The Procter & Gamble Company
Cincinnati, Ohio USA

A CLINICAL STUDY TO EVALUATE ANTI-PLAQUE EFFICACY OF A GEL IN A MODIFIED 4-DAY PLAQUE MODEL

13 April 2018
Protocol Number 2018009

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	

Section Head Oral Care Clinical	PII

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE(s)	Adverse Event(s)
CFR	Code of Federal Regulations
CRF(s)	Case Report Form(s)
DPIA	Digital Plaque Image Analysis
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IRB/IEC	Institutional Review Board/Independent Ethics Committee
TMQHPI	Turesky Modified Quigley Hein Plaque Index
OST	Oral Soft Tissue Exam
SOP(s)	Standard Operating Procedure(s)

PROTOCOL BODY

1. Background Information

Oral hygiene products containing chemotherapeutic ingredients such as stannous fluoride have been shown to provide anti-plaque and anti-gingivitis benefits. Optimization of the delivery of the ingredients to the oral cavity is key to enhance the therapeutic benefits. The present study is designed to evaluate the plaque control benefit of an 0.4% SnF2 preventive treatment gel.

2. Study Objective

The objective of the study is to evaluate anti-plaque efficacy of a preventive treatment gel in a modified 4-day plaque model.

3. Overall Study Design and Plan

This will be a controlled, examiner-blind, randomized, 2-treatment, 3-period cross-over 4-day partial brushing plaque study. Up to 32 subjects will be enrolled into the study. Prior to the treatment phase of the study, each subject will have a full mouth, supragingival dental prophylaxis and be provided with acclimation product. Before the treatment period, subjects will be randomly assigned to a treatment sequence. At the baseline visit of each period, an Oral Soft Tissue Exam (OST), a digital plaque image (DPIA), and a plaque exam using Turesky Modified Quigley-Hein Plaque Index (TMQHPI) will be conducted, followed by a polishing on both the lingual and buccal surfaces of the teeth. During the treatment phase, subjects will be asked to brush with Crest Cavity Protection on their lingual surfaces for 30 seconds, then without expectoration, subjects will be instructed to swish with the slurry left in their mouth for 60 seconds. After that, subjects will be asked to spit out the slurry and rinse their mouth with 20 ml water. Subjects assigned to the Treatment Gel l Leg will have the gel applied by site staff. Only subjects assigned to the treatment gel will be asked to stay at the site for 15 minutes following the gel application. On Day 4, subjects will return for an OST Exam, a digital plaque image (DPIA), and a final plaque exam (TMQHPI). At period 2 Day 3, 10 minutes after product usage ,the subjects will be asked to provide 5 ml of saliva into a labeled vial. There will be a washout period of approximately 7 days between treatment periods to prevent treatment carryover.

Table 1: Study Schedule by Procedure Type and Visit

PROCEDURES	ACCLIMATION / PROPHYLAXIS	PERIODS 1, 2, & 3									WASHOUT PERIOD
		DAY 0		DAY 1		DAY 2		DAY 3		DAY 4	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	
Informed Consent	X										
Medical History	X										
Demographics	X										
Inclusion/Exclusion	X										
Continuance Criteria		X								X	
Acclimation/Washout Product Distribution	X									X	
Prophylaxis	X										
Oral Soft Tissue Exam		X								X	
Digital Plaque Imaging (DPIA)		X								X	
Plaque Exam (TMQHPI)		X								X	
Lingual/Buccal Polish		X									
Supervised Test Product Usage		X		X		X		X			
At-Home Product Usage			X		X		X		X		
Saliva Collection								X**			
General Comments	X	X		X		X		X		X	
AEs				X		X		X		X	
Product Return		X								X*	
Subject Accountability										X*	

* Period 3 only, or as subjects discontinue participation
** Period 2 only

Prophylaxis and Acclimation

Written informed consent will be obtained from each subject and they will be given a copy. Personal medical history information will be obtained, reviewed, and retained as site source documentation. Demographic information and inclusion/exclusion criteria will be obtained and documented on the appropriate case report form (CRF). Subjects will receive a dental prophylaxis. Subjects will be given acclimation/washout products to use for the duration of the acclimation period. Subjects will be instructed to brush all of their teeth as they normally do twice a day using Crest® Cavity Protection dentifrice and an ADA reference manual toothbrush. Subjects will be reminded to abstain from chewing gum, flossing, using toothpicks, eating, drinking, or performing any oral hygiene after 11:00 p.m. the evening before the Baseline visit of each treatment period.

