will be selected by the clinician for the study. Eligibility will be determined via a Schiff score >1 and Yeaple probe score between 10-20 g. If the qualifying eligible teeth are in the same quadrant, the two test teeth should be separated by at least 2 other teeth. Data for subjects with 2 qualifying teeth will be transcribed from source documents into the study database.

Qualifying subjects will be randomly assigned to either an experimental potassium oxalate dentifrice, marketed potassium oxalate dentifrice, marketed stannous fluoride dentifrice, or a regular anticavity dentifrice (negative control) to use at home daily for the first 8 weeks of the study. Subjects will complete their first brushing supervised onsite. Subjects will then receive a post-treatment oral examination approximately 5 minutes after brushing.

Screening and Baseline may be conducted at separate visits based on logistical considerations.

All general comments, and AE's if any, will be recorded on the appropriate eCRF.

Day 3, Visit 2

Subjects will return to the site after 3 days. Continuance criteria will be assessed. A comprehensive oral examination will then be conducted to evaluate the oral and perioral region, including hard and soft tissues. Tactile sensitivity will be assessed using a standard calibrated Yeaple probe beginning at 10 g probing force. Approximately 5 minutes later, thermal sensitivity will be assessed using a standard cold air challenge (Schiff Index). All general comments and AEs, if any, will be recorded on the appropriate eCRF.

Week 2 (+/- 2 days), Visit 3

Subjects will return to the site after 2 weeks. Continuance criteria will be assessed. A comprehensive oral examination will then be conducted to evaluate the oral and perioral region, including hard and soft tissues. Tactile sensitivity will be assessed using a standard calibrated

Yeaple probe beginning at 10 g probing force. Approximately 5 minutes later, thermal sensitivity will be assessed using a standard cold air challenge (Schiff Index). All general comments and AEs, if any, will be recorded on the appropriate eCRF.

Week 4 (+/- 2 days), Visit 4

Subjects will return to the site after 4 weeks. Continuance criteria will be assessed. A comprehensive oral examination will then be conducted to evaluate the oral and perioral region, including hard and soft tissues. Tactile sensitivity will be assessed using a standard calibrated Yeaple probe beginning at 10 g probing force. Approximately 5 minutes later, thermal sensitivity will be assessed using a standard cold air challenge (Schiff Index). All general comments and AEs, if any, will be recorded on the appropriate eCRF

Week 8 (+/- 2 days), Visit 5

Subjects will return to the site after 8 weeks and will bring their kit box with them. Continuance criteria will be assessed, and subjects will be asked to complete a post-treatment questionnaire. A comprehensive oral examination will then be conducted to evaluate the oral and perioral region, including hard and soft tissues. Tactile sensitivity will be assessed using a standard calibrated Yeaple probe beginning at 10 g probing force. Approximately 5 minutes later, thermal sensitivity will be assessed using a standard cold air challenge (Schiff Index). All general comments and AEs, if any, will be recorded on the appropriate eCRF. Subjects will return treatment products and will be given a new kit box with washout product to use for three weeks.

Week 11 (+/- 2 days), Visit 6

Subjects will return to the site after 11 weeks and will bring their kit box with them. Continuance criteria will be assessed. A comprehensive oral examination will then be conducted to evaluate the oral and perioral region, including hard and soft tissues. Tactile sensitivity will be assessed using a standard calibrated Yeaple probe beginning at 10 g probing force. Approximately 5 minutes later, thermal sensitivity will be assessed using a standard cold air challenge (Schiff Index). All general comments and AEs, if any, will be recorded on the appropriate eCRF. Subjects will receive a bottle of Crest Kids Anti-Cavity fluoride rinse to take home and use at their discretion. Subjects will return wash-out products, and a subject accountability form will be completed.

Subject Accountability

A subject accountability form will be completed for each subject. If, for any reason, a subject does not complete the study, an explanation will be entered on the Subject Accountability eCRF. All data gathered on the subject prior to discontinuation will be made available to the Sponsor.

