The Procter & Gamble Company
Cincinnati, Ohio USA

AN EXPERIMENTAL CLINICAL STUDY TO ASSESS THE GINGIVITIS AND PLAQUE REDUCTION EFFICACY OF AN ORAL-IRRIGATOR AFTER THREE WEEKS OF USE

20 April 2021

NCT04899440
Protocol Number 2021043

Signatures below indicate approval of the Protocol.

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

PII

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE(s)	Adverse Event(s)
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CRF(s)	Case Report Form(s)
FDA	Food and Drug Administration
GBI	Gingival Bleeding Index
GCP	Good Clinical Practices
IRB/IEC	Institutional Review Board/Independent Ethics Committee
MGI	Modified Gingival Index
TQHPI	Turesky Modified Quigley Hein Plaque Index
SOP(s)	Standard Operating Procedure(s)

PROTOCOL BODY

1. Background Information

Gingivitis represents perhaps the most common disease of the periodontium, with a majority of adolescents and dentate adults affected worldwide. Various factors have been implicated in disease extent or severity. Of these, the microorganisms in dental plaque are recognized as playing a prominent etiological role. In the absence of adequate oral hygiene, supra gingival plaque accumulation may be rapid, and visible gingival inflammation manifested within a few days.

Even in extreme plaque accumulation conditions, thorough oral hygiene and mechanical plaque removal is reported to reduce gingivitis and restore health. Control of supra gingival plaque is an essential element in effective oral hygiene programs. Oral hygiene devices are under continuous review for efficacy and safety, as new devices or improvements of features on existing devices are developed.

2. Study Objective

The primary objective of this exploratory study is to evaluate the efficacy of an Oral Irrigator in the reduction of gingivitis compared to a negative control over a 3 week period by using the Modified Gingival Index and the Gingival Bleeding Index.

The secondary objective is to evaluate the efficacy of an Oral Irrigator in the reduction of plaque compared to a negative control using the extended Turesky Modified Quigley-Hein Index (TQHPI) after 3 weeks of use.

3. Overall Study Design and Plan

This is a single-center, examiner-blind, three (3) week, two (2) treatment, parallel group, randomized study design. Thirty (30) subjects who have shown evidence of gingivitis and plaque will be enrolled in this study. Subjects will be evaluated for gingivitis using the Modified Gingival Index (MGI) and the Gingival Bleeding Index (GBI) and evaluated for plaque using the Turesky Modified Quigley-Hein Plaque Index (TQHPI) at two (2) time points: Baseline and after three (3) weeks of product use. Prior to each visit (Baseline and Week 3) subjects will be instructed to abstain from brushing and performing any oral hygiene 12 hours prior and to abstain from eating, drinking (small sips of water will be allowed up to 45 minutes prior to the visit), chewing gum and tobacco use for four (4) hours prior to the visits.

Qualified subjects will be stratified and randomly assigned to one of the two treatment groups, toothbrushing on conjunction with an Oral Irrigator or toothbrushing without an Oral Irrigator, (N=15/treatment) based on Baseline gingivitis (MGI) score, Baseline whole mouth mean TQHPI score, Baseline number of bleeding sites, and tobacco use. Subjects will be given product use instructions and asked to perform a supervised usage of their assigned products. Subjects will be instructed to brush twice a day for approximately three (3) weeks with their assigned products and return for plaque and gingivitis measures at approximately three (3) weeks after the Baseline visit. Specific procedures are detailed below (Table 1).