Periods 1, 2, & 3:

Baseline – Day 0, Morning

Subjects will return their acclimation products and continuance criteria will be assessed. Subjects will have an OST exam. Then subjects will swish with fluorescein for 1 minute, rinse with phosphate buffer and have a digital plaque image taken. Immediately following the imaging, the subjects will swish their mouth with red disclosing solution for 60 seconds and expectorate. Subjects will receive a Turesky modification of the Quigley-Hein Index plaque exam followed by a polishing on the lingual and buccal surfaces of their teeth. At Period 1, subjects will be randomly assigned to a treatment sequence. Morning product usage during the treatment period will be supervised at the clinic. Subjects will be instructed to brush only their lingual surfaces for 30 seconds, then without expectoration, subjects will be instructed to swish with the slurry left in their mouth for 60 seconds. After brushing, the subjects will be instructed to rinse their mouth with water. Subjects assigned to the treatment gel will have the gel applied on their maxillary buccal and lingual teeth.. Only the subjects assigned to the treatment gel will be instructed to stay at the clinic for 15 minutes following the gel application. Prior to leaving the clinic, subjects will be instructed to use their assigned products in the evening at home and to abstain from chewing gum, flossing, or using toothpicks until they have completed their plaque exam on Day 4.

Evening: Subjects will perform the second product usage at their homes.

Day 1

Morning: Subjects will return to the test site to perform a supervised product usage, as previously described.

Evening: Subjects will perform the second product usage at their homes.

Day 2

Morning: Subjects will return to the test site to perform a supervised product usage, as previously described.

Evening: Subjects will perform the second product usage at their homes.

Day 3

Morning: Subjects will return to the test site to perform a supervised product usage, as previously described. At the morning visit on Day 3 visit, subjects will be reminded to abstain from eating, drinking and oral hygiene after 11:00 PM.

Only at Period 2 Day 3 the subjects will be provided with a labeled sterile tube and asked to collect 5 ml of unstimulated saliva 10 minutes after product usage. After the saliva is collected the tube will be stored on ice.

Evening: Subjects will perform the second product usage at their homes.

Final Visit – Day 4, Morning

Subjects will bring their treatment products with them to the visit. Continuance criteria will be assessed. Subjects will receive an OST exam. Then subjects will swish with fluorescein for 1 minute, rinse with phosphate buffer and have a digital plaque image taken. Immediately after the imaging, the subjects will swish their mouth with red disclosing solution for 60 seconds and expectorate. Subjects will receive a Turesky modification of the Quigley-Hein Index plaque exam. Subjects will be allowed to brush the dye off their teeth prior to leaving the clinic. Subjects will then be re-issued their acclimation/washout kit and instructed on brushing during the Washout

period. Finally, subjects will be reminded 1) to perform the evening brushing before 11:00 PM the night before their next Baseline visit, 2) to abstain from chewing gum, flossing, using toothpicks, eating, drinking, or performing any oral hygiene after 11:00 PM the night before their next Baseline visit, and 3) to bring their acclimation/washout kits to their next Baseline visit.

Washout Period

After the Day 4 plaque examination, subjects will return to using the acclimation/washout products provided twice a day for approximately 7 days.

Subject Accountability

Subjects will complete their participation in this study at the end of Period 3. A Subject Accountability CRF will be completed for each subject as they complete the study or discontinue participation in the study. If, for any reason, a subject does not complete the study, an explanation will be entered on the CRF. 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 AEs will be recorded. Any subject reported 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. Examiner reported AEs will be followed-up at the discretion of the Medical Monitor. 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.