General Comments and Adverse Event Recording

General comments and AEs may be recorded at any time during the study. All serious AEs will be recorded. In addition, non-serious oral-related AEs will be recorded. Any recorded AE that remains unresolved by study end should be followed up until resolution by the Investigator and the resolution should be documented as source documentation by the Investigator. If a subject is unreachable to determine whether the AE has been resolved, the attempts to contact the subject should be documented as source documentation by the Investigator.

Optional Documentary Image

Subjects may have a documentary image of their oral cavity taken to document any research findings, at the discretion of the examiner.

3. Inclusion Criteria

In order to be included in the study, each subject must:

1. be at least 18 years of age;
2. provide written informed consent prior to participation and be given a signed copy of the informed consent form;
3. sign a Confidentiality Disclosure Agreement (CDA);
4. be in good general health as determined by the Investigator/designee;
5. agree not to participate in any other oral/dental product studies during the course of this study;
6. agree to delay any dentistry (including dental prophylaxis) until the study has been completed;
7. agree to refrain from the use of any non-study oral hygiene products*;
8. exhibit adequate oral hygiene (i.e., brush teeth daily and exhibit no signs of oral neglect);
9. have an absence of extensive calculus above the gum line;
10. agree to return for all scheduled visits and follow study procedures; and
11. have two teeth with a Schiff sensitivity score > 1 in response to air challenge and a Yeaple probe score of 10-20 g in response to tactile challenge. (If these two eligible teeth are located in the same quadrant, they have to be separated by 2 other teeth.)

    * Regular floss users will be permitted to continue flossing in their customary manner. However, those subjects who do not report regular floss use will not be permitted to floss for the duration of the study.

4. Exclusion Criteria

Subjects are excluded from study participation where there is evidence of:

1. having taken anti-inflammatory, analgesic, or psychotropic drugs, chronically;
2. chronic medical debilitating disease associated with constant or intermittent episodes of daily pain;
3. any home-care bleaching, whitening products or have had a professional bleaching treatment within 4 weeks of the Baseline visit;
4. dental prophylaxis within 2 weeks prior to Baseline visit;
5. having received professional desensitizing treatment or having used over-the-counter desensitizing products within 6 weeks of the Baseline visit;
6. having periodontal surgery, orthodontic treatment, or teeth restored in the preceding three months;
7. having teeth or periodontium with pathology or defects likely to cause pain;
8. having a history of allergies or hypersensitivity to ingredients in commercial dental products or cosmetics;
9. self-reported pregnancy or lactation;
10. having self-reported eating disorders, uncontrolled gastroesophageal reflux disease (GERD or Acid Reflux), excessive dietary or environmental exposure to acids, or other systemic conditions that are predisposing to dentinal hypersensitivity;
11. history or presence of kidney disorders, kidney stones, have celiac disease, inflammatory bowel disease (ulcerative colitis or Crohn's disease), chronic pancreatitis, have had intestinal

or weight-loss surgery, or if have stomach or intestinal problems that keep them from absorbing certain foods or nutrients;

12. any diseases or condition that might interfere with the safe participation in the study;
13. inability to undergo study procedures;
14. having severe xerostomia;
15. having had active caries within the 12 months;
16. having high risk for caries development (rampant caries, multiple dental restorations, crowns with compromised margin) per examiners discretion;
17. teeth will be excluded from study measurements if they:
    - have deep, defective, or facial restorations;
    - have full crowns, extensive caries, cracked enamel, or are abutment teeth for fixed or removable prosthesis;
    - present with tendency for spontaneous bleeding;
    - have been scaled/root planed or restored within the past 3 months.

5. Continuance Criteria

Subjects may be excluded from the study or the analysis due to:

1. started taking anti-inflammatory, analgesic, or psychotropic drugs, chronically;
2. developed chronic medical debilitating disease associated with constant or intermittent episodes of daily pain;
3. a dental prophylaxis or other dentistry since the last visit;
4. use of any non-study oral hygiene products since the last visit;
5. reported pregnancy since the last study visit;
6. participation in any other oral care study since the last visit; or
7. being unable or unwilling to comply with study procedures since the last study visit.