Table 1. Study Schedule by Procedure Type and Visit

PROCEDURE	BASELINE	WEEK 3
Informed Consent	X	
Medical History Review	X	
Demographics	X	
Inclusion/Exclusion Criteria	X	
Continuance Criteria		X
Oral Examination	X	X
Gingivitis Evaluation (MGI)	X	X
Gingival Bleeding Evaluation (GBI)	X	X
Plaque Exam (TQHPI)	X	X
Treatment Randomization/Balance and Assignment	X	
Product Distribution	X	
Oral Hygiene Instructions	X	
Product usage	X	
General Comments	X	
Product Return		X
AEs	X	X
Subject Accountability		X

Baseline
Subjects will be asked to read and sign an informed consent, of which they will receive a signed copy. Medical history information will be obtained, reviewed, and retained as site source documentation. Demographic information and study inclusion/exclusion criteria will be obtained and documented on the appropriate electronic case report form (eCRF). Subjects will be eligible to enroll in the study after meeting study entrance criteria.

Subjects will then receive an Oral Examination by an experienced examiner. Then the subjects will receive an MGI and GBI examination, in that order. Following that, subjects swish their mouth with disclosing solution and an experienced examiner will conduct a pre-brushing plaque exam: Turesky Modified Quigley-Hein Index (TQHPI). Subjects will qualify for participation if they have a baseline whole mouth mean MGI score between 1.75 and 2.5, a Baseline whole mouth mean TQHPI score ($\geq$2.00), and between 20 and 80 bleeding sites. All the data will be recorded on the appropriate eCRF.

Qualified subjects will be randomized to a treatment group and receive their test products. Subjects will proceed to an area separated from the examination area to receive supervised oral hygiene instructions and product usage instructions. Subjects will brush according to the provided usage instructions with their assigned oral hygiene products (toothbrush and toothpaste with/without Oral Irrigator). The group with the Oral Irrigator will also use the device before brushing with the provided toothbrush and toothpaste. This on-site practice brushing will be considered one of the subject's two daily brushings. Subjects will be instructed to use their assigned products twice per day,

following the provided usage instructions for approximately 3 weeks. The Oral Irrigator will only be used once a day at the evening brushings.

Prior to leaving the clinic, subjects will be scheduled for their next visit (Week 3, ± 2 days) and reminded to refrain from using their oral hygiene products for 12 hours and refrain from eating, chewing gum, drinking (small sips of water will be allowed up to 45 minutes), and tobacco use for 4 hours prior to their next visit.

Any Adverse Events or general comments will be recorded on the appropriate eCRF. All serious AEs will be reported. As for non-serious AEs, only voluntarily reported whole body adverse events that are potentially product related will be reported as will all oral related Adverse Events.

Week 3 (± 2 day):
Subjects will return to the site and bring their test products. Continuance criteria will be assessed and recorded on the appropriate eCRF. Subjects will then receive Oral Examination, MGI, and GBI assessments (in that order) by the experienced examiner. Following that, subjects will swish their mouth with disclosing solution and the same experienced examiner will conduct a pre-brushing plaque exam: Turesky Modified Quigley-Hein Index (TQHPI).

Any Adverse Events or general comments will be recorded on the appropriate eCRF. All serious AEs will be reported. As for non-serious AEs, only voluntarily reported whole body adverse events that are potentially product related will be reported as will all oral related Adverse Events.

Subject accountability will be recorded on the appropriate eCRF and subjects will be dismissed from the study. Subjects must return all test products in order to be exited from the study.

4. Inclusion Criteria

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

- give written informed consent and receive a copy of the signed Informed Consent form;
- be at least 18 years of age;
- typically use a manual toothbrush;
- be in good general health as determined by the investigator/designee based on a review/update of their medical history;
- possess a minimum of 16 scorable teeth (excluding third molars) with facial and lingual scorable surfaces;
- have a Baseline MGI score between 1.75 and 2.5;
- have a Baseline TQHPI score of at least 2.00;
- have a Baseline between 20 and 80 Bleeding sites;
- abstained from all oral hygiene procedures for approximately 12 hours prior to this visit and agree to do the same prior to the subsequent visit;
- abstained from eating, drinking*, chewing gum and using tobacco for at least 4 hours prior to this visit and agree to do the same prior to the subsequent visit. *(Exception: Allowed small sips of water up until 45 minutes prior to their appointment time.)
- agree not to participate in any other oral care study for the duration of this study;
- agree to delay any elective dentistry, including dental prophylaxis, and to report any non-study dentistry received during the course of this study;
- agree to refrain from using any non-study toothbrushes, dentifrices, mouth rinses, tooth whitening products or floss for the study duration;
- agree to return for their scheduled visits and to follow all study procedures.