4. Inclusion Criteria

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

- Provide written informed consent prior to participation and be given a signed copy of the informed consent form;
- Be 18 years of age or older;
- Agree not to participate in any other oral/dental product studies during the study;
- Agree to delay any elective dentistry (including dental prophylaxis) until the study has been completed;
- Agree to refrain from the use of any non-study oral hygiene products (subjects who are regular flossers will be allowed to floss during acclimation and wash-out periods);
- Agree to use an oral hygiene product that contains stannous fluoride;
- Agree to refrain from any form of non-specified oral hygiene during the treatment period, including the use of products such as floss, toothpicks for plaque removal, and chewing gum;
- Agree to refrain from any oral hygiene, eating and drinking after 11:00 PM the evening before plaque measurements on Day 0 and Day 4 of the treatment periods;

- Agree to return for all scheduled visits and follow study procedures;
- Possess a minimum of 20 natural teeth with scorable facial and lingual surfaces, of which at least 4 are molars; and,
- Be in good general health, as determined by the Investigator/designee based on a review of the health history/update for participation in the study.

5. Exclusion Criteria

Subjects are excluded from study participation if they:

- Have a medical condition requiring pre-medication prior to dental procedures;
- Have taken antibiotics within 2 weeks of the acclimation period or anticipate taking antibiotics at any time during the study;
- Have a history of allergies or hypersensitivity to dyes or dentifrices that contain stannous fluoride;
- Have removable or orthodontic appliances which interfere with obtaining 20 gradable teeth;
- Have previously demonstrated an inability to comply with study visit requirements;
- Have rampant caries, open or untreated caries, severe gingivitis or advanced periodontitis requiring prompt treatment; or,
- Present with any disease or condition(s) that could be expected to interfere with examination procedures or the subject's safe completion of the study.

6. Continuance Criteria

Subjects may be excluded from the study or the analysis if they:

- Have taken antibiotics since their Baseline Visit;
- Have participated in any other oral/dental product studies since their Baseline Visit;
- Have received any non-study dentistry (including dental prophylaxis) since their Baseline Visit;
- Have used any oral hygiene products other than the assigned study products (subjects who are regular flossers will be allowed to floss during acclimation and washout periods);
- Performed any oral hygiene, ate, or drank after 11:00 PM the night before their visit;
- Have used floss, toothpicks, or chewing gum since their Baseline visit;
- Have been unable or unwilling to comply with product usage instructions for any reason.

Subjects may withdraw or be withdrawn from the study at any time. Subjects who are withdrawn from the study after randomization to treatment and product assignment will not be replaced.

7. Identity of Investigational Product(s)

	DENTIFRICE/GEL	**TOOTHBRUSH**
ACCLIMATION/ WASHOUT (MARKETED)	Crest Cavity Protection Regular Flavor Toothpaste Sodium Fluoride (0.243% sodium fluoride)	ADA, soft, manual toothbrush
NEGATIVE CONTROL DENTIFRICE (MARKETED)	Crest Cavity Protection Regular Flavor Toothpaste Sodium Fluoride (0.243% sodium fluoride)	
TREATMENT GEL	0.4% Stannous Fluoride Gel	

8. Method of Assigning Subjects to Treatment Groups

Study Design	n	Number of Treatment Periods	Treatment Sequences
Crossover	32	3	ABB BAA BBA AAB

Treatment Sequence Schedule

Eligible subjects will be randomly assigned to one of the treatment sequences. Subjects will be assigned to a treatment sequence in the order they come to the site for their first Product Usage Visit using a Treatment Sequence Schedule. The site will keep the Treatment Sequence Schedule while the study is on-going. Should a subject miss a treatment period, that treatment in the sequence will be skipped. Subjects who drop from the study prior to the randomization to the treatment sequence might be replaced.