6. Identity of Investigational Product(s)

- **Control:** Colgate® Cavity Protection toothpaste (0.76% sodium monofluorophosphate) and Oral-B® Indicator soft toothbrush.
- Experimental Potassium oxalate toothpaste and Oral-B® Indicator soft toothbrush.
- Crest® Pro-Health Sensitive and Enamel Shield (0.454% stannous fluoride) toothpaste, and Oral-B® Indicator soft toothbrush.
- Sensodyne® Extra Whitening toothpaste (5% potassium nitrate) and Oral-B® Indicator soft toothbrush.

Week 8-11 Washout Product:

- Colgate®Cavity Protection Toothpaste (0.76% sodium monofluorophosphate) and Oral-B® Indicator soft toothbrush.

7. Method of Assigning Subjects to Treatment Groups

Study Design	N	n/group	B&A Program	PRA Block Size	Strata	Cut-offs
Parallel	120	30 per group	Yes	4	Pre-treatment Schiff Index	≤2.5 or >2.5

					Pre-treatment Yeaple Probe Age Gender	=10 or >10 <40 or ≥40 Male or Female

B&A Program

Eligible subjects will be stratified based on the Pre-treatment Schiff Index and Yeaple probe sensitivity scores, age, and gender. Within strata, subjects will be randomly assigned to one of the treatment groups using an encoded program supplied by the Sponsor. This assignment process and the distribution of test products will be conducted in a protected area that will ensure blinding of the examiner to the identity of the test products. Product distribution and product return will be recorded on the Product Distribution Log provided by the Sponsor. Subjects from the same household will be assigned to the same treatment group.

8. Product Usage

Subjects will be instructed to brush twice daily. Subjects will be instructed to apply at least a 1-inch strip of the toothpaste onto the toothbrush and to brush thoroughly for 1 minute and expectorate.

All subjects will be instructed to use only the assigned products in place of normal oral hygiene for the duration of the study.

9. Blinding, Labeling, and Shipping Plan

The identity of the toothpaste will be disguised. Kit boxes will contain 2 tubes of toothpaste, 1 toothbrush, 1 timer and subject instructions. Week 8 kit boxes will contain 1 tube of toothpaste, and subject instructions (subjects will use the same timer from previous kit box) for the 3-Week washout period.

The kit boxes will be labeled with a unique kit number. Control and test kit boxes will be identically sized; the kit box labels will be identical except for a unique kit number used for assignment. Kit box labels will also contain the study number, emergency phone number, distributor name/address, appropriate caution statements, content statement and other information as required by internal regulations and clinical SOPs. The shipping containers will be labeled with the clinical site address and a content statement listing study number and kit box numbers contained within. Supplemental products will be provided to site.

The site will be provided with a code breaker report in a sealed envelope. The sealed code breaker report contains documents that list the kit box number or treatment code while the identity of the treatment products is hidden by an opaque scratch-off seal. If the study blind needs to be broken, an individual subject's investigational product may be ascertained by opening the sealed code breaker report, locating the subject's kit box number or treatment code and scratching off the opaque seal to reveal the treatment identity. The sealed code breaker report will be opened if a clinically serious AE occurs or management of the subject requires knowledge of the identity of the investigational product. The Investigator should immediately inform the Sponsor that the code will be broken and record the date, time and reason for breaking the code in writing. After the study is complete and the study database has been finalized and locked, the site will return

the code breaker report to the Sponsor using the self-addressed, stamped envelope provided by the Sponsor.

10. Determination of Sample Size

Power analyses were conducted with α=0.05, using a 2-sided test. Up to 120 subjects will be enrolled in the study assuming ~5% dropout rate. Data were utilized from a similarly designed study with the same examiner and endpoints (2018095). Twenty-eight subjects per group completing this trial should provide at least 90% power to detect a difference in Schiff mean scores of at least 0.80 units between treatments assuming the variability(s) of Schiff score is 0.88. Assuming the variability(s) of Yeaple score is 12.44, a sample size of 28 subjects per group should provide at least 90% power to detect a difference in Yeaple score of at least 10.97 units between treatments.