5. Exclusion Criteria

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

- hypersensitivity to dyes;
- severe periodontal disease, as characterized by purulent exudate, generalized mobility, and/or severe recession;
- any carious lesions requiring restorative treatment;
- active treatment for periodontitis;
- any fixed facial orthodontic appliances or retainers;
- use of any antibiotic medication or a prescription mouth rinse any time within the 2 weeks prior to study initiation;
- any disease or conditions that could be expected to interfere with examination; procedures or the subject safely completing the study.

6. Continuance Criteria

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

- receiving any non-study dentistry, including dental prophylaxis, since their last study visit;
- performing any oral hygiene procedures any time within approximately 12 hours prior to each visit;
- having eaten, drank*, chewed gum or used tobacco any time within the 4 hours prior to each visit. *(Exception: Allowed small sips of water up until 45 minutes prior to their appointment time);
- using any antibiotics or a prescription mouth rinse any time since their last study visit;
- using any oral care products other than assigned study products including tooth whitening products since their last study visit;
- participation in any other oral care study since their last study visit.

7. Identity of Investigational Product(s)

Type of Regimen	Oral Irrigator	Toothbrush	Dentifrice
Test	Oral-B Water Flosser advanced cordless irrigator “Aquacare 6” (MDH20.3) with Nozzle “Aquafloss” ED17	Indicator Soft 35 (OM010I-AP)	Crest Cavity Protection toothpaste
Control		Indicator Soft 35 (OM010I-AP)	Crest Cavity Protection toothpaste

8. Product Usage

Test Regimen

Subjects will use the Oral Irrigator according to the verbal and written use instruction in the evenings before they brush their teeth. Afterwards they will brush their teeth for one minute with the products provided. Subjects will rinse their mouth with water after brushing to remove excess paste.

The Oral Irrigator will be used through all teeth are reached with the device. If necessary, water can be refilled in the water reservoir. The Oral Irrigator has to be used in “continuous” stream type with focused stream (switch in upper position) and in intense mode.
Subjects will be instructed (both verbal and written) to brush their teeth with their assigned toothbrush and toothpaste for one minute twice a day for the duration of the study (approximately 3 weeks). Before the evening brushings subjects will use the Oral Irrigator as described above. Only at the Baseline Visit the Oral Irrigator will be used in the morning for device training. Brushing and use of the Oral Irrigator at the clinical site will be supervised by a site staff person.

Control Regimen
Subjects will brush their teeth for one minute with the products provided. Subjects will rinse their mouth with water after brushing to remove excess paste.

Subjects will be instructed (both verbal and written) to brush their teeth with their assigned toothbrush and toothpaste for one minute twice a day for the duration of the study (approximately 3 weeks). Brushing at the clinical site will be supervised by a site staff person.

9. Blinding, Labeling, and Shipping Plan

Test products will be supplied in subject kit boxes which are labeled with a unique kit box number. The kit boxes will be unique for each treatment leg as follows:

- **Test Group**: Oral-B® Indicator, soft 35 (OM010I-AP) manual toothbrush, overtubed Crest Cavity Protection dentifrice (0.243% NaF), Oral-B Water Flosser advanced cordless irrigator “Aquacare 6” (MDH20.3) handle with nozzle “Aquafloss” ED17, 1 charger (MDH20 charger), and a timer . The water flosser handle, nozzle, and charger will be packed in a baggie.
- **Control Group**: Oral-B® Indicator soft 35 (OM010I-AP) manual toothbrush, overtubed Crest Cavity Protection dentifrice (0.243% NaF), and a timer.