9. Product Usage

	Investigational Dentifrice/Gel:	
Frequency per day	Twice daily	AM – Supervised at the clinic
		PM - At home
Amount of Product	A Full Brush Head of Toothpaste	
Brushing	30 seconds (lingual surfaces only)	
Rinsing	60 seconds (swishing with left-over paste in mouth)	
Rinse-off	Rinse with 20 ml water for 30 seconds	
Gel *	0.5g of gel on maxillary/buccal and 0.5g of gel on maxillary/lingual	

*Only subjects assigned to the gel treatment

Acclimation/Washout Product Use

During the acclimation and washout periods, subjects will brush their teeth thoroughly twice daily as they normally do with the products provided. Subjects will rinse their mouth with water after brushing to remove excess paste.

Dentifrice usage (Treatment Periods)

AM treatment product usage will be supervised by clinic staff.

Subjects will be asked to only brush their lingual surface with their assigned dentifrice for 30 seconds. Without expectoration, subjects will be instructed to swish with the slurry left in their mouth for 60 seconds. After that, subjects will be asked to spit out the slurry and rinse their mouth with 20 ml of water and swish for 30 seconds. Subjects assigned to the gel treatment will have the gel applied by a dental professional. Site staff will weigh out 0.5 g of gel and place the gel on a polyethylene strip. One strip will be applied on the maxillary buccal and one strip on the maxillary lingual side in the mouth. Once the gel has been applied the strip will be immediately

removed and discarded. Subjects will be instructed to stay at the clinic for 15 minutes following the gel application. All subjects will be asked not to eat or drink anything for 30 minutes following use of the test products.

PM treatment usage will be at subject's home.

Subjects will be asked to only brush their lingual surface with their assigned dentifrice for 30 seconds. Without expectoration, subjects will be instructed to swish with the slurry left in their mouth for 60 seconds. After that, subjects will be asked to spit out the slurry and rinse their mouth with 20 ml water and swish for 30 seconds. Subjects assigned to the gel treatment will be instructed to use only the assigned paste. The gel will not be used at the subject's homes.

10. Blinding, Labeling, and Shipping Plan

Acclimation Kit Boxes

Subjects will receive 2 tubes of Crest® Cavity Protection dentifrice (over-labeled to blind the product), one ADA soft manual toothbrush and written usage instructions. Subjects will use the dentifrice for acclimation and washout periods. A new brush will be distributed at the beginning of each washout period. These items will be shipped in subject kit boxes to the investigational site and distributed to the subjects by site personnel.

Dentifrice Treatment Legs

Product will be supplied in subject kit boxes. Each kit will contain 1 over-labeled tube of the assigned toothpaste, ADA soft manual toothbrush, and subject instructions. The shipping containers will be labeled with the "ship to" clinical site address and a "content statement" listing study number and subject numbers contained within. Supplemental product (4 boxes) will be provided.

11. Determination of Sample Size

Up to 32 subjects will be enrolled in the study. Thirty subjects completing this study will provide at least 80% power to detect a mean difference of 0.15 between treatments for the whole mouth average TMQHPI score using two-sided testing with a 5% significance level. This estimate assumes the model mean square error is 0.05 or smaller in a 3-period design.

12. Safety Variables

Safety Observations and/or Measurements

Adverse event data will not be solicited by the clinical investigation staff. However, all volunteered AEs that have the potential to be product-related, will be recorded in the AE CRF. Safety will be assessed by the absence of irreversible side effects associated with use of the test product.

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.

13. Efficacy Variables

Fluorescein Plaque Disclosing Procedure and Digital Plaque Image Analysis (DPIA) Collection System and Analysis

Fluorescein Plaque Disclosing Procedure

- Rinse for 10 seconds with 25 ml of phosphate buffer;
- Rinse for 1 minute with 5.0 ml of 1240 ppm fluorescein in phosphate buffer;
- Rinse 3 times for 10 seconds with 25 ml of phosphate buffer.