11. Safety Variables

Safety Observations and/or Measurements

Safety will be assessed by the absence of irreversible side effects.

Oral Examination

Assessment of the oral soft tissue is conducted via a visual examination of the oral cavity and perioral area utilizing a standard dental light, dental mirror, and gauze. The structures examined include the gingiva (free and attached), hard and soft palate, oropharynx/uvula, buccal mucosa, tongue, floor of the mouth, labial mucosa, mucobuccal/mucolabial folds, lips, and perioral area. Assessment of the oral hard tissues will be conducted via a visual examination of the dentition and restorations utilizing a standard dental light, dental mirror, and air syringe. All abnormal findings will be recorded and categorized by their location; hard tissue findings will be categorized as “other.” An AE will be recorded if a new abnormal finding is noted after product distribution or any previously noted abnormal finding increases in severity during the treatment period.

12. Efficacy Variables

Yeaple Probe Calibration

The Yeaple probe will be calibrated each day subjects are seen and in accordance with the site’s internal SOPs. The settings should be recorded, dated, and initialed by the person performing the calibration on an appropriate form. A new form will not be necessary for each calibration; however, care should be taken so as not to use a different day's force settings. This record will serve as the guide for the force setting for that day's examinations.

Tactile Threshold Determination

Tactile sensitivity at test teeth will be assessed at the Baseline, Week 2 and Week 4 and Week 8 visits using the Yeaple probe test. A #16 explorer tip will be used with the Yeaple probe. The tip will be kept perpendicular to the root surface of the tooth being tested. The tip will be moved horizontally across the facial surface over the sensitive area. Two horizontal sweeps across the entire facial surface are made at each force setting.

At Baseline (before treatment), testing will be performed beginning at 10 g. The examiner will record tactile scores for responding teeth. After treatment, testing will begin at 10 g and

increase by 10 g to a maximum of 50 g. Each successive challenge shall increase until a "yes" response will be repeated. If a second "yes" is not obtained, the force setting is increased to the next step and continued until a force is found which elicits two consecutive "yes" responses, which will be recorded as the threshold on the Tactile Sensitivity Score form. If no sensitivity is found up to 50 g, 50 will be recorded as the threshold.

Cold Air Challenge

A one second application of cold air will be delivered onto each tooth tested from a standard dental unit syringe.

Schiff Index Sensitivity Scale

The examiner will record the Schiff Index score corresponding to the response to the cold air challenge.

Schiff Index Sensitivity Scale	
SCORE	**CRITERIA**
0	Tooth/Subject does not respond to stimulus
1	Tooth/Subject responds to stimulus, but does not request discontinuation of stimulus
2	Tooth/Subject responds to stimulus and requests discontinuation or moves from stimulus
3	Tooth/Subject responds to stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus

13. Hypothesis

The following hypotheses will be tested for each post-treatment assessment.

Null: There is no mean score difference between treatment groups.
Alternative:
There is a mean score difference between treatment groups.

For each treatment group, the following hypothesis will be tested for each post-treatment assessment.

Null: The post-treatment mean is equal to the pre-treatment mean.
Alternative: The post-treatment mean is not equal to the pre-treatment mean.

The Schiff Index Sensitivity Scale at Week 4 will be of primary interest.

14. Statistical and Analytical Plans

The following statistical analyses will be performed for the sensitivity data (Schiff Index and Yeaple Tactile Sensitivity). Sensitivity scores will be averaged amongst test teeth within each subject for each assessment before and after treatment. For each treatment group and assessment, mean post-treatment assessments will be compared to pre-treatment using a statistical analysis for paired data that is either non-parametric or parametric (e.g., Wilcoxon signed rank test or one sample t-test). For each post-treatment assessment, mean comparisons between treatment groups will be analyzed using analysis of covariance with the

baseline score as a covariate with either non-parametric or parametric methods. If necessary, a mathematical transformation to the data may be performed to aid statistical assumptions associated with parametric analysis methods. Statistical comparisons will utilize two-sided testing with a 5% significance level. Demographic and safety data will also be summarized. Additional statistical methods may be used to further investigate these data.