Kit boxes will be labeled with a unique kit number representing the test product and supplemental product. Kit box labels will also contain the study number, emergency phone number, distributor name/address, appropriate caution statements, and other information as required by internal regulations and clinical SOPs. The shipping containers will be labeled with the "ship to" clinical site address and a "content statement" listing study number and kit box numbers contained within. Supplemental product will be provided if additional product is needed. Supplemental product may be dispensed only after consulting with the sponsor for correct treatment group identification; the subject identification number and original kit box number must be provided to the sponsor.

The site will be provided with a code breaker report in a sealed envelope. If the study blind needs to be broken, a subject’s investigational product may be ascertained by opening the sealed code breaker report (appropriate procedure for breaking the blind). 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.

10. Method of Assigning Subjects to Treatment Groups

Subjects who meet enrollment criteria will be stratified based on Baseline MGI (≤ 2.4 vs > 2.4), Baseline number of bleeding sites (≤ 45 vs > 45), Baseline whole mouth mean TQHPI (≤ 3.0 vs. > 3.0) and smoking status (yes/no). Subjects will then be randomized to one of the two (2) treatment groups using a balance and assignment procedure on site. 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 will be distributed according to a randomization schedule provided by the Sponsor. Product distribution and product return will be recorded on the Clinical Materials Inventory provided by the Sponsor. Subjects from the same household will be assigned to the same treatment group.

11. Determination of Sample Size

Thirty (30) subjects, 15 per treatment group, will be enrolled in this study. The sample size was based on logistical considerations.

12. Safety Variables

Safety Observations and/or Measurements
Safety will be assessed by the absence of irreversible side effects. Adverse event (AE) data will not be solicited by the clinical investigation staff. However, all AEs will be recorded in eCRF.

Oral Examination
Assessment of the oral soft tissue will be conducted via a visual examination of the oral cavity and perioral area utilizing a standard dental light, dental mirror, and gauze. The examined structures will 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 oral”. An AE will be recorded if a new abnormal finding is noted after investigational product usage or any previously noted abnormal finding increases in severity during a treatment period.

Examiner: K. Milleman, RDH, BSEd, MS

13. Efficacy Variables

The same examiner will evaluate clinical measurements for each subject at all time points. The examiner will be blinded as to the treatment assigned to each subject in each period. Clinical information will be recorded for all scorable teeth present excluding 3rd molars, teeth with crowns, or large restorations, i.e., covering 50% or more of the tooth surface, bridges, orthodontic appliances, or implants.

The order of clinical measurements will be as follows:
A. Modified Gingival Index
B. Gingival Bleeding Index
C. Turesky Modified Quigley-Hein Plaque Index (extended)

A. Modified Gingival Index (MGI):

Gingivitis will be scored on the buccal and lingual marginal gingival and interdental papilla of all scorable teeth (six scores per tooth):

0 = normal (absence of inflammation)
1 = mild inflammation (slight change of color, little change in texture) of any portion of the gingival unit
2 = mild inflammation of the entire gingival unit

3 = moderate inflammation (moderate glazing, redness, edema and/or hypertrophy) of the gingival unit
4 = severe inflammation (marked redness and edema/hypertrophy, spontaneous bleeding or ulceration) of the gingival unit

MGI whole mouth score is computed by summing the scores and dividing by the number of scorable sites examined.

Examiner: K. Milleman, RDH, BSEd, MS

B. Gingival Bleeding Index (GBI): as defined by Saxton and van der Ouderaa.

The gingiva should be lightly air-dried and a periodontal probe with a 0.5 mm diameter tip inserted into the gingival crevice to a depth of 2mm or until slight resistance is felt. The probe is then run gently around the tooth at an angle of approximately 60◦ and in contact with the sulcular epithelium. Minimum axial force is used to avoid undue penetration into the tissue and the probe is moved around the crevice, gently stretching the epithelium. Each of the 3 gingival areas, i.e., buccal, mesial/dystal and lingual, of the teeth will be probed in this manner waiting approximately 30 seconds before recording the number of gingival units which bleed, according to the following scale:

0 = absence of bleeding after 30 seconds
1 = bleeding observed after 30 seconds
2 = immediate bleeding observed
GBI whole mouth score is computed by summing the scores and dividing by the number of scorable sites examined.