Digital Plaque Imaging Analysis Collection
The photographic system consists of a high-resolution digital camera. Two Long Wave UV flash lights located on each side of a camera provides the lighting. The unit is connected to a personal computer, which records and analyzes the images. Prior to daily use, the system is standardized to assure proper operation. Additionally, a color standard is centered and imaged prior to imaging the subjects. A digital image of the maxillary and mandibular anterior facial surfaces is captured. Tooth and plaque pixels are quantified in the digital image and the percent plaque area on the teeth is calculated.

Each image is collected in a darkened room. The subject sits on a stool in front of a chin rest used to hold the head still. The subject places the chin on the chin rest and then positions two sterile plastic retractors to retract the lips and cheeks. It is also acceptable for the subject to position the retractors, and then place the chin on the chin rest. The subject is instructed to retract the lips and cheeks (toward the ears) as far as possible. The incisal edges of the front teeth are placed about 5mm – 10mm from each other and centered in the camera. Prior to exposure the subject is instructed to draw air through the teeth and to position the tongue away from the teeth so that the tongue is not visible. The image is taken of the lips, teeth and gums only; the whole face is not visible in the image. Each image is saved in a file with the subject ID number.

Plaque Examination

The plaque deposits on the teeth will be scored on six surfaces (distobuccal, midbuccal, mesiobuccal, distolingual, midlingual and mesiolingual) of all 28 teeth (excluding 3rd molars, crowns and surfaces with cervical restorations) according to the Quigley-Hein Index as modified by Turesky *et al* which emphasizes plaque in contact with the gingiva. Buccal, lingual, and whole mouth average plaque scores will be calculated for each subject and tooth surfaces by totaling the scores and dividing by the number of gradable sites examined. Scoring criteria are shown in Table 3.

Table 3: Turesky Modified Quigley-Hein Index

Score	Description
0	No Plaque
1	Separate flecks of plaque at the cervical margin.
2	A thin, continuous band of plaque (up to 1 mm) at the cervical margin.
3	A band of plaque wider than 1 mm, but covering less than one third of the side of the crown of the tooth.
4	Plaque covering at least one third, but less than two thirds of the side of the crown of the tooth.
5	Plaque covering two thirds or more of the side of the crown of the tooth.
8	Non-gradable site
9	Missing tooth

Examiner: A. Das

Red Plaque Disclosing Dye Procedure and Preparation

Approximately twenty (20) drops of undiluted plaque disclosing solution is dispensed directly from the manufacturer's original bottle into plastic dosage cups. Study Subjects are given the dosage cup to swish the disclosing solution orally for 15 seconds and then expectorate. The Subjects then rinse with 10ml of tap water for 10 seconds and expectorate.

Saliva Sample

Subjects will be asked to expectorate approximately 2 mL of unstimulated saliva into a labeled tube. The subjects will have up to 5 minutes to provide this amount. Collected samples will be kept on ice at the site and then frozen at -70C. The saliva samples will be analyzed for tin and fluoride outside of the study protocol.

14. Hypothesis

For TMQHPI plaque scores (whole mouth, buccal and lingual surfaces) and percent plaque area the following hypotheses will be tested.

Null: The mean plaque score is equal between the treatments.
Alternative: The mean plaque score is not equal between the treatments.

15. Statistical and Analytical Plans

The primary endpoint is the whole mouth average TMQHPI plaque scores. Plaque scores and percent plaque area will be analyzed separately for each surface using a general linear mixed model. The statistical model will include treatment and period as fixed effects as well as subject as a random effect. Carryover effect will be assessed and may be included in the model if reasonably appropriate. Baseline may be used as a covariate. Statistical comparisons will be two-sided with a significance level of 0.05. Additional analyses of the data may be performed.

APPENDIX

Advertising

If the Oral Health Science Center chooses to advertise for subjects, whether in professional or consumer publications, radio, television, or any other means, all advertising must be approved by the IRB prior to use, documented, and retained.

Confidentiality

Subject files will be maintained in a locked location for the duration of the study. The recipients will treat this information confidentially. In the event of any publication regarding this study, subject identity will not be disclosed.