APPENDIX

Adverse Event Reporting

Abnormal findings which may qualify as AEs are those that: 1) were not present at Baseline and occurred after product usages of any duration, or, 2) were present at Baseline and worsened in severity after product usage of any duration. All AEs will be recorded on the CRF. If a question should arise about the causal relationship of an AE to product usage, the Medical Monitor will be contacted to make the determination of relatedness.

An ***unexpected*** event is defined as one that is not identified in nature, severity, or frequency in the current safety assessment. The events will be reported to the FDA as required, upon receipt of pertinent clinical data and completion of the required forms.

Any clinically significant abnormal laboratory finding, serious or unexpected AE, or medical event which results in the withdrawal of a subject from the study, must be followed to resolution with appropriate medical management, or as deemed necessary (with the Sponsor's agreement).

Advertising

Any advertisements used in recruitment of subjects must receive prior approval from P&G and the Investigator's IRB. A copy of the IRB-approved advertising and the documentation thereof must be provided to P&G.

Data Collection

The Investigator has the responsibility for ensuring that all source documents (i.e., study and/or medical records) and CRFs are completed and maintained according to the study protocol and are available at the site.

Case Report Forms

The Data Manager will supply the paper and/or electronic CRFs to be used in this study. It is the responsibility of the Investigator to maintain and submit accurate and timely CRFs to the Sponsor. All hard copy CRFs will be filled out legibly in ink.

All questions should be answered. For paper CRFs, if an entry requires correction, a single line will be placed through the entry so as not to obscure the original record, the corrected entry will be initialed and dated by the individual making the change, and a reason will be given for the change. There will be no whiteouts or erasures. For electronic CRFs, if an entry requires correction, the change is made directly to the CRF in the database, the user is prompted to provide a reason for the change, and the correction is logged in by an electronic audit trail.

As necessary, the Data Manager may make specified allowable changes to the database without issuing a query to the site, as agreed upon by study site per this protocol. Examples of allowable changes include incorrect date formats, incorrect current year recorded (as in the start of a new year), and unambiguous spelling errors. Changes to common abbreviations and symbols to equivalent text to meet system or coding constraints (e.g., @ = at, ~ = approximately), may also be allowable. Values that are ambiguous or open to interpretation will be queried to the sites. It is the responsibility of the Data Manager to ensure all changes are supported by information contained elsewhere and/or are unambiguous.

Source Documents

The Investigator has the responsibility for ensuring that all source documents (i.e., study and/or medical records) and CRFs are completed and maintained according to the study protocol and is available at the site. Any CRF used as a source document must be identified as such in the Investigator Notebook.

Protocol Amendments/Changes

Changes to the Protocol following IRB approval affecting the safety of subjects, scope or objectives of the investigation, or the scientific quality of the study will be documented as amendments. Such changes will require the Sponsor, Investigator, and IRB approval prior to implementation, unless immediate action is required to safeguard subject safety. Administrative or minor changes (e.g., typographical errors, changes in Sponsor personnel, etc.) will be documented as revisions but may not need to be submitted as amendments unless required by the IRB. Any change in the Sponsor's monitoring staff, Clinical Trial Manager or Medical Monitor during the conduct of the study, will be reported to the Investigator.

Good Clinical Practices

This study is classified non-AMG, non-MPG according to German study classification but conducted in compliance with applicable sections of the US Federal Regulations governing informed consent (21 CFR 50) and IRBs (21 CFR 56). The conduct of this study will be in accordance with ICH-GCPs as published by the FDA, with the Commission Directive 2005/28/EC published by the European Union, and ISO 14155:2011. During the course of the trial, the clinical site will allow monitoring by the Sponsor (Clinical Trial Manager or designee) to check compliance with the Protocol, regulations and guidelines, adequacy of the equipment and facilities, and satisfactory data collection.

Institutional Review

Prior to study initiation, the Investigator must obtain institutional review and approval of the Protocol, the consent form, and other necessary study-related documents in compliance with the US Code of Federal Regulations, Title 21, Part 56 or the ICH-GCPs Consolidated Guidelines, Chapter 3 and in compliance with Procter & Gamble SOP QS-CL-05 ("Institutional Review Board/Independent Ethics Committee Review and Approval"). The Investigator will maintain any original authorization letter(s) and will be available for review by the Sponsor. IRB approval letters should include the study title, Sponsor study number, the address of the IRB, date of request, and the signature of the IRB chairperson or designate. Additionally, the letter must acknowledge that both the Protocol and consent form have been approved by the IRB. The study will not begin until the Sponsor has received confirmation of IRB approval. The IRB shall also review the investigation at least once a year during study execution. The Investigator will notify the IRB when the study is terminated and provide confirmation that the study has been closed with the IRB to the Sponsor.

Investigator Final Report

Following completion of the study, the Investigator shall submit a final report to the Sponsor describing the conduct of the study, deviations from planned conduct, early withdrawals and subject accountability, adverse events, and other information on study conduct. The Investigator's IRB may require more frequent status reports.

Records Retention

The Investigator must retain the subject identification codes, informed consent documentation, clinical materials inventory, CRFs (paper or electronic media), medical records and other source data for a minimum of 2 years after the last regulatory approval has been received or the discontinuation of the study. The Investigator must receive written authorization from the Sponsor before destroying any study document. The Investigator will make the records available for inspection and copying upon the request of an authorized employee of a government authority or the Sponsor, at reasonable times. In the event the Investigator retires, relocates, or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records may be transferred to another person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the Sponsor.

The Research Participant's identification codes are a unique identifier assigned by the Principal Investigator to each trial subject to protect the Research Participant's identity and privacy. The identification codes are used in lieu of the Research Participant's name when the Principal Investigator reports all adverse events and other trial related data. These codes will be used on all study documents for the Research Participant's confidentiality (In order to protect the confidentiality of information concerning Research Participants, as stated in section 2.11 of the International Conference on Harmonization Good Clinical Practice: Consolidated Guideline (ICH-GCP).)

Serious Adverse Event Reporting

A *serious adverse event* is defined as an event, which suggests a definite hazard or handicap to the subjects. Serious adverse events are any events resulting in death, life threatening situation, disability or permanent damage, hospitalization or prolongation of existing hospitalization, or congenital anomaly/birth defects; events requiring intervention to prevent permanent impairment/damage; or other serious (important) medical events.

When an Investigator is notified of a serious AE, the Investigator must promptly (within 24 hours) notify the Sponsor (Clinical Trial Manager or the Medical Monitor) of the serious or unexpected event, regardless of causality. Within 5 working days, a written and/or electronic report describing the circumstances of the event must be submitted to the Sponsor. The Investigator will be responsible for SAE reporting to the IRB.

Study Medication Dispensing and Storage

Study products will be stored in a secure area, under environmental condition as required by label instructions or as described in the Protocol and dispensed only under the authorization of the Investigator. The storage condition shall be properly documented. Both the receipt and dispensation of all test products (used and unused) will be documented using forms provided by the Sponsor or suitable forms provided by the site. Study products will be returned to the Sponsor following the trial, or alternatively, they will be destroyed at the clinical site provided the site has an existing SOP for the destruction of clinical materials and prior written approval from the Sponsor.

Subject Consent

The Investigator will obtain written informed consent for each subject prior to participation in the study, per the US Code of Federal Regulations, Title 21, Parts 50.25 and 50.27 and ICH-GCPs, Chapter 4, subpart 4.8 and in compliance with Procter & Gamble SOP QS-CL-04 ("Informed Consent Form, Ethics Approval and Investigator Use"). Subjects, or their legal guardian, are

required to read, sign and date an IRB approved consent form with the Investigator also maintaining a signed and dated copy. The subject or legal guardian will be given a copy of the consent form. All study procedures must be explained in non-technical terms.