Examiner: K. Milleman**,** RDH, BSEd, MS

C. Turesky Modified Quigley-Hein Plaque Index (extended)

The plaque deposits on the teeth will be scored on six sites (distobuccal, midbuccal, mesiobuccal, distolingual, midlingual and mesiolingual) of all 28 teeth (excluding buccal surfaces of the upper 1st and 2nd molars, 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 gingival. 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 (the examiner will score all 168 sites however the whole mouth mean will later be computed from only 162 sites - the 6 sites used in the plaque sampling will be excluded from plaque calculation). Scoring criteria are shown below.

Scoring criteria are shown in Table 2.

Table 2. 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	Ungradable site
9	Missing tooth

Examiner: K. Milleman, RDH, BSEd, MS

14. Hypothesis

The following hypotheses will be investigated for each efficacy endpoint at Week 3:

Gingivitis Hypothesis:

Null Hypothesis: There is no difference between treatment groups with respect to the mean GI change from baseline (MGI, GBI, or number of bleeding sites) at 3 weeks when an adjustment is made for the respective baseline GI score.

Alternative Hypothesis: There is a difference between the treatment groups with respect to mean GI change from baseline (MGI, GBI, or number of bleeding sites) at 3 weeks when an adjustment is made for the respective baseline GI score.

Plaque Hypothesis:

Null Hypothesis: There is no difference between treatment groups with respect to the mean TQHPI change from baseline at 3 weeks when an adjustment is made for baseline TQHPI score.

Alternative Hypothesis: There is a difference between the treatment groups with respect to mean TQHPI change from baseline at 3 weeks when an adjustment is made for baseline TQHPI score.

15. Statistical and Analytical Plans

Statistical analyses for gingivitis efficacy will be based on whole-mouth average MGI, GBI, and number of bleeding sites change from baseline scores (Baseline minus Week 3). An ANCOVA will be performed to determine treatment differences on the whole mouth average gingivitis reduction with the respective baseline gingivitis score as the covariate. Baseline by treatment interaction will be investigated and included in the final ANCOVA model if significant at the 10% level. Separate analyses will be performed for each gingivitis endpoint with MGI being primary.

Statistical analyses for plaque efficacy will be based on average whole mouth TQHPI change from baseline score (Baseline minus Week 3). The 3-week plaque reduction will be analyzed for treatment differences using an ANCOVA with baseline whole mouth TQHPI score as the covariate. Baseline by treatment interaction will be investigated and included in the final ANCOVA model if significant at the 10% level.

The within-treatment differences from baseline gingivitis scores (MGI, GBI, number of bleeding sites) will be tested versus zero using a paired difference t-test. Similar within-treatment analyses will be carried out for TQHPI.

The lingual and buccal surfaces of the gingivitis and plaque endpoints will be analyzed separately for treatment differences as described above.

If the data does not satisfy the normality criterion, transforming the data or analogous nonparametric methods will be employed. Additional analyses may also be performed in order to more fully understand the data. All treatment comparisons will be considered two-sided with an α=0.10 significance level.

Demographic and baseline variables will be summarized by treatment group, and adverse events reported or noted during the study will be documented and listed by treatment group.

APPENDIX

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 event* is defined as an event, which suggests a definite hazard or handicap to the subjects. Serious events are any events resulting in death, life threatening situation, permanent disability, hospitalization or prolonged hospitalization, or congenital anomaly.

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. The Investigator will be responsible for AE reporting to the IRB. Within 5 working days, a written report describing the circumstances of the event must be submitted to the Sponsor.

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.