Direct access to study records and source data/documentation, including subject medical records, will be provided as needed to appropriate parties for the purpose of trial-related monitoring, auditing, IRB/IEC review, and regulatory inspection. Prior to participating in the study, subjects will consent, in writing, to the release of their medical records for said purposes.

Data Collection

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 are available at the site. Any CRF used as a source document must be identified as such in the Investigator Notebook.

Good Clinical Practices

This study is conducted in compliance with applicable sections of the US Federal Regulations governing informed consent (21 CFR 50), IRBs (21 CFR 56), study conduct (21 CFR 312) and

the International Conference on Harmonization's Good Clinical Practice Consolidated Guidelines, [ICH-GCPs, as published by the FDA on 9 May 1997, Federal Register, Volume 62, Number 90 pages 25691-25709]). During the course of the trial, the clinical site is monitored by P&G staff (Clinical Trial Manager or designee) to ensure compliance with the Protocol, regulations and guidelines, adequacy of the equipment and facilities, and satisfactory data collection.

Informed Consent

A subject consent form will comply with all applicable regulations governing the protection of human subjects. The elements of informed consent and the documentation of informed consent are specified in 21 CFR 50.25 and 50.27 and/or ICH GCPs chapter 4. Each subject must sign and date an informed consent to serve as a participant in the study. A signed copy of the consent form will be given to the subject and a signed copy will be retained by the Oral Health Science Center. Subjects may withdraw from participation in the study at any time. Additionally, the Investigator may withdraw subjects from the study if it is in the best interest of the subjects. The reason for all subject withdrawals from the study will be documented on the appropriate CRF.

Institutional Review

Prior to study initiation, the Investigator must obtain institutional review and approval of both the Protocol and the consent form, in compliance with the US Code of Federal Regulations, Title 21, Part 56 or the ICH-GCPs Consolidated Guidelines, Chapter 3. The Investigator maintains any original authorization letter(s) and forwards copies to P&G. IRB approval letters should include the study title, P&G study number, the address of the IRB, date of request, and the signature of the IRB chairperson/designate. Additionally, the letter must acknowledge that both the Protocol and consent form have been approved by the IRB, with notification of any changes required. The study does not begin until P&G has received written confirmation of IRB approval. This IRB shall also review the investigation at least once a year during study execution. The Investigator notifies the IRB when the study is terminated.

Monitoring

Prior to commencement of the study, an initiation meeting will be held with the appropriate Oral Health Science Center personnel to review the objectives and procedures of the clinical trial. To assure accurate, complete, consistent, and reliable data, the Oral Health Science Center and study procedures will be monitored by a Clinical Trial Manager in accordance with 21 CFR 312 and ICH GCPs Chapter 5.

The Oral Health Science Center study coordinator is expected to contact the Clinical Trial Manager or designee as needed regarding study concerns and/or questions.

Protocol Amendments/Changes

Changes to the Protocol following Institutional Review Board (IRB) approval affecting the safety of subjects, scope/objectives of the investigation, or the scientific quality of the study are documented as amendments. Such changes require P&G, Investigator, and IRB approval prior to implementation, unless immediate action is required to safeguard subject safety. Administrative/minor changes (e.g., typos, changes in P&G personnel [excluding medical monitor], etc.) are documented as revisions but do not have to be submitted as amendments unless required by the IRB. Any change in P&G's monitoring staff, Clinical Trial Manager or Medical Monitor during the conduct of the study, must be reported to the Investigator.

Study Medication Dispensing, Storage and Accounting

Study products are 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) are documented using forms provided by P&G or suitable forms provided by the site. Study products are returned to P&G following the trial, or alternatively, they are destroyed at the clinical site provided the site has an existing SOP for the destruction of clinical materials and prior written approval from P&G.

Study Termination

The study is terminated upon completion of all subject treatments and evaluation. The study may be discontinued at any time.

Subject Consent

The Investigator obtains written informed consent for each subject prior to that subject's 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. 